Pregabalin Population Pharmacokinetic and Exposure-Response Analyses for Focal Onset Seizures in Children (4–16 years) and Adults, to Support Dose Recommendations in Children

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Pregabalin is approved in multiple countries as adjunctive therapy for adult patients with focal onset seizures (FOS; previously termed partial onset seizures). This study used population pharmacokinetic (PK) and exposure–response (E-R) analyses from pooled pregabalin concentration and efficacy data to compare pregabalin exposure and E-R relationships in pediatric and adult patients with FOS, to support pediatric dosage recommendations. A one-compartment disposition model was used, with first-order absorption and body surface area-normalized creatinine clearance on clearance. Individual pregabalin average steady-state concentrations were predicted and used in an E-R analysis of efficacy. The E-R relationship of pregabalin was similar in pediatric (4–16 years) and adult patients with FOS after accounting for differences in baseline natural log-transformed 28-day seizure rate and placebo effect. Population PK simulations showed that children aged 4–16 years and weighing ≥ 30 kg required pregabalin 2.5–10 mg/kg/day to achieve similar pregabalin exposure at steady-state to adult patients receiving the approved doses of 150–600 mg/day. For children 4–16 years weighing < 30 kg, a higher pregabalin dose of 3.5–14 mg/kg/day was required to achieve equivalent exposure at steady-state. The results support the dosage guidance provided in the pregabalin prescribing label, whereby pediatric patients (4–16 years) weighing < 30 kg should receive a 40% higher pregabalin dose (per kg of body weight) than patients weighing ≥ 30 kg to achieve similar exposure. Our combined modeling approach may provide guidance for future extrapolation assessment from adult to pediatric patients.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Full extrapolation of the efficacy of drugs approved for the treatment of focal onset seizures in adults, to children 2 years of age and older, is accepted by the US Food and Drug Administration (FDA).

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ Population pharmacokinetics (PK) in adults and children, and subsequent exposure–response (E-R) analyses confirmed drug exposure and E-R relationship similarities in the two populations with focal onset seizures, and supported pregabalin pediatric dosage recommendations.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ The similarities in PK exposure and E-R relationship of pregabalin in adult and pediatric patients served as further validation of the established full extrapolation in focal onset seizures.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ Applying the extrapolation, modeling and simulation approach may facilitate more efficient pediatric drug development and approval, and more timely access to new treatments for pediatric patients.

Pregabalin (LYRICA) is a second-generation antiepileptic drug (AED) approved as adjunctive therapy (either b.i.d. or t.i.d. daily-dosing) for adults with focal onset seizures (FOS; previously termed partial onset seizures1), in addition to being approved for other indications, including neuropathic pain.2,3 In the United States, pregabalin is also approved as adjunctive therapy for FOS in pediatric patients aged 1 month and older.2 Approval in pediatric patients with FOS occurred after completion of pediatric phase I, phase III safety and efficacy, and long-term safety trials,4 and 15 years after approval for adults with FOS.2 In adults with FOS, adjunctive flexible-dosed pregabalin (150–600 mg/day) reduces seizure frequency and increases responder rates (i.e., proportion of patients achieving ≥ 50% reduction in seizure frequency) vs. placebo.5–7

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Pregabalin has a linear and predictable pharmacokinetic (PK) profile. In adults, pregabalin is well absorbed after oral administration with time to peak plasma concentrations (T_{max}) within 1.5 hours postdose under fasting conditions, and oral bioavailability is ≥ 90% independent of dose. Pregabalin does not bind to plasma proteins. The apparent volume of distribution (V/F) following oral administration is ~ 0.5 L/kg. Pregabalin undergoes negligible metabolism in humans, and is largely eliminated by renal excretion, with elimination half-life of ~ 6 hours. 

Population PK analyses in adults have shown that creatinine clearance (CLcr) is a significant covariate predicting apparent clearance (CL/F). Although a small additional relationship with body weight has been detected, the relationship with CLcr (mL/min) accounts for most of the changes in CL/F due to both size and renal function, and is the only clinically relevant covariate in adults. In a phase I study, including pediatric patients aged 1 month to 16 years, the observed pregabalin T_{max} was similar to that observed in adults. However, body weight–normalized pregabalin CL/F was ~ 40% higher in patients weighing < 30 kg vs. those weighing ≥ 30 kg, consistent with the lower area under the concentration–time curve (AUC) observed in younger children when pregabalin is administered on a mg/kg basis. Body weight is also a factor on V/F, but when normalized for body weight, V/F was similar across age cohorts and body weight. As a result, mean terminal half-life of pregabalin was lower in patients weighing < 30 kg, consistent with the higher body weight-normalized CL/F in patients 1 month to 6 years and the constant body weight-normalized V/F across age cohorts, as reported in full elsewhere. A 40% higher pregabalin dose (in mg/kg) is safe and effective for pediatric patients weighing < 30 kg, to achieve similar PK exposures to adults, or to pediatric patients weighing ≥ 30 kg. These extrapolations were subsequently used in the design of the phase III PERIWINKLE study in pediatric patients (4–16 years) with FOS (NCT01389596; A0081041), where two dose groups of adjunctive pregabalin (2.5 mg/kg/day (max 150 mg/day); 10 mg/kg/day (max 600 mg/day)) were investigated. Doses were adjusted to 3.5 and 14 mg/kg/day, respectively, for children weighing < 30 kg to match corresponding exposures in adults. PERIWINKLE demonstrated that pregabalin (10 mg/kg/day) significantly reduced FOS frequency vs. placebo. The lower dose (pregabalin 2.5 mg/kg/day) showed a numerical, but non-significant reduction in FOS frequency vs. placebo. The US Food and Drug Administration (FDA) has since issued guidance indicating that efficacy of treatments in adults with FOS can be extrapolated to pediatric patients aged ≥ 2 years. We sought to use population PK and exposure–response (E-R) analyses to compare pregabalin exposure and E-R relationships in pediatric and adult patients with FOS. These analyses informed dosage guidance in the pregabalin prescribing label.

Predicted individual pregabalin average steady-state concentrations (C_{av,ss}) in pediatric and adult efficacy studies were subsequently used in the pooled E-R efficacy analysis. Based on pregabalin E-R similarity in pediatric and adult patients with FOS, population PK simulations were performed to assess the proposed dosing recommendations for pediatric patients 4–16 years, aiming for children to achieve similar pregabalin concentrations to approved doses in adults with FOS.

**Population PK model**

Pregabalin plasma concentrations from healthy participants with various degrees of renal function and from patients with FOS across 10 studies were included in the population PK dataset. These included two studies in pediatric patients with FOS, three phase III studies in adult patients with FOS, and four phase I studies in healthy adults, and one study in adults with various degrees of renal function. All studies were approved by relevant institutional review boards, as detailed elsewhere.

The population PK model was built using nonlinear mixed-effects modeling (NONMEM), first-order conditional estimation with interaction and NONMEM software version 7.3 (Icon Development Solutions, Dublin, Ireland). The base model was a one-compartment model with first-order elimination and absorption (first-order absorption rate constant (k_{a}), which was modeled as a fraction of the elimination rate constant to avoid flip-flop), with lag time (T_{lag}).

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**Methods**

**Overall strategy**

Population PK modeling was performed using pooled pregabalin concentration data in pediatric and adult patients, and an adapted version of a previously developed population PK model based on adult data.
to test for differences in E-R between pediatric and adult populations. **Figure 1** graphically illustrates the drug effect vs. placebo response in pediatric and adult populations, showing the common $E_{\text{max}}$ and $EC_{50}$ parameters but different placebo responses, based on individuals’ baseline LSR28. Model selection was based on Akaike Information Criterion, model stability, plausibility, and precision (standard error of parameter estimates and residual error). Adult data were used initially to develop the structural model, and pediatric data were added to test for population differences. A graphical analysis was used to assess adequacy of the final regression model in describing the E-R relationship for subgroups of covariates of interest (age, sex, race, geographic region, and number concomitant AEDs).

**Pediatric dosage recommendations**

In order to evaluate the pediatric dosage recommendations, simulation data sets ($n = 1,000$) with appropriate covariates were created by bootstrapping with replacement from 331 pediatric patients with FOS (4–16 years) in the two pediatric studies (including placebo arms), and by sampling without replacement from 1,040 adult patients with FOS in the three phase III studies. Population PK simulations were performed under fasted conditions, with final parameter estimates, all covariate effects, IIV, and residual errors from the final population PK model for 150 and 600 mg/day equivalent adult doses. The simulated steady-state pregabalin concentrations ($C_{\text{av,ss}}$, maximum $C_{\text{max,ss}}$, minimum $C_{\text{min,ss}}$) for pediatric and adult patients were compared. Dosage recommendations for children aged 4–16 years were determined based on matching adult exposures at approved dosages per the FDA’s guidance on full extrapolation of efficacy from adults to pediatric patients with FOS. Although only the b.i.d. regimen was investigated in PERIWINKLE, both b.i.d. and t.i.d. regimens were simulated in pediatric patients, as both regimens are approved in adult patients.

**RESULTS**

**Population PK model**

Serum concentrations were included for PK analysis from 724 adults and 255 pediatric patients across the 10 pregabalin studies. The majority of patients were white in each age category, with approximately equal proportions of male and female patients (Table 1). CLcr ranged between 42.2 and 261 mL/min in adults, and between 15.5 and 293 mL/min in pediatric patients. A total of 45 of 162 patients aged < 12 years had absolute CLcr < 60 mL/min. After adjusting for body size (based on BSA), BSA-NCLcr was comparable in pediatric patients aged < 12 years and those ≥ 12 years (Table 1).

Based on highly correlated covariates of absolute CLcr, body weight, and age, particularly in the pediatric population, the BSA-NCLcr one-compartment model (including allometric scaling of body weight on pregabalin CL/F and V/F with estimated exponents) was chosen as the final model as it was more stable than the model with absolute CLcr (Table 2). Although the initial approach is still valid, the BSA-NCLcr (mL/min/1.73 m$^2$) approach was used to reduce colinearities among covariates and stabilize model building. IV on $T_{\text{lag}}$ was fixed to 0 due to limited number of observations prior to the estimated $T_{\text{lag}}$ (~ 0.32 hours). The goodness-of-fit plots and the prediction-corrected visual predictive check, stratified by study design variables and covariates, indicated that the final combined pediatric and adult population PK model adequately described the pregabalin PK in pediatric patients with FOS, healthy adults, adults with various degrees of renal function, and adults with FOS (Figure S1; Figure S2). The two nominal dose levels, 2.5 and 10 mg/kg/day, were observed to deliver similar concentrations to the adult doses, 150 and 600 mg/day, respectively (Figure S3) as predicted from prior modeling, including phase I pediatric data. The estimated exponent of allometric function was 0.52 for CL/F and 0.70 for V/F. This translates to ~ 40% higher CL/F for a typical child weighing 20 kg compared to a typical child weighing 40 kg. In addition to the previously identified covariate effects (food effect on $k_a$ and $T_{\text{lag}}$, body weight and sex on V/F), a statistically significant sex effect on CL/F was observed, but the 8% lower CL/F in female patients was not considered clinically relevant (Table S1). Inclusion of food effect on $T_{\text{lag}}$ and sex on CL/F only slightly reduced IV on CL (from 20.8% to 20.2%), V/F (from 13.0% to 12.8%), and $k_{a,\text{fed}}$ (from 59.2% to 57.9%), whereas IV on $k_a$ remained unchanged (117%).

**Exposure–response model**

The E-R model was developed based on data from 280 pediatric patients (4–16 years) in the PERIWINKLE study and 858 adult patients (including 8 adolescents 13–16 years) in the 3 adult studies with FOS (Table S2). There was an approximately equal proportion of male and female patients among the adult and pediatric populations. Most patients were white (82%) and from the United States (62%); 29% of pediatric patients were Asian vs. 1% of adult

![Figure 1](image-url) Graphical representation of exposure–response (E-R) in children and adult patients with FOS. $C_{\text{av,ss}}$, average steady-state concentration; $EC_{50}$, half maximal effective concentration; $E_{\text{max}}$, maximum response achievable; FOS, focal onset seizures.
patients. The proportions of patients on one or two concomitant AEDs were comparable between pediatric and adult patients. None of the pediatric patients were on ≥ 4 concomitant AEDs (Table S2).

The relationship between pregabalin \( C_{\text{avss}} \) and LSR28 in pediatric patients aged 4–16 years and adult patients with FOS was best described with a model based on a common \( E_{\text{max}} \) (sum of population-specific placebo effect and maximum drug effect), a common EC\text{50}, and separate baseline LSR28 and placebo effects for the two populations (Figure 1). There was a trend for dose-response relationship despite the large between-subject variability in both pediatric and adult patients (Figure 2). The mean change from baseline for 600 mg/day b.i.d in adults and the highest dose (10 mg/kg/day) in pediatric patients were similar (–0.545 vs. –0.551). The group means (–0.313 vs. –0.0296) and medians (–0.185 vs. –0.0150) of change from baseline in LSR28 for pediatric patients on placebo were higher than adults on placebo, respectively. The E-R relationship of pregabalin was similar across pediatric patients aged 4–16 years and adult patients with FOS, after accounting for differences in baseline LSR28 and placebo effect in the 2 populations (Table 3; Figure S4). When assessed graphically, none of the covariates appeared influential on the E-R relationship of LSR28 and pregabalin \( C_{\text{avss}} \) for pediatric and adult patients, including age or sex (Figures S5a,b).

Projected dosage recommendations in children

Population PK simulations demonstrated that in pediatric patients aged 4–16 years, weighing ≥ 30 kg, a pregabalin dose of 2.5–10 mg/kg/day given either b.i.d. or t.i.d. achieved similar pregabalin exposure to adult patients receiving 150–600 mg/day (the approved dose in adults\(^2,3\)). For pediatric patients 4–16 years, weighing < 30 kg, a 40% higher pregabalin dose (3.5–14 mg/kg/day) was required to achieve this exposure given either b.i.d. or t.i.d. (Table 4; Table S3).

DISCUSSION

The pregabalin pediatric FOS program was started in 2005, prior to regulatory guidelines on Paediatric Investigational Plans (PIP),\(^{,19}\) Pediatric Study Plans (PSP),\(^{,11}\) and the acceptance of efficacy extrapolation by the FDA from adult to pediatric patients with FOS.\(^{11,12}\) The program included a phase I PK study in pediatric patients with FOS (1 month to 16 years),\(^{10}\) and two randomized, double-blind, placebo-controlled efficacy and safety studies in pediatric patients with FOS, aged 4–16 years (PERIWINKLE)\(^4\) or 1 month to < 4 years;\(^{20}\) in addition to long-term safety and tolerability assessments. Shortly before completion of PERIWINKLE in 2016, the FDA announced that efficacy data could be extrapolated from adults to represent pediatric patients with FOS,\(^{21}\) in order to improve pediatric drug development efficiency and early access to therapeutics. The confirmation of efficacy extrapolation took > 2 decades of multidisciplinary collaboration among multiple sectors from the initial extrapolation proposal,\(^{22,23}\) to the consensus of disease similarity,\(^{24}\) to confirmation of efficacy response similarity,\(^{25}\) and drug E-R similarity across multiple drugs in multiple mechanisms of actions.\(^{11,21}\) Collectively, guidances were issued

### Table 1 Demographic characteristics of patients included in the population PK analysis

|                      | 3 months to < 12 years | 12–16 years | All     | Adults |
|----------------------|------------------------|-------------|---------|--------|
| N                    | 162                    | 93          | 255     | 724    |
| Females, n (%)       | 80 (49.4)              | 41 (44.1)   | 121 (47.5) | 367 (50.7) |
| Age, years, median (range) | 7 (0.25–11)     | 14 (12–16)  | 10 (0.25–16) | 38 (17–75) |
| Race, n (%)           |                        |             |         |        |
| White                 | 112 (69)               | 65 (70)     | 177 (69) | 608 (84) |
| Black                 | 11 (7)                 | 2 (2)       | 13 (5)  | 38 (5)  |
| Asian                 | 34 (21)                | 23 (25)     | 57 (22) | 11 (2)  |
| Others                | 5 (3)                  | 3 (3)       | 8 (3)   | 67 (9)  |
| Body weight, kg, median (range) | 23.6 (6.6–69) | 52.3 (24–108) | 32.9 (6.6–108) | 75.5 (40–180) |
| CLcr, mL/min, median (range) | 79.1 (15.5–193) | 128 (67.2–293) | 95.5 (15.5–293) | 108\(^a\) (42.2–261) |
| NCLcr, mL/min/1.73 m\(^2\), median (range) | 149 (74–315) | 149 (94–284) | 149 (74–315) | 101\(^b\) (49–227) |
| Total no. PK samples | 628                    | 313         | 941     | 4,317  |

CLcr, creatinine clearance; NCLcr, creatinine clearance estimated using Cockcroft-Gault equation (normalized for body surface area) for patients ≥ 13 years and Schwartz equation for patients < 13 years; PK, pharmacokinetic.

\(^{a}\)Excluded 26 patients with renal dysfunction from a phase I study.\(^{10}\) \(^{b}\)Patients in protocol 1008-049 included adults with various degrees of renal function, including normal renal function.
by the FDA in an attempt to limit the need for a full, controlled clinical efficacy trials in young patients, and these are based on the assumptions that, compared with adults, even young children have a similar progression of disease, similar response of disease to treatment, and similar E-R relationship.

Using data pooled from 10 adult and pediatric clinical studies of pregabalin, we first demonstrate that in pediatric and adult patients with FOS, pregabalin CL/F was proportional to absolute CLcr (mL/min). However, the high correlations among absolute CLcr, body weight, and age, particularly in the pediatric population, made it difficult to assess these covariate effects independently. The final BSA-NCLcr model, including scaling of body weight on pregabalin CL/F and V/F with estimated exponents, was more stable than the model using the absolute CLcr. Model instability was judged by difficulties in minimization and large changes (> 20%) in parameter estimates. When BSA-NCLcr (mL/min/1.73 m²) was used to remove colinearities among the covariates, the change in CL/F with size in pediatric patients was accounted for by a relationship with body weight. Pregabalin clearance was proportional to BSA-NCLcr up to an estimated breakpoint of 96.4 mL/min/1.73 m², where it was then estimated to be constant for higher BSA-NCLcr. We also noted that most pediatric patients had normal renal function with BSA-NCLcr close to or above the estimated breakpoint.

The IIVs for pregabalin CL/F and V/F were ≤ 20% and the proportional residual errors were ≤ 35%, suggesting pregabalin exposures (Cav,ss and Cmax,ss) are highly predictable in both adult and pediatric patients with known body weight and BSA-NCLcr. There was a high ETA-shrinkage for V/F (60.7%), potentially due to limited pregabalin concentrations around T max with the sparse sampling approach in the included phase III outpatient studies. The high ETA-shrinkage for V/F could be a potential limitation of the current simulation approach to predict Cmax, and assess Cmax ratio between pediatric and adult populations. The ETA-shrinkage for ka under fed condition was also high (89.6%), but this was likely due to only 200 pregabalin readings from 11 patients in study phase I adult studies collected under unknown food status. The food status in study A0081041 was a diary end point that did not provide information on quantity of type of food consumed. Covariate equations are detailed in the Appendix, Equations I.

### Table 2 Final population PK model (NCLcr) parameter estimates

| Model parameter | Estimate [RSE] |
|-----------------|---------------|
| OFV (ΔOFV²)     | –2803.456 (–227.23) |
| CL/F            | 4.96 [1.78] L/hr (4.71–5.20) |
| Body weight on CL/Fd | 0.52 [4.72] (0.48–0.57) |
| Sex on CL/F²    | 0.92 [2.00] (0.88–0.95) |
| CLcr breakpoint | 96.4 [1.91] mL/min/1.73 m² (90.7–104) |
| V/F             | 39.8 [1.62] L (38.6–41.0) |
| Sex on V/F²     | 0.83 [2.48] (0.79–0.87) |
| Body weight on V/Fd | 0.70 [4.59] (0.64–0.76) |
| ka, fasted       | 10.0 [16.2]/hr (7.44–15.1) |
| Food: fed        | 0.71 [2.39] (0.33–5.14) |
| Food: unknown    | 1.22 [3.26] (0.49–3.57) |
| Tlag             | 0.32 [1.52] hr (0.31–0.32) |
| Food: fed      | 0.43 [10.5] (0.34–0.83) |
| Interindividual variability | |
| CL/F            | 20.2 [18.7] % (16.3–23.4) |
| V/F             | 12.8 [21.7] % (10.3–15.3) |
| ka             | 117 [13.9] % (103–149) |
| ka: fed | 57.9 [74.4] % (25.5–204) |
| Proportional error | |
| Phase I adult   | 16.6 [10.1] % (15.2–18.6) |
| Phase III adult | 28.9 [7.49] % (26.3–30.8) |
| Phase I pediatric | 29.8 [22.7] % (23.2–36.2) |
| Phase III pediatric | 35.0 [21.0] % (28.1–40.3) |
| Additive error  | |
| Phase I adult   | 0.021 [66.8] μg/mL (0.0074–0.033) |
| Phase III adult | 0.047 [77.3] μg/mL (0.00047–0.092) |

**CLcr, creatinine clearance; CL/F, apparent clearance; ka, absorption rate constant; NCLcr, creatinine clearance (normalized for body surface area); OFV, objective function value; ΔOFV, difference in OFV; PK, pharmacokinetics; RSE, relative standard error; Tlag, lag time; V/F, volume of distribution.**

| Estimate [RSE] | 95% confidence interval | Shrinkage |
|----------------|-------------------------|------------|
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95% confidence intervals were generated from 1,000 nonparametric bootstrap data sets. Comparison with the base body-surface area-normalized CLcr model. CL/F estimated as a proportionality factor for the relationship between CL/F and CLcr when CLcr ≤ CLcr breakpoint. Normalized to 70 kg with a power function. Reference sex is male. ka estimated as a proportionality factor for the relationship between ka and elimination rate constant. Estimated as a fractional change in ka. Fractional change in Tlag using fed data from a phase I adult study. All phase III adult studies were collected under unknown food status. The food status in study A0081041 was a diary end point that did not provide information on quantity of type of food consumed. Covariate equations are detailed in the Appendix, Equations I.
with known fed conditions, and was not used in the simulations. In contrast, the ETA-shrinkages for $k_a$ under fasted and unknown food status, as well as for CL/F, were lower (46.2% and 27.4%, respectively), consistent with more data being available to support the parameter estimates.

Population dose-response models using a Poisson model or a negative binomial distribution with factors of dose or exposure, absence or presence of seizures on preceding day, placebo effect, and the use of mixture model to separate out patients who respond (responders) or do not respond (nonresponders) to treatment, have been used to describe longitudinal daily seizure count data. However, this type of analysis requires intensive computing time given the amount of data and highly variable day-to-day seizure count over a long trial period. We utilized an E-R analysis for a simpler approach, with regression analysis on the seizure data during the double-blind treatment period (LSR28) and factors of

Figure 2 Distribution of change from baseline of log-transformed 28-day seizure rate (all partial onset seizures) by population and treatment. Circles represent the individual observations. Boxes indicate the interquartile range with the median of the individual treatment group shown by a horizontal line. Grey diamonds represent the group means. Whisker lines represent 1.5 times the interquartile range below the first quartile or above the third quartile. For pediatric study A0081041, 2.5 mg/kg/day included 2.5 mg/kg/day in patients ≥ 30 kg or 3.5 mg/kg/day in patients < 30 kg, with maximum 150 mg/day; 10 mg/kg/day included 10 mg/kg/day in patients ≥ 30 kg or 14 mg/kg/day in patients < 30 kg, with maximum 600 mg/day.

Table 3 Final E-R model parameters for pregabalin in adults and children (aged 4–16 years)

| Data         | Baseline effect | Placebo response | Treatment effect |
|--------------|-----------------|------------------|-----------------|
|              | Intercept       | Slope$_{baseline}$ | $E_{max}$ | EC$_{50}$, μg/mL |
| Adult (A)    | 0.099 ± 0.066  | 0.948 ± 0.022    | 2.37     | –1.06 ± 0.363 | 5.93 ± 3.49 |
| Children (C) | C: –0.409 ± 0.106 | C: 1.03 ± 0.026   | C: 2.68  | –0.924 ± 0.214 | 4.69 ± 2.17 |
| Adult (A)    | A: 0.110 ± 0.066 | A: 0.945 ± 0.022  | A: 2.38  |                      |                |

Values are estimate and standard error. EC$_{50}$, half maximal effective concentration; $E_{max}$, maximum response achievable; E-R, exposure-response.

*Computed as intercept + slope$_{baseline}$·baseline$_{median}$, for patients with median log-transformed 28-day seizure rate of 3.00 for children or 2.40 for adults. †Included 8 patients aged 13–16 years in 1 adult study (protocol 1008-034).
the individual’s baseline LSR28 and placebo effect. Although this simpler approach does not allow prediction of individual patterns in seizure frequency over time,29 it is considered adequate for the broad comparison of the dose-response or E-R relationship across patient populations.

The present study also demonstrates that the E-R relationship for pregabalin in patients with FOS was similar in pediatric (4–16 years) and adult patients, after accounting for differences in baseline LSR28 and placebo effect. It should be noted that the adult and pediatric studies were conducted ~20-years apart, where differences in clinical practice and management may have contributed to placebo response differences. This is considered in light of data suggesting an increasing placebo effect on efficacy with ongoing AED treatment, and a decreasing placebo-adjusted drug effect of AEDs over the past 2 decades.30 More specifically, Rheims et al., in 2011, demonstrated that responder rates were significantly higher in more recent studies than in older studies.30 For pediatric patients 4–16 years, anatomic and clinical features of FOS are similar to adults, as are responses to AEDs31–33 and E-R relationships.29 Our analyses utilizing pregabalin data are consistent with these conclusions, and provide further validation of E-R relationship similarity in adult and pediatric FOS populations.

Considering the difficulty in recruiting pediatric patients with FOS, only the b.i.d. regimen was investigated in PERIWINKLE. Pregabalin 10 mg/kg/day (including 14 mg/kg/day in children < 30 kg) demonstrated significant reduction in seizure frequency, whereas pregabalin 2.5 mg/kg/day (including 3.5 mg/kg/day in children < 30 kg) showed a numerical decrease in seizure frequency but not of statistical significance.4 As the sparse pregabalin concentrations and the population PK modeling confirmed pregabalin exposure, the lack of statistical difference at the lower dose in PERIWINKLE could be due to a larger placebo response, hence the smaller placebo-adjusted efficacy vs. adult studies.4 After taking into account the different placebo responses in the joint analysis, pregabalin demonstrated a similar E-R relationship in adult and pediatric (4–16 years) patients with FOS, consistent with the analysis that supported the full efficacy extrapolation from adults with FOS to this age group.29 Considering the FDAs advice notice and the totality of the pregabalin data, pregabalin dosage recommendations in the prescription label23 were based on full efficacy extrapolation by matching pregabalin exposures at the approved adult doses, and the safety and tolerability observed in the pregabalin pediatric studies. Safety data cannot generally be extrapolated from adults to children, and still requires specific clinical study.12 Both b.i.d. and t.i.d. regimens were simulated for the pediatric patients as they had been approved for adult patients. Our simulations and dose predictions collectively supported the pregabalin b.i.d. and t.i.d. dosage recommendations for pediatric patients aged 4–16 years, which were subsequently approved by the FDA as reflected in the pregabalin prescription label.2

Future perspectives

There are many challenges in pediatric drug development, particularly in recruitment and PK sampling of vulnerable populations, which may delay the completion of necessary studies to support approval for pediatric use.34 Model-informed drug development, including the use of extrapolation to replace or reduce the number of required clinical trials in pediatric populations, would help speed up pediatric drug development, and thus deliver medicines to pediatric patients faster.35,36 Had the extrapolation approach been used for the pregabalin FOS pediatric program, regulatory approval could have been obtained up to a decade earlier. The full efficacy extrapolation in FOS will greatly facilitate more efficient future pediatric drug development in FOS, by reducing the need for phase III studies. There are still significant needs in many other disease areas using extrapolation in place of clinical trials to minimize potential delays and provide effective therapy to pediatric patients. As exemplified in the FOS example, the extrapolation evaluation will require multidisciplinary collaborations, especially modeling and simulations to address questions on similarities in disease, PK exposure, and E-R relationship between adult and pediatric patients.32,37 This may require the incorporation of more innovative and quantitative approaches to improve the robustness of the analysis.38,39

In addition to efficacy extrapolation, we would also like to advocate for pediatric PK extrapolation to potentially replace or minimize pediatric phase I studies, an area which has been gaining credence

Table 4 Median ratio (children vs. adults) for pregabalin PK exposure based on simulations using bootstrapped data

| Parameter | Frequency | Adults (≥ 17 years) | Children (4–16 years) | Ratio to adults |
|-----------|-----------|--------------------|----------------------|----------------|
|           | (n = 1,000) |                   | (< 30 kg<sup>b</sup>) |                |
|           | (n = 1,000) |                   | (≥ 30 kg<sup>b</sup>) |                |
| C<sub>max</sub> | b.i.d. | 1.34 | 5.37 | 0.91 | 0.89 | 0.92 |
|           | t.i.d. | 1.34 | 5.35 | 0.90 | 0.88 | 0.91 |
| C<sub>min</sub> | b.i.d. | 2.43 | 9.73 | 1.01 | 1.05 | 0.99 |
|           | t.i.d. | 1.97 | 7.86 | 0.99 | 1.02 | 0.97 |
| C<sub>av</sub> | b.i.d. | 0.60 | 2.39 | 0.75 | 0.68 | 0.80 |
|           | t.i.d. | 0.81 | 3.23 | 0.78 | 0.72 | 0.81 |

C<sub>av</sub>, average steady-state concentration; C<sub>max</sub>, maximum steady-state concentration; C<sub>min</sub>, minimum steady-state concentration; PK, pharmacokinetics.

<sup>a</sup>3.5 mg/kg/day (max 150 mg/day) or 14 mg/kg/day (max 600 mg/day) for the equivalent adult doses of 150 and 600 mg/day, respectively.<sup>b</sup>2.5 mg/kg/day (max 150 mg/day) or 10 mg/kg/day (max 600 mg/day) for the equivalent adult doses of 150 and 600 mg/day, respectively. C<sub>av</sub>, ss represents the trough value at 12 hours for b.i.d. dosing and 8 hours for t.i.d. dosing.

| Parameter | Frequency | Adults (≥ 17 years) | Children (4–16 years) | Ratio to adults |
|-----------|-----------|--------------------|----------------------|----------------|
|           | (n = 1,000) |                   | (< 30 kg<sup>b</sup>) |                |
|           | (n = 1,000) |                   | (≥ 30 kg<sup>b</sup>) |                |
| C<sub>max</sub> | b.i.d. | 1.34 | 5.37 | 0.91 | 0.89 | 0.92 |
|           | t.i.d. | 1.34 | 5.35 | 0.90 | 0.88 | 0.91 |
| C<sub>min</sub> | b.i.d. | 2.43 | 9.73 | 1.01 | 1.05 | 0.99 |
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| C<sub>av</sub> | b.i.d. | 0.60 | 2.39 | 0.75 | 0.68 | 0.80 |
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since 2015.\textsuperscript{18,40} The issues can be highlighted by our earlier trials, such as the phase I pediatric study investigating pregabalin, which took \sim 5 years to complete, and more specifically, the 1 month to \textless 2 years age group, for which it took \textgreater 2 years to recruit sufficient patients. We have demonstrated that a retrospective analysis using population PK analysis\textsuperscript{18} and physiologically-based PK modeling confirmed that the pediatric PK of pregabalin, a renally eliminated drug, could be confidently predicted using adult PK observations.\textsuperscript{31} Merging pediatric with adult data had minimal impact on adult PK and E-R parameter estimates. For future studies of drugs that are primarily eliminated via renal excretion, or for compounds with well-defined PK properties and high confidence in pediatric PK prediction, we suggest that pediatric PK may be collected using sparse sampling in long-term safety studies, rather than a dedicated pediatric phase I study, to increase the speed of pediatric drug development, allowing earlier access to novel treatments for pediatric patients.

**CONCLUSION**

We observed similar exposure and E-R relationships in adults and children (4–16 years) treated with pregabalin for FOS. This is consistent with data from clinical trials evaluating other AEDs after accounting for differences in baseline seizure rate and placebo effect. Our modeling and simulation approach used extrapolation to inform and support the dosage guidance provided in the pregabalin prescribing label for pediatric patients. Specifically, the prescribing label states for pediatric patients weighing \textgeq 30 kg, dosing should be initiated at 2.5 mg/kg/day (maximum 150 mg/day) divided as two or three doses (b.i.d. or t.i.d., respectively), based on individual response and tolerability. The dose may be increased weekly up to a maximum of 10 mg/kg/day (maximum 600 mg/day). For pediatric patients < 17 years and weighing < 30 kg, dosing should be initiated at 3.5 mg/kg/day (maximum 150 mg/day) b.i.d. or t.i.d. The dosage may be increased approximately weekly up to a maximum of 14 mg/kg/day (maximum 600 mg/day) based on individual response and tolerability.\textsuperscript{2} Our observations are further supported by evidence from adequate and well-controlled studies in adults with FOS and PK data from adult and pediatric patients. Our combined modeling approach may provide guidance for future extrapolation assessment from adult to pediatric patients.

**SUPPORTING INFORMATION**

Supplementary information accompanies this paper on the Clinical Pharmacology & Therapeutics website (www.cpt-journal.com).

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**CONFLICTS OF INTEREST**

P.L.S.C., S.F.M., L.M., and J.L. are full-time employees of Pfizer and all own Pfizer stock.

**AUTHOR CONTRIBUTIONS**

P.L.S.C., S.F.M., L.M., and J.L. wrote the manuscript. J.L. designed the research. J.L. performed the research. P.L.S.C., S.F.M., L.M., and J.L. analyzed the data.

**DATA AVAILABILITY STATEMENT**

Upon request, and participant to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices: (1) for indications that have been approved in the United States and/or European Union; or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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1. Fisher, R.S. et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia 58, 522–530 (2017).

2. Pfizer Inc. LYRICA® (pregabalin) [US prescribing information] <http://labeling.pfizer.com/ShowLabeling.aspx?id=561> (2019). Accessed November 22, 2019.

3. Pfizer Europe MA EEIG. LYRICA® (pregabalin) hard capsules. Summary of product characteristics <https://www.ema.europa.eu/en/documents/product-information/lyrica-epar-product-information_en.pdf> (2019). Accessed November 22, 2019.

4. Antinew, J. et al. Pregabalin as adjunctive treatment for focal onset seizures in pediatric patients: a randomized controlled trial. J. Child Neurol. 34, 248–255 (2019).

5. Arroyo, S. et al. Pregabalin add-on treatment: a randomized, double-blind, placebo-controlled, dose-response study in adults with partial seizures. Epilepsia 45, 20–27 (2004).

6. Beydoun, A. et al. Safety and efficacy of two pregabalin regimens for add-on treatment of partial epilepsy. Neurology 64, 475–480 (2005).

7. French, J.A., Kugler, A.R., Robbins, J.L., Knapp, L.E. & Garofalo, E.A. Dose-response trial of pregabalin adjunctive therapy in patients with partial seizures. Neurology 60, 1631–1637 (2003).

8. Shoji, S., Suzuki, M., Tomono, Y., Bockbrader, H.N. & Matsui, S. Population pharmacokinetics of pregabalin in healthy subjects and patients with post-herpetic neuralgia or diabetic peripheral neuropathy. Br. J. Clin. Pharmacol. 72, 63–76 (2011).

9. Bockbrader, H.N., Burger, P., Knapp, L. & Corrigan, B.W. Population pharmacokinetics of pregabalin in healthy subjects and patients with chronic pain or partial seizures. Epilepsia 52, 248–257 (2011).

10. Mann, D. et al. Safety, tolerability, and pharmacokinetics of pregabalin in children with refractory partial seizures: a phase 1, randomized controlled study. Epilepsia 55, 1934–1943 (2014).

11. US Food and Drug Administration (FDA). Pediatric study plans: content of and process for submitting initial pediatric study plans and amended initial pediatric study plans guidance for industry <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended> (2016). Accessed November 18, 2019.
12. US Food and Drug Administration (FDA). Drugs for treatment of partial onset seizures: full extrapolation of efficacy from adults to pediatric patients 2 years of age and older guidance for industry <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drugs-treatment-partial-onset-seizures-full-extrapolation-efficacy-adults-pediatric-patients-2-years> (2019). Accessed November 18, 2019.

13. Bockbrader, H.N., Alvey, C.W., Corrigan, B.W. & Radulovic, L.L. Bioequivalence assessment of a pregabalin capsule and oral solution in fasted healthy volunteers: a randomized, crossover study. *Int. J. Clin. Pharmacol. Ther.* 51, 244–248 (2013).

14. Bockbrader, H.N. et al. Clinical pharmacokinetics of pregabalin in healthy volunteers. *J. Clin. Pharmacol.* 50, 941–950 (2010).

15. Randinitis, E.J., Posvar, E.L., Alvey, C.W., Sedman, A.J., Cook, J.A. & Bockbrader, H.N. Pharmacokinetics of pregabalin in subjects with various degrees of renal function. *J. Clin. Pharmacol.* 43, 277–283 (2003).

16. Michels, W.M., Grootendorst, D.C., Verduijn, M., Elliott, E.G., Dekker, F.W. & Krediet, R.T. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. *Clin. J. Am. Soc. Nephrol.* 5, 1003–1009 (2010).

17. Bergrstrand, M., Hooker, A.C., Wallin, J.E. & Karlsson, M.O. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. *AAPS J.* 13, 143–151 (2011).

18. Chew, M.L., Bockbrader, H.N., Chapel, S., Pitman, V.W., Mann, D. & Liu, J. Population pharmacokinetic analysis of pregabalin in pediatric patients with partial onset seizures. *Clin. Pharmacol. Ther.* 95, S37–S38 (2014).

19. European Medicines Agency. Paediatric investigation plans <https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans>. Accessed May 25, 2020.

20. Mann, D. et al. 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* 61, 617–626 (2020).

21. Pediatric News. FDA conducts analysis to assess acceptability of extrapolation of antiepileptic drug (AED) effectiveness in adults to children four years of age and older with partial onset seizures (POS). *J. Pediatr. Pharmacol. Ther.* 21, 98 (2016).

22. Sheridan, P.H. & Jacobs, M.P. The development of antiepileptic drugs for children. Report from the NIH workshop, Bethesda, Maryland, February 17–18, 1994. *Epilepsia Res.* 23, 87–92 (1996).

23. Chiron, C., Dulac, O. & Pons, G. Antiepileptic drug development in children: considerations for a revisited strategy. *Drugs* 68, 17–25 (2008).

24. European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-epileptic-disorders-revision-2-en.pdf> (2010). Accessed May 25, 2020.

25. Pellock, J.M., Carman, W.J., Thyagarajan, V., Daniels, T., Morris, D.L. & D’Cruz, O. Efficacy of antiepileptic drugs in adults predicts efficacy in children: a systematic review. *Neurology* 79, 1482–1489 (2012).

26. Snoeck, E. & Stockis, A. Dose-response population analysis of levetiracetam add-on treatment in refractory epileptic patients with partial onset seizures. *Epilepsia Res.* 73, 284–291 (2007).

27. Ahn, J.E., Pian, E.L., Karlsson, M.O. & Miller, R. Modeling longitudinal daily seizure frequency data from pregabalin add-on treatment. *J. Clin. Pharmacol.* 52, 880–892 (2012).

28. Schoemaker, R., Wade, J.R. & Stockis, A. Brivaracetam population pharmacokinetics and exposure-response modeling in adult subjects with partial-onset seizures. *J. Clin. Pharmacol.* 56, 1591–1602 (2016).

29. Mehrotra, S. Quantitative analysis to support full extrapolation of efficacy in children for partial onset seizures in autism setting: FDA-peace initiative <https://www.pharmacy.umaryland.edu/media/SOP/wwwpharmacyumarylandedu/centers/cersievent/s/pedsextrapolation/mehrotra-presentation-notes.pdf> (2016). Accessed September 19, 2019.

30. Rheims, S., Perucca, E., Cucherat, M. & Ryvlin, P. Factors determining response to antiepileptic drugs in randomized controlled trials. A systematic review and meta-analysis. *Epilepsia* 52, 219–233 (2011).

31. Arzimanoglou, A., D’Cruz, O., Nordli, D., Shinnar, S. & Holmes, G.L., & Pediatric Epilepsy Academic Consortium for Extrapolation. A review of the new antiepileptic drugs for focal-onset seizures in pediatrics: role of extrapolation. *Paediatr. Drugs* 20, 249–264 (2018).

32. Sun, H., Temec, J.W., Chambers, W., Perkins, G., Bonnel, R. & Murphy, D. Extrapolation of efficacy in pediatric drug development and evidence-based medicine: progress and lessons learned. *Ther. Innov. Regul. Sci.* 2017, 1–7 (2017).

33. Pellock, J.M. 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* 58, 1686–1696 (2017).

34. Dunne, J. et al. Extrapolation of adult data and other data in pediatric drug development programs. *Pediatrics* 128, e1242–e1249 (2011).

35. Mehrotra, N. et al. Role of quantitative clinical pharmacology in pediatric approval and labeling. *Drug Metab. Dispos.* 44, 924–933 (2016).

36. Bi, Y. et al. Role of model-informed drug development in pediatric drug development, regulatory evaluation, and labeling. *J. Clin. Pharmacol.* 59 (suppl. 1), S104–S111 (2019).

37. Barrett, J.S. et al. Challenges and opportunities in the development of medical therapies for pediatric populations and the role of extrapolation. *Clin. Pharmacol. Ther.* 103, 419–433 (2018).

38. Zhang, Y. et al. Exposure-response assessment in pediatric drug development studies submitted to the US Food and Drug Administration. *Clin. Pharmacol. Ther.* 108, 90–98 (2020).

39. Balevic, S.J. & Cohen-Wolkowiez, M. Innovative study designs optimizing clinical pharmacology research in infants and children. *J. Clin. Pharmacol.* 58 (suppl. 10), S58–S72 (2018).

40. US Food and Drug Administration (FDA). General clinical pharmacology considerations for pediatric studies for drugs and biological products <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-pediatric-studies-drugs-and-biological-products> (2014). Accessed November 19, 2019.