Extrapolation of a Brivaracetam Exposure–Response Model from Adults to Children with Focal Seizures

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Abstract

Introduction Prediction of brivaracetam effects in children was obtained by scaling an existing adult pharmacokinetic/pharmacodynamic (PK/PD) model for brivaracetam to children, using an existing population PK model for brivaracetam in children. The scaling was supported by estimating the change from adults to children in the concentration–effect relationship parameters for levetiracetam, a compound interacting with the same target protein (synaptic vesicle protein SV2A).

Methods The existing adult PK/PD model for brivaracetam was applied to a combined adult–pediatric dataset of levetiracetam. This model was then used to predict the effective oral twice-daily dose of brivaracetam in children aged ≥4 to <16 years as adjunctive treatment for focal (partial onset) seizures. The existing model described daily seizure counts using a negative binomial distribution, taking previous-day seizure frequencies into account, and using a mixture model to separate ‘placebo-like’ and ‘responder’ subpopulations. The model was adapted to describe aggregated monthly seizure counts for adult patients in the levetiracetam studies: daily seizure counts were only available for children in the levetiracetam studies.

Results The levetiracetam PK/PD model successfully described both the adult and pediatric data using the same drug effect parameters, and using a model structure similar to the existing adult brivaracetam PK/PD model.

Conclusion Simulation with the adult brivaracetam PK/PD model in combination with an existing pediatric brivaracetam population PK model allowed characterization of the dose–response curve, suggesting maximum response at brivaracetam 4 mg/kg/day dosing (capped at 200 mg/day, the maximum adult dose) in children aged ≥4 years.

Key Points

Adult and children seizure-count data under levetiracetam add-on treatment of focal seizures were described using a population concentration–effect model.

Effects of brivaracetam in adults were scaled to children using an adult brivaracetam population concentration-effect model, a pediatric brivaracetam population pharmacokinetic model, and the estimated scaling from adults to children (≥4 years) for levetiracetam.

Maximum response is predicted with brivaracetam 4 mg/kg/day dosing (capped at 200 mg/day, the maximum adult dose) in children aged ≥4 years.

1 Introduction

The incidence of epilepsy varies greatly with age, with high rates occurring in childhood and falling to lower levels in early adult life [1]. Epilepsy affects approximately...
4–6 out of 1000 children below the age of 20 years, and the overall annual incidence rates of epilepsy range between 45 and 86 out of 100,000 children. Despite the availability of new antiepileptic drugs (AEDs), more than 25% of pediatric patients have inadequate seizure control on currently available AEDs, or experience significant adverse drug effects [2]. There remains a need for potent AEDs with a positive benefit–risk profile in the pediatric population.

Brivaracetam is a selective, high-affinity SV2A ligand that possesses a 15- to 30-fold higher affinity compared with levetiracetam [3–5]. Brivaracetam is approved as adjunctive therapy in the treatment of focal (partial-onset) seizures in patients 16 years of age and older with epilepsy [6–10]. A brivaracetam population pharmacokinetic/pharmacodynamic (PK/PD) model using daily seizure counts has been previously developed for adult patients [11]. Furthermore, a population PK model for brivaracetam has been previously developed for children with epilepsy [12], but pediatric studies have not yet been performed where the effect of brivaracetam on daily focal seizure counts has been assessed. By combining the brivaracetam adult PK/PD model with the brivaracetam pediatric PK model, predictions can be made of effects in the pediatric population, minimizing the need for dose-finding clinical trials in children. This can be done by either just assuming that concentration–effect parameters are the same for adults and children, or by finding support for this assumption.

Levetiracetam is an AED interacting with the same SV2A target protein as brivaracetam [3, 4]. The correspondence in concentration–effect parameters between adults and children was investigated by building combined levetiracetam adult and pediatric population PK and PK/PD models using the levetiracetam PK and PD data available in both adult and pediatric patients aged ≥4 years. The change in levetiracetam concentration–effect parameters was subsequently used to scale the brivaracetam effects from adults to children in the combined adult/pediatric population PK/PD model for brivaracetam. This enabled the prediction of seizure-count changes in children receiving brivaracetam, and facilitated dose selection of brivaracetam in pediatric patients aged ≥4 years.

2 Methods

2.1 Data

All clinical trials were conducted in accordance with the International Conference on Harmonization notes for Guidance on Good Clinical Practice and the Declaration of Helsinki. The study protocols were approved by the Institutional Review Boards at all study sites, and written informed consent was obtained from all patients, parents or legal guardians prior to enrollment.

The brivaracetam adult data originated from two placebo-controlled, phase III clinical studies with adjunctive brivaracetam in refractory adult patients with focal seizures [11]. Daily seizure count recordings were extracted from patient diaries. The brivaracetam pediatric data originated from an open-label, single-arm, multicenter, fixed three-step up titration study evaluating the PK, safety, and efficacy of brivaracetam in children with refractory epilepsy syndromes or epilepsy, aged ≥1 month to <16 years [13]. In the absence of a placebo group, the absence of baseline seizure count assessments, and a wide range of epilepsy syndromes, available seizure count data were not subjected to modeling.

The levetiracetam adult data originated from four double-blind, placebo-controlled, parallel-group, phase III clinical studies with adjunctive levetiracetam in refractory adult patients with focal epilepsy [14–17]. Seizure count recordings from patient diaries were aggregated over monthly between-visit periods. The levetiracetam pediatric data originated from a double-blind, placebo-controlled, multicenter study evaluating the efficacy and tolerability of levetiracetam as add-on treatment in refractory children (≥4 years to <16 years of age) with focal seizures [18]. Daily seizure count recordings were extracted from patient diaries. Details of the studies are provided in Table 1.

The levetiracetam PK data were obtained from a total of 101 pediatric and 799 adult patients receiving active treatment who contributed 415 and 3686 quantifiable levetiracetam concentrations, respectively. The pediatric levetiracetam PD data were obtained from a total of 211 patients receiving active or placebo treatment and who contributed 32,958 daily seizure-count records. The adult levetiracetam PD data were obtained from a total of 883 patients receiving active or placebo treatment and who contributed 6107 aggregated seizure-count records, corresponding to a total of 175,088 seizure-count assessment days. Patients with less than two focal seizures per 4 weeks prior to treatment administration were removed from the analysis. Descriptive statistics for demographic data are provided in Table 2.

2.2 Software

The analyses were performed using NONMEM version 7.2.0 [19] software supplemented with the PsN toolkit [20]. PK data were analyzed using first-order conditional estimation with the interaction option, while seizure-count data were analyzed using Laplacian estimation. Data were further processed using 64-bit R version 3.1.2 software [21]. Simulations were performed using R and NONMEM.

△ Adis
2.3 Development of Population Pharmacokinetic (PK) Model for Levetiracetam in Adults and Children

The population PK model for levetiracetam was a one-compartment model with first-order absorption and elimination. The influence of body weight on clearance (CL) and volume (V) of distribution was estimated using the following allometric equation:

$$\text{PAR}_j = \Theta_1 \cdot \left(\frac{\text{WT}_j}{70}\right)^{\Theta_2} \cdot e^{\eta_j},$$  \hspace{1cm} (1)

where $\Theta_1$ is the population value of the estimated PK parameter, and $\text{WT}_j$ is the individual body weight scaled to the population typical value of 70 kg. Interindividual variability (IIV) is described using $\eta_j$. The parameter $\Theta_2$ is the scaling parameter for the weight range, which can either be freely estimated or fixed to theoretical allometric values of $\frac{3}{4}$ and 1 for CL and V, respectively [22].

Exponential models were used to describe the IIV. Correlation between parameters was investigated by estimating a full or suitably reduced omega matrix. Both proportional and combined additive and proportional models were investigated to describe the residual variability.

Comparison between nested models was based on a likelihood ratio test using the difference in objective function value ($\Delta$OFV). Structural model updates were required to be associated with a $p$ value $<0.05$.

The effects of the hepatic enzyme-inducer AEDs carbamazepine, phenytoin, and phenobarbital or primidone, or one or more of these AEDs (IND), were also investigated as potential covariates on CL. 95% confidence intervals (CIs) were calculated for the fixed effects parameters using the standard error of the estimates.

The empirical Bayes estimates (EBEs) from the final levetiracetam pediatric PK model were used to generate daily levetiracetam concentration profiles using recorded

Table 1  Summary of studies

| Study   | Population trial type drug N active/placebo$^a$ | Treatment regimen and entry criteria |
|---------|--------------------------------------------|-----------------------------------|
| N051    | Adult phase III levetiracetam 234/0         | 12 weeks baseline assessment, followed by two 16-week crossover periods (4 weeks transition and 12 weeks evaluation) with two of three possible treatments of placebo, and 1000 or 2000 mg/day levetiracetam as bid administration, and a 4-week withdrawal period. Subjects were required to have at least four POS per 4 weeks prior to treatment administration |
| N052    | Adult phase III levetiracetam 80/40         | 4 weeks baseline assessment, 24 weeks of placebo, 2000 or 4000 mg/day levetiracetam as bid administration without up titration. Subjects were required to have at least four seizures of any type in the 24 weeks prior to treatment administration |
| N132    | Adult phase III levetiracetam 120/40        | 12 weeks baseline assessment, 4 weeks up titration, 14 weeks of placebo, and 1000 or 3000 mg/day levetiracetam as bid administration, 8 weeks down-titration or conversion to open long-term follow-up study. Subjects were required to have at least two POS per 4 weeks prior to treatment administration |
| N138    | Adult phase III levetiracetam 172/86        | 12 weeks baseline assessment, 4 weeks up titration, 12 weeks of placebo, or 3000 mg/day levetiracetam as bid administration, followed by a monotherapy study in responding subjects (monotherapy not analyzed). Subjects were required to have at least two complex POS per 4 weeks prior to treatment administration |
| N159    | Pediatric phase III levetiracetam 100/100   | 8 weeks baseline assessment, three 2-week fixed-dose titration intervals (20, 40, and 60 mg/kg/day levetiracetam, capped at 1000, 2000 and 3000 mg/day, respectively, as bid administration), followed by 8 weeks at the maximum tolerated dose, and a 6-week withdrawal period. Subjects were required to have at least four POS per 4 weeks prior to treatment administration |
| N01252  | Adult phase III brivaracetam 300/100        | 8 weeks baseline assessment, 12 weeks of 20, 50, or 100 mg/day brivaracetam as bid administration. Subjects were required to have at least two POS per month prior to treatment administration |
| N01253  | Adult phase III brivaracetam 300/100        | 8 weeks baseline assessment, 12 weeks of 5, 20, or 50 mg/day brivaracetam as bid administration. Subjects were required to have at least two POS per month prior to treatment administration |
| N01358  | Adult phase III brivaracetam 480/240        | 8 weeks baseline assessment, 12 weeks of 100 or 200 mg/day brivaracetam as bid administration. Subjects were required to have at least two POS per month prior to treatment administration |
| N01263  | Pediatric phase IIa brivaracetam 100/0      | 1-week baseline assessment, 3-week evaluation period with a weekly fixed three-step up titration of 0.8, 1.6, and 3.2 mg/kg/day as bid administration of oral solution for subjects $\geq$8 years of age, and 1.0, 2.0, and 4.0 mg/kg/day as bid administration of oral solution for subjects $<8$ years of age. Subjects were required to have at least one seizure (any type) during the 3 weeks prior to treatment administration |

POS partial-onset seizures, bid twice daily

$^a$ As planned per protocol
daily levetiracetam doses. Areas under the curve over 24 h were calculated using the simulated profiles and divided by 24 h, resulting in daily average concentration values ($C_{av}$) that were then used to drive the PK/PD model. This procedure allowed changes in daily dose to result in gradual changes of predicted concentrations without having to assume steady state. For the adult data, the EBEs for $CL$ were used to simulate $C_{av}$ values using the median dose during the assessment period.

### Table 2 Descriptive statistics for demographic data

|                      | Levetiracetam | Brivaracetam |
|----------------------|---------------|--------------|
|                      | Adults        | Children     | Adults        | Children     |
| **Categorical data [n (%)]** |               |              |               |              |
| Total number of subjects | 883           | 211          | 1912          | 96           |
| Sex                   |               |              |               |              |
| Female                | 407 (46.1)    | 102 (48.3)   | 945 (49.4)    | 49 (51.0)    |
| Male                  | 476 (53.9)    | 109 (51.7)   | 967 (50.6)    | 47 (49.0)    |
| **AED background**    |               |              |               |              |
| Carbamazepine         | 610 (69.1)    | 73 (34.6)    | 764 (40.0)    | 9 (9.4)      |
| Phenytoin             | 192 (21.7)    | 15 (7.1)     | 205 (10.7)    | 1 (1.0)      |
| Phenobarbital         | 122 (13.8)    | 11 (5.2)     | 139 (7.3)     | 16 (16.7)    |
| Inducer AEDs          | 770 (87.2)    | 92 (43.6)    | 1000 (52.3)   | 25 (26.0)    |
| **Continuous data [median (minimum/maximum)]** | |              |               |              |
| Weight, kg            | 73 (39/140)   | 34 (12/87)   | 71 (24/176)   | 19 (3.9/75)  |
| Age, years            | 37 (14/70)    | 10 (3/17)    | 37 (15/80)    | 5 (0.2/15)   |
| Baseline seizure frequency, day$^{-1}$ | 0.306 (0.073/24.3) | 0.750 (0.099/99.7) | 0.321 (0.029/32.8) | Not assessed |

$AED$ antiepileptic drug

### 2.4 Existing Population Pharmacokinetic/Pharmacodynamic (PK/PD) Model for Brivaracetam

A population PK/PD model using daily seizure counts has been previously developed [11]. In short, the brivaracetam PK/PD model was developed using a count model with a negative binomial distribution [23], to describe daily seizures where seizure rates were a function of both placebo and drug effects. The negative binomial distribution is an extension of the Poisson distribution that uses an overdispersion parameter to allow an increase in variability of seizure counts. Clustering of seizures was described using a Markovian component [24] by influencing the seizure rate on a particular day by seizures on the previous day [25]. Significant decreases in seizure frequency were observed under placebo treatment. Some of the patients receiving active treatment were best described by the placebo-response distribution, while the remaining patients displayed a decrease in seizure frequency following brivaracetam administration. This was implemented by assuming two populations: the ‘mixture-model responder population’ where a concentration-dependent decrease in seizure frequency was added onto the placebo distribution, and the ‘mixture-model placebo-like population’, with a response governed only by the placebo model parameter. Seizure rates were modeled on the log scale, and the model for the two populations was described using Eqs. 2 and 3:

$$\lambda_{ijP1} = e^{\log(S_{0ij})+Q_2 \left( \log(\text{Placebo})+\eta_3 \right) + \frac{\log(E_{\text{max}})}{\ln(\text{EC}_{50})} + \frac{\lambda_4 \cdot C_{av}}{C_{av}}$$  \hspace{1cm} (2)

$$\lambda_{ijP2} = e^{\log(S_{0ij})+Q_2 \left( \log(\text{Placebo})+\eta_3 \right) + \lambda_4 \cdot C_{av}}$$ \hspace{1cm} (3)

where $\lambda$ is the modeled seizure rate, $Q_2 = 0$ for baseline and 1 for post-baseline, and $C_{av}$ is the average daily concentration. Basal seizure rates ($S_{0ij}$) are seizure rates in the absence of placebo and drug effects, while placebo and $E_{\text{max}}$ describe the individual specific change due to the placebo effect and the maximum brivaracetam effect, and are estimated with IIV ($\eta_3$ and $\eta_4$). Finally, $\text{EC}_{50}$ is the typical population $C_{av}$ associated with reaching 50% of the maximum effect. NONMEM estimated the probability of a patient ending up in one of the two populations.

### 2.5 Adaptation of the Existing Brivaracetam PK/PD Model to Levetiracetam Study Data

The structure of the PK/PD model for levetiracetam in adults and children aimed to match the existing PK/PD model structure for brivaracetam in adults [11] as closely as possible. The daily seizure-count model was modified to describe total seizure counts over specified periods for the...
adult levetiracetam PD data; expected values for total counts per period were given by \( \lambda \) times number of days counted. For the daily counts in children, the number of days counted was 1 for every record.

The following equation was used to describe the basal seizure rate:

\[
\log(S_{0ij}) = \log(S_0) + \eta_{1i} + PED \cdot \left( \frac{\log(S_{\text{max}}) + \eta_{2i}) \cdot \text{DPD}V_{ij}}{ES_{50} + \text{DPD}V_{ij}} \right).
\]

The pediatric population marker (PED) was 0 for adults and 1 for children. The basal seizure rate for adult patients was given by the population value \( S_0 \) with added IIV \( (\eta_{1i}) \), and, for children, this was combined with an \( E_{\text{max}} \) function depending on the observed number of seizures on the preceding day \( (\text{DPD}V_{ij}) \), the maximum increase in seizure rate \( (S_{\text{max}}) \) with IIV \( (\eta_{2i}) \), and the number of preceding-day seizures associated with 50% of the maximum increase \( (ES_{50}) \). Basal seizure rates were transformed using a Box–Cox transformation [26] to correct for marked skewness.

Parameter values for levetiracetam in Eqs. 2, 3, and 4 for adult patients, and multiplication factors from adults to children, were estimated for \( S_0 \), placebo, \( E_{\text{max}} \cdot EC_{50} \), and the mixing fraction. These multiplication factors (if significant) were used to scale the existing adult brivaracetam PK/PD model to predict concentration-dependent seizure reduction for children receiving brivaracetam.

### 2.6 Levetiracetam PK/PD Model Qualification: Predictive Checks

A visual predictive check (VPC) [27] was performed to evaluate the predictive performance of the levetiracetam adult and pediatric population PK/PD model. The VPC examines the model’s ability to simulate back the data that has been used for the model development. Seizure counts were simulated 500 times using the levetiracetam dose and covariate data from the patients who were included in the analysis at the same sampling times. Mean seizure frequencies were calculated for every patient during baseline and during treatment, and normalized to 28-day seizure frequencies. The \( \log(x + 1) \) values of the mean 28-day seizure frequencies (to allow log transformation of seizure frequencies of zero) of the baseline and treatment values were taken, and the differences between log-baseline and log-treatment values were calculated to quantify change from baseline. These log differences were then back-transformed, yielding percentage change estimates from baseline.

Posterior predictive checks were performed by calculating the median percentage change from baseline for the raw data and the simulated studies by randomized treatment dose; the raw data median percentage change from baseline values were compared with the simulated distributions arising from the 500 simulated studies. Additionally, the proportion of 50% responders for each randomized treatment dose was calculated, defined as the proportion of patients with a decrease from baseline seizure frequency of at least 50%.

The 50% responders (both simulated and observed) should not be confused with the mixture-model responder population: the 50% responders are the patients who demonstrate an actual seizure frequency reduction of at least 50%, possibly due to both placebo effect and drug effect, while the mixture-model responder population identifies the patients who show a decrease in seizure frequency that can be attributed to levetiracetam \( C_{av} \). At low doses, patients can still be assigned to the mixture-model responder population even though maximum effect has not been reached, and, conversely, patients can be considered 50% responders during placebo treatment if they have a sufficient decrease in seizure frequency from baseline.

### 2.7 Brivaracetam Pediatric PK/PD Simulations

The previously derived pediatric brivaracetam population PK model [12] used lean body weight (LBW) to allometrically scale CL and V. The National Health and Nutrition Examination Survey (NHANES) Dual X-ray Absorptiometry (DXA) database [28] was used to provide LBW values for children 4–16 years of age to drive the simulations; corresponding age and WT values were used to categorize the simulated responses. Primidone, carbamazepine, and valproate coadministration, identified as significant covariates in the pediatric brivaracetam population PK model, was sampled from the brivaracetam pediatric dataset, where the combination, within a patient, of primidone, carbamazepine, and valproate coadministration was kept intact. Brivaracetam concentrations for milligrams/kilogram body weight doses of 1, 2, 3, 4, 5, and 6 mg/kg/day, with a maximum dose of 200 mg/day, were simulated. The simulated brivaracetam concentrations were then used to simulate individual daily seizure-count profiles using the scaled adult-to-pediatric brivaracetam PK/PD population model. The simulations were used to generate a sequence of 8 weeks at baseline, followed by 12 weeks of brivaracetam treatment at the simulated \( C_{av} \) value. Change from baseline was calculated as described above, and summarized using the median and the interquartile range.
Levetiracetam Population PK Model for Adults and Pediatric Patients 4 Years

Levetiracetam PK data were adequately described using a one-compartment model with first-order absorption and allometric scaling of CL and V using body weight and a full omega matrix to describe IIV. A combined proportional and additive residual error model provided no improvement over a proportional residual error model. Implementing allometric scaling of levetiracetam CL and V with fixed theoretical allometric exponents resulted in a 196.00 point OFV drop \((p < 0.0001)\). Freely estimating the allometric exponents resulted in an additional OFV drop of 78.88 points \((p < 0.0001)\).

Coadministration of carbamazepine, primidone, and phenytoin was associated with an OFV drop of 86.40 points \((p < 0.0001)\), which translates into changes in \(C_{av}\) (95% CI) of \(-16.0\% \(-13.0\% \text{ to } \text{ -18.8\%}\) for carbamazepine, \(-5.9\% \(-1.1\% \text{ to } \text{ -10.4\%}\) for phenytoin, and \(-10.4\% \(-6.5\% \text{ to } \text{ -14.2\%}\) for primidone. Switching to an aggregated covariate for administration of hepatic enzyme-inducing AEDs resulted in a further OFV drop of 25.56 points \((p < 0.0001)\), associated with a \(-22.0\% \text{ (17.9}\% \text{ to } \text{ -5.8\%}\) change in \(C_{av}\). This estimated change was larger

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than for the individual AEDs, likely because patients can have more than one inducer AED concurrently co-administered. The final levetiracetam population PK model parameter estimates are provided in Table 3.

Goodness of fit plots (electronic supplementary Figs. S1, S2, and S3) indicated that the levetiracetam population PK model provided an excellent description of the data, with absence of systematic deviations related to either age or WT. These results classified the final levetiracetam population PK model as suitable for obtaining exposure predictions to be used for subsequent PK/PD modeling. Daily predicted $C_{av}$ values for children are provided in electronic supplementary Fig. S4, demonstrating the IIV in exposure, and illustrating that recorded compliance is taken into account.

### 3.2 Levetiracetam Population PK/PD Model for Adults and Pediatric Patients ≥4 Years

The initial levetiracetam PK/PD model with a Poisson distribution improved markedly by switching to a negative binomial distribution, resulting in an OFV drop of 23,867 points. Markovian (previous day) features and overdispersion can only be detected in daily seizure-count data, and not in the aggregated levetiracetam data for the adults. Inclusion of a Markovian effect for children to describe the dependency on the number of preceding-day seizures resulted in an OFV drop of 2404 points. Implementing IIV on overdispersion for the pediatric daily seizure-count data resulted in an OFV drop of 6760 points ($p < 0.0001$).

Adding a mixture model for the drug effect resulted in an OFV drop of 169.6 points ($p < 0.0001$).

The investigation of potential differences in response to levetiracetam between adults and children was performed by extending the levetiracetam PK/PD model with single factors to describe the possible percentage change in children for the different model parameters. Basal seizure rate was highly significantly different between pediatric and adult patients, associated with an OFV drop of 38.75 points ($p < 0.0001$).

Continuing from the levetiracetam PK/PD model with a different basal seizure rate for adults and children, and adding single pediatric factors, no significant effects were found for
the mixture fraction, placebo, \( E_{\text{max}} \), or \( EC_{50} \) parameters
\( \Delta OFV = -0.02, \ p = 0.8960; \ \Delta OFV = -2.41, \ p = 0.1208; \ \Delta OFV = -0.27, \ p = 0.6029; \ \Delta OFV = -0.41, \ p = 0.5239, \) respectively). Compared with the adult values, the pediatric mixture fraction was estimated to be associated with a change of 2.6% (95% CI –36 to 41%), the placebo effect with a -6.4% (-17 to 5.0%) change, the \( E_{\text{max}} \) with a 36% (-70 to 510%) change, and the \( EC_{50} \) with a 26% (-48 to 200%) change. As none of these effects were statistically significant, the final model did not contain separate estimates for pediatric drug effects. NONMEM parameters for the final levetiracetam adult and pediatric PK/PD model are provided in Table 4 and the model syntax is provided in the electronic supplementary material.

Model evaluation for count models cannot be performed using the standard goodness-of-fit plots. Instead, simulation approaches are the only option to assess whether the model can describe and reproduce the original data [23]. Simulating sequences of count data with Markovian properties is possible using NONMEM, and an example syntax is provided in the electronic supplementary material. Electronic supplementary Fig. S5 provides an illustration of five observed and simulated example levetiracetam daily seizure frequency profiles using the parameters from the final model. The timing of seizures in the simulations is generated by a random process, therefore simulated profiles are not identical to observed profiles, but the general aspects of the profiles (clusters of seizures or their absence, intensity of seizures; note the large difference in y-axis scaling between patients) are well-captured by the simulations.

The results of a VPC for the final levetiracetam adult and pediatric PK/PD model, where 500 studies were simulated using the same covariates, dosing records, and sample times as the original dataset, are shown in Figs. 1, 2. These VPCs show the observed and simulated derived parameters of median percentage change from baseline, and proportion of \( \geq 50\% \) responders. For all applied levetiracetam doses, for both adults and children, the observed outcome falls well within 95% of the distribution of simulated outcomes, with only the placebo response in adult patients being slightly underpredicted. These VPCs demonstrate that the final levetiracetam adult and pediatric
PK/PD model is capable of simulating the various study outcome measures. The VPCs demonstrate that the same levetiracetam PK/PD parameters may be used for adults and children, in line with the absence of significant differences in model parameters between adults and children.

3.3 Simulations of Brivaracetam PD Effects in Pediatric Patients ≥4 Years

Modeling of levetiracetam PK/PD effects across adults and children aged ≥4 years with epilepsy has shown that both populations can be described using the same set of PK/PD drug–effect parameters. This finding lends credence to the application of the adult brivaracetam population PK/PD model to data from children.

The left panels of Fig. 3 provide the simulation results for the full population, while the right panels have the results split by mixture-model responder population. Individual changes from baseline were calculated on simulated individual daily seizure-count pediatric time profiles, and summarized using the median and interquartile range of the change from baseline across patients. The top and bottom panels show the simulated percentage change in seizure frequency from baseline as a function of $C_{av}$ or of dose in mg/kg/day, respectively. The simulations show that maximum response is predicted to occur at approximately 4 mg/kg/day dosing of brivaracetam (capped at 200 mg/day, the maximum adult dose) in children aged ≥4 and <16 years.

A fixed mg/kg/day dosing schedule may lead to lower brivaracetam concentrations for younger and smaller children, and the consequences for the simulated effects for patients in the ‘mixture-model responder population’ are shown in Fig. 4. Lower doses (1 and 2 mg/kg/day) demonstrate smaller effects for younger children, but these effects saturate for doses up to 4 mg/kg/day.

4 Discussion

The overarching goal of the work presented in this report was to predict the optimal dosage regimen for brivaracetam in children with focal seizures, thus minimizing the need for dose-finding clinical trials in this population. This is not a new concept and was addressed in the literature over 20 years ago [29]. The framework put in place to address the overarching goal was contingent on two separate, important assumptions. The first assumption was that the
disease type, focal epilepsy, is similar in adults and children, which permits that results obtained in adults can be used to predict results in children. The second assumption was that the combined adult and pediatric PK/PD relationship for one compound can be used as a basis to inform the prediction of pediatric PD results for a second compound that interacts on the same target protein.

Regarding the first assumption, there is considerable evidence to support that focal epilepsy in adults is the same as in children, for children aged 2 years and older [30, 31]. These findings are in line with the review by Pellock et al. [32], which supports the extrapolation of efficacy results in adults to predict a similar adjunctive treatment response in 2- to 18-year-old children with focal seizures for a range of AEDs. Similarly, a US FDA collaborative effort has resulted in a conclusion that extrapolation of the efficacy results from adults to children 4 years of age and older with focal seizures is acceptable, and that independent clinical efficacy trials in these children will not be needed [33]. This view is further supported by the Pediatric Epilepsy Academic Consortium for Extrapolation (PEACE) [34].

Regarding the second assumption, this approach has been used previously under the more general term ‘model-based meta-analysis’ [35], where the results from one or more compounds of the same class have been used to predict the outcome of another compound with the same mechanism of action [36, 37]. In the field of pediatric drug development, this is important as it is a means of reducing the burden of unnecessary clinical trials. In the present analysis, a new combined adult and pediatric PK/PD model was built for levetiracetam, to support using an existing adult brivaracetam PK/PD model to predict brivaracetam outcomes in children with focal seizures. Reusing the same structural model from the existing adult brivaracetam population PK/PD model [11] and applying it to a combined adult-pediatric levetiracetam PK/PD dataset, found that the outcome provided no indication of different drug-related PK/PD parameters between adults and children with focal epilepsy.

Simulation allowed characterization of the brivaracetam dose–response curve, suggesting that the maximum response would be obtained for responsive patients when brivaracetam 4 mg/kg/day, capped at 200 mg/day (the
maximum adult dose), is administered as adjunctive treatment. Doses of 1 mg/kg/day are already considered to be effective. In view of the high variability in seizure frequency outcomes, it may be optimal to progress patients to the sufficiently high brivaracetam dose of 2–3 mg/kg/day to allow detection of patients who will respond to treatment, and, subsequently, the dose may be increased up to 4 mg/kg/day, especially for smaller children. For patients experiencing dose-limiting side effects, the dose may be reduced accordingly.

5 Conclusions

Development of a combined adult pediatric levetiracetam population PK/PD model found no difference between adults and pediatric patients aged ≥4 years for the drug-related levetiracetam PD model parameters. The lack of difference in levetiracetam PD parameters between adults and children endorses the use of the existing adult brivaracetam PK/PD model to predict brivaracetam efficacious doses in children with focal epilepsy. Maximum response is expected to occur at brivaracetam doses of approximately 4 mg/kg/day (capped at 200 mg/day, the maximum adult dose) in children aged ≥4 and <16 years.

6 Online Source

The NONMEM code for the final model, its output, NONMEM code to simulate new data, and a simulated data file to allow running the model, is provided online at the DDMoRe model repository (http://repository.ddmore.eu/model/DDMODEL00000239).

Compliance with Ethical Standards

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Conflict of Interest At the time this manuscript was submitted for publication, Armel Stockis was a full-time employee of UCB Pharma, and Rik Schoemaker and Janet R. Wade were paid consultants for UCB Pharma.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants (adult studies) or their parents or legal guardians (pediatric studies) included in the study.

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References

1. Brodie MJ, Barry SJE, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. Neurology. 2012;78:1548–54.
2. Hadjiloizou SM, Bourgeois BF. Antiepileptic drug treatment in children. Expert Rev Neurother. 2007;7:179–93.
3. Lynch BA, Lambeng N, Nocka K, Kensel-Hammels P, Bajjalieh SM, Matagne A, et al. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. Proc Nat Acad Sci USA. 2004;101:9861–6.
4. Gillard M, Fuks B, Leclercq K, Matagne A. Binding characteristics of brivaracetam, a selective, high affinity SV2A ligand in rat, mouse and human brain: relationship to anti-convulsant properties. Eur J PharmacoL 2011;664:36–44.
5. Wood M, Urbain D, Gillard M. Evidence for a differential interaction of brivaracetam and levetiracetam with the SV2A protein [abstract no. p0879]. Epilepsia. 2015;56(Suppl 1):215.
6. French JA, Costantini C, Brodsky A, von Rosenstiel P. Adjunctive brivaracetam for refractory partial-onset seizures. A randomized, controlled trial. Neurology. 2010;75:519–25.
7. van Paaschen W, Hirsch E, Johnson M, Falter U, von Rosenstiel P. Efficacy and tolerability of adjunctive brivaracetam in adults with uncontrolled partial-onset seizures: a phase IIb, randomized, controlled trial. Epilepsia. 2013;54:89–97.
8. Biton V, Berkovic SF, Abou-Khalil B, et al. Brivaracetam as adjunctive treatment for uncontrolled partial epilepsy in adults: a phase III randomized, double-blind, placebo-controlled trial. Epilepsia. 2014;55:57–66.
9. Ryvlin P, Werhahn KJ, Blasszczyk B, Johnson ME, Lu S. Adjunctive brivaracetam in adults with uncontrolled focal epilepsy: results from a double-blind, randomized, placebo-controlled trial. Epilepsia. 2014;55:47–56.
10. Klein P, Schiemann J, Sperling MR, et al. A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of adjunctive brivaracetam in adult patients with uncontrolled partial-onset seizures. Epilepsia. 2015;56:1890–8.
11. 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(12):1591–602.
12. Schoemaker R, Wade JR, Stockis A. Brivaracetam population pharmacokinetics in children with epilepsy aged 1 month to 16 years. Eur J Clin Pharmacol. 2017;73:727–33.
13. Liu E, Hepner A, Dilley D, Stockis A, Daniels A. Safety and tolerability of adjunctive brivaracetam administered as oral solution in pediatric patients aged ≥1 month to 16 years with epilepsy. Epilepsy Curr. 2014;14(4Suppl S1):390–1.
14. Shorvon SD, Löwenthal A, Janz D, Bielen E, Loiseau P, the European Levetiracetam Study Group. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. Epilepsia. 2000;41:1179–86.
15. Betts T, Waegemans T, Crawford P. A multicentre, double-blind, randomized, parallel group study to evaluate the tolerability and efficacy of two oral doses of levetiracetam, 2000 mg daily and
4000 mg daily, without titration in patients with refractory epilepsy. Seizure. 2000;9:80–7.

16. Cereghino JJ, Biton V, Abou-Khalil B, Dreifuss F, Gauer LJ, Leppik I, the US Levetiracetam Study Group. Levetiracetam for partial seizures. Results of a double-blind, randomized clinical trial. Neurology. 2000;55:236–42.

17. Ben-Menachem E, Falter U, the European Levetiracetam Study Group. Efficacy and tolerability of levetiracetam 3000 mg/d in patients with refractory partial seizures: a multicenter, double-blind, responder-selected study evaluating monotherapy. Epilepsia. 2000;41:1276–83.

18. Glauser TA, Ayala R, Elterman RD, Mitchell WG, Van Orman CD, Gauer LJ, on behalf of the N159 Study Group, et al. Double-blind placebo-controlled trial of adjunctive levetiracetam in pediatric partial seizures. Neurology. 2006;66:1654–60.

19. Beal SL, Sheiner LB, Boeckmann AJ, Bauer RJ. NONMEM users guides 1989–2009. Ellicott City: Icon Development Solutions; 2009.

20. Lindbom L, Pihlgren P, Jonsson EN. PsN-Toolkit: a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Programs Biomed. 2005;79:241–57.

21. R Development Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. 2011. http://www.R-project.org. Accessed 20 Nov 2014.

22. Anderson BJ, Holford NHG. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol. 2008;48:303–32.

23. Plan EL. Modeling and simulation of count data. CPT Pharmacoecon Syst Pharmacol. 2014;3:1–12.

24. Trocóniz IF, Plan EL, Miller R, Karlsson MO. Modelling overdispersion and Markovian features in count data. J Pharmacokinet Pharmacodyn. 2009;36:461–77.

25. Ahn JE, Plan EL, Karlsson MO, Miller R. Modeling longitudinal daily seizure frequency data from pregabalin add-on treatment. J Clin Pharmacol. 2012;52:880–92.

26. Petersson KJ, Hanze E, Savic RM, Karlsson MO. Semiparametric distributions with estimated shape parameters. Pharm Res. 2009;26(9):2174–85.

27. Karlsson MO, Holford N. A tutorial on visual predictive checks. 2008 [abstract no: 1434]. http://www.page-meeting.org/?abstract=1434. Accessed 1 Sept 2017.

28. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey. The 1999–2004 dual energy x-ray absorptiometry (DXA) multiple imputation data files and technical documentation. 2008. https://wwwn.cdc.gov/nchs/data/nhanes/dxa/dxa_techdoc.pdf. Accessed 1 Sept 2017.

29. Sheridan PH, Jacobs MP. The development of antiepileptic drugs for children report from the NIH workshop, Bethesda, Maryland, February 17–18, 1994. Epilepsy Res. 1996;23:87–92.

30. Chiron C, Dulac O, Pons G. Antiepileptic drug development in children: considerations for a revisited strategy. Drugs. 2008;68(1):17–25.

31. Chiron C, Pons G. POS (partial onset seizures). Extrapolation from adults to children. Clinical setting. EMA 2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/05/WC500207579.pdf. Accessed 7 Dec 2016.

32. Pellock JM, Carman WJ, Thyagarajan V, Daniels T, Morris DL, D’Cruz O. Efficacy of antiepileptic drugs in adults predicts efficacy in children. Neurology. 2012;79:1482–9.

33. News Pediatric. 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. 2016;21:98.

34. Pellock JM, Arzimanoglou A, D’Cruz O, Holmes GL, Nordli D, Shinnar S. Extrapolating evidence of antiepileptic drug efficacy in adults to children ≥2 years of age with focal seizures: the case for disease similarity. Epilepsia. 2017. doi:10.1111/epi.13859 (Epub 29 Jul 2017).

35. Mould DR. Model-based meta-analysis: an important tool for making quantitative decisions during drug development. Clin Pharmacol Ther. 2012;92:283–6.

36. Mandema JW, Salinger DH, Baumgartner SW, Gibbs MA. A dose-response meta-analysis for quantifying relative efficacy of biologics in rheumatoid arthritis. Clin Pharmacol Ther. 2011;90:828–35.

37. Demin I, Hamrén B, Luttringer O, Pillai G, Jung T. Longitudinal model-based meta-analysis in rheumatoid arthritis: an application toward model-based drug development. Clin Pharmacol Ther. 2012;92:352–9.