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# Pharmacometrics of clobazam in pediatrics: Prediction of effective clobazam doses for Dravet syndrome

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ABSTRACT

*Objective:* : To describe the use of a population pharmacokinetic (PopPK) model incorporating weight and ontogeny to identify effective clobazam (CLB) dosing for use in a clinical trial in pediatric patients with Dravet syndrome.

*Methods:* : Pharmacokinetic data were combined from 3 CLB trials (OV-1012, OV-1017, and study 301) and a simulated study (study 401) for a total of 1306 CLB and 1305 *N*-desmethyl clobazam (*N*-CLB) samples from 193 Lennox-Gastaut syndrome patients and healthy subjects aged 6 months to 45 years. A structured approach based on US Food and Drug Administration guidance and pharmacometric knowledge discovery was developed using a nonlinear mixed-effects approach. Graphing and fitting using logistical weight regression were used to identify covariates for inclusion in the final model, which was evaluated using goodness-of-fit criteria and validated using prediction-corrected visual predictive check (pcVPC). Using the final PopPK model, a simulation study determined CLB and *N*-CLB distributions after 4 weeks of 1.5 and 2.0 mg/kg CLB.

*Results:* : The parameters of the final PopPK model were similar to previous reports. Fixed-effect parameters were precisely estimated, with no significant increase in NONMEM objective function value. Intersubject variability estimates were similar to previous reports, with < 35% shrinkage associated with parameter variability, except for intercompartmental clearance and apparent volumes of distribution of peripheral compartments. Goodness-of-fit plots and pcVPC show that the model adequately described CLB and *N*-CLB data. The CLB/*N*-CLB ratio in virtual study subjects aged < 3 years was 0.23 for 1.5 and 2.0 mg/kg and was 0.14 for subjects aged ≥3 years, which is 2 to 3 times those reported in a previous stiripentol/CLB/valproate study in which seizure improvement was reported.

*Significance:* : The PopPK model dosing parameters of 1.5 and 2.0 mg/kg are likely to result in efficacious concentrations of CLB and *N*-CLB in pediatric patients as young as 16 months. Dosages exceeding 1.5 mg/kg should be monitored for tolerability, particularly in patients aged < 2 years, as there may be a higher incidence of sedation.

## 1. Introduction

The management of difficult-to-treat childhood epilepsies such as Dravet syndrome (DS) is further complicated by the lack of controlled clinical studies evaluating potential therapies, particularly in very young patients < 2 years of age (Wallace et al., 2016; Wirrell, 2016). In the absence of evidence-based data, treatment decisions are mostly based on expert opinion and retrospective, open-label studies (Wallace et al., 2016; Wirrell, 2016). One randomized, placebo-controlled, double-blind study provided evidence of the efficacy of stiripentol in combination with clobazam and valproate in pediatric patients with DS (Chiron et al., 2000). However, the relative contributions of stiripentol

*Abbreviations:* CL/F, apparent clearance; $CL_M$, apparent clearance of metabolite; $C_{min}$, minimum observed concentration; CYP, cytochrome P450; DS, Dravet syndrome; FDA, US Food and Drug Administration; FM, fraction of administered dose converted to metabolite; FOCE, first-order conditional estimation; KA, first-order absorption rate constant; LGS, Lennox-Gastaut syndrome; *N*-CLB, *N*-desmethylclobazam; pcVPC, prediction-corrected visual predictive check; PK, pharmacokinetics; PM, the scalar quantity estimated for the derivation of FM fraction of drug metabolized; PopPK, population pharmacokinetic; Q/F, intercompartmental clearance; RSE, relative standard error; V2/F, apparent volumes of distribution of central compartments; V3/F, apparent volumes of distribution of peripheral compartments

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and clobazam to the observed improved seizure control were unclear, given that stiripentol substantially increased clobazam concentrations via inhibition of cytochrome P450 (CYP) isozyme CYP3A4 and CYP2C19, which are responsible for the metabolism of clobazam and *N*-desmethylclobazam (*N*-CLB), its active metabolite (Giraud et al., 2004; Volz et al., 1979). The focus of our study was to investigate the doses and dose regimens of clobazam that would yield exposures similar to those observed in the above-mentioned study by Chiron et al (2000), which included patients ≥3 years of age (mean age of 9 years) (Chiron et al., 2000).

Clobazam, a 1,5 benzodiazepine, is approved in patients aged ≥2 years for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS). Previous studies in patients with LGS used weight-based dosing for pediatric patients ≥2 years of age (Conry et al., 2009; Ng et al., 2011); however, when dosing in younger pediatric patients with DS, the potential effects of CYP isozyme ontogeny should also be taken into consideration. CYP expression is immature at birth and continues to mature during the first years of childhood, which can lead to reduced drug clearance in infants and children aged < 2 years (de Wildt et al., 1999; Lu and Rosenbaum, 2014; Sadler et al., 2016).

This study describes the use of a population pharmacokinetic (PopPK) model incorporating both weight and CYP isozyme ontogeny to identify an effective clobazam dosing regimen for use in a clinical trial in pediatric patients with DS similar to the study by Chiron et al (2000), which stratified patients by ≥3 years of age (Chiron et al., 2000).

## 2. Methods

### 2.1. Subjects and data source

Detailed information on the subjects and PK sampling schemes of data used in the PopPK modeling is shown in Table 1. Pharmacokinetic (PK) data were combined from the following 3 clobazam clinical studies: OV-1012 (Ng et al., 2011), OV-1017 (Walzer et al., 2010), and study 301[unpublished]), as well as a simulated study (study 401), for a total of 1306 clobazam and 1305 *N*-CLB samples from 193 patients with LGS and healthy subjects aged 6 months to 45 years, with an average of 6.77 clobazam and 6.76 *N*-CLB observations per patient. Although OV-1017 was conducted in a healthy adult rather than a pediatric population, the adult patients were intensively sampled for PK data; in contrast, the pediatric population in OV-1012 were only sparsely sampled. Inclusion of study OV-1017 was necessary for the identification of the appropriate structural models for use in characterizing clobazam and *N*-CLB PK, thereby avoiding model misspecification. Because CYP3A4 activity reaches adult levels by approximately 1 year of age (Salem et al., 2014), the addition of Study OV-1017 data to the analysis dataset improved the efficiency of parameter estimation and enabled adequate characterization of the PK of clobazam and *N*-CLB in pediatric as well as the adult patients in the dataset. As noted previously, because CYP3A4 activity reaches adult levels by approximately 1 year of age, the pediatric patients in the analysis dataset used in this investigation were ≥2 years of age (Salem et al., 2014).

Briefly, the 10th percentile of parameters obtained with the base model was used in generating clobazam and *N*-CLB exposures for children with ages ranging from approximately 0.5 to 2.0 years and weights ranging from 6 to 12 kg. The 10th percentile was used for the parameter values because the PopPK parameters of the younger children in the original dataset fell within this percentile. The mean age and weight were 1.3 years and 10.54 kg, respectively. A sparse sampling scheme (a hybrid between that used in studies OV-1012 and 301) was used, but the duration of sampling was similar to that used in study 301. Data synthesis was performed and a random sample of 13 subjects was selected to constitute study 401. The 13 subjects were similar to the subjects in study 301 in terms of weight and age distribution. The only difference was that the 13 subjects in study 401 provided an average of 3.2 samples per subject for clobazam and 3.2 samples per subject for *N*-CLB, while those in study 301 provided 1.7 samples per subject for clobazam and 1.9 samples per subject for *N*-CLB. The data were combined with data from studies 301, OV-102, and OV-1017 for the development of the PopPK model, incorporating ontogeny. Thus, the synthesized data complemented the data in the lower age range.

### 2.2. Clobazam PopPK model development

A structured approach based on US Food and Drug Administration (FDA) guidance (US Department of Health and Human Services, 1999) and pharmacometric knowledge discovery (Ette et al., 2005; Tolbert et al., 2016) was used to develop a PopPK model to predict distributions of clobazam and *N*-CLB in pediatric patients after daily adjunctive doses of clobazam 1.2 and 2.0 mg/kg, as a function of weight, age, and ontogeny. A flow chart of the development, evaluation, validation (predictive performance), and application of the PopPK model is shown in Fig. 1.

#### 2.2.1. Structural model

The structural (base) model was developed using a nonlinear mixed-effects approach implemented in NONMEM 7.3 (Globomax, Ellicott City, MD), assuming a 2-compartment linear PK model with first-order absorption for clobazam and a 1-compartment model for *N*-CLB based on previous work (Tolbert et al., 2016). The model was parameterized in terms of apparent clearance (CL/F), intercompartmental clearance (Q/F), apparent volumes of distribution of central (V2/F) and peripheral (V3/F) compartments, and first-order absorption rate constants (KA). The metabolite model was parameterized in terms of its formation and metabolite clearance rate. Metabolite formation was parameterized to constrain the fraction of metabolite formed

**Table 1**
Summary of Data Used in PopPK Modeling.

| Study number/type | Subjects | n | Subject age | PK sampling scheme[a] | Samples/subject, mean | |
|---|---|---|---|---|---|---|
| | | | | | CLB | *N*-CLB |
| OV-1012/Phase 3 efficacy | LGS patients | 153[b] (142 children/adolescents[c]) | 2–29 y | 1.08, 2.25, 4.75, 11.92, 15.92 | 4.84 | 4.84 |
| OV-1017/Phase 1 bioequivalence | Healthy subjects | 18 | 19–45 y | 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, 96, 120, 168, 217 | 28 | 28 |
| 301/Observational | LGS patients | 9 | 6 m–2 y | 24 | 1.7 | 1.9 |
| 401/Simulated data | NA | 13 | 6 m–2 y | 4, 6, 24 | 3.2 | 3.2 |

CLB, clobazam; LGS, Lennox-Gastaut syndrome; m, months; NA, not applicable; *N*-CLB, *N*-desmethylclobazam; PK, pharmacokinetics; PopPK, population pharmacokinetics; y, years.
[a]Hours after dosing.
[b]Patients with PK sampling data.
[c] Of the 153 patients, 142 were children/adolescents 2–18 years old; 7 were < 3 years of age; 135 were ≥3 years of age.

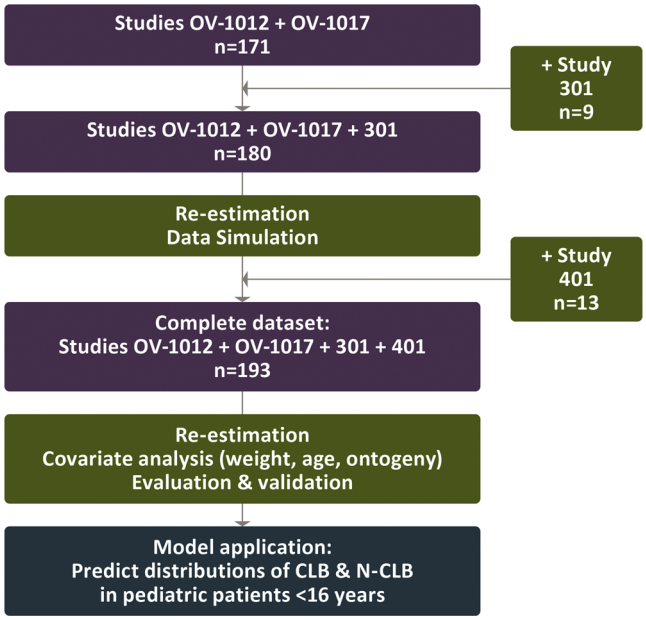


**Fig. 1.** Clobazam PopPK model development. CLB, clobazam; *N*-CLB, *N*-desmethylclobazam; PopPK, population pharmacokinetics.

between 0 and 1 using a logistic function (equations 1 and 2, Supporting Information S1.1) as previously reported (Tolbert et al., 2016).

#### 2.2.2. Data synthesis

Due to sparse PK sampling in OV-1012, data from study OV-1012 were merged with intensively sampled data from study OV-1017 (Fig. 1). Parameter estimates obtained from OV-1012 and OV-1017 were used as priors for re-estimation following addition of PK data from study 301, which included younger patients (6 months to 2 years). Additional PK data were synthesized for a random sample of 13 younger subjects (similar in weight and age to those of Study 301) using a pharmacometric knowledge creation approach (Ette et al., 2005; Tolbert et al., 2016). It was necessary to keep the number of synthesized subjects to a minimum; therefore, 13 subjects were used. These subjects were only needed for improved parameter precision, especially the estimates of variability, making it necessary to keep the number to a minimum. These estimates are influenced by the number of samples per subject and the spread of informative times. Synthesized data from these 13 subjects constituted study 401. A hybrid sampling scheme from OV-1012 and 301 was used, such that subjects in study 401 provided an average of 3.2 samples per subject of clobazam and *N*-CLB. The synthesized data from study 401 were pooled with the previous studies to form the complete dataset (OV-1012, OV-1017, 301, 401) used to develop the PopPK model (Table 1).

#### 2.2.3. Covariate analysis

The final PopPK model was developed using nonlinear mixed-effects modeling implemented in the NONMEM software (ICON Early Phase, Gaithersburg, MD) and data visualization (graphing and fitting using logistical weight regression) with SPLUS version 8 (Spotfire, Somerville, MA) to identify covariates for inclusion as explanatory variables in the final model. Covariates considered were disease state, study, weight, age, and ontogeny. Model parameters for this analysis are included in Supporting Information S1.2.

#### 2.2.4. Evaluation and predictive performance

Model evaluation was performed using standard model diagnostics and other goodness-of-fit criteria such as log-likelihood difference, residual error variance, intersubject variability, and the fits of individual subject profiles. Plots of conditional weighted residuals with interaction versus time were also examined. The extent of shrinkage of empiric Bayesian parameter estimates for structural and final PopPK models were obtained directly from NONMEM outputs. Model predictive performance was determined using prediction-corrected visual predictive check (pcVPC; implemented using PSN version 3.5.3) to compare PopPK model predictions with observations from 500 simulated datasets.

### 2.3. PopPK model application

Using the final PopPK model and a titration-to-maintenance clobazam dosing regimen (to establish CLB steady-state dosage and mimic the clinical setting), a simulation study was performed to determine the steady-state minimum observed concentration ($C_{min}$) of clobazam and *N*-CLB that would be obtained after 4 weeks of maintenance treatment with clobazam 1.5 and 2.0 mg/kg. The simulated titration schedule was as follows: Week 1: 0.25 mg/kg/d (max10 mg/d); Week 2: 0.5 mg/kg/d (max: 20 mg/d); Week 3: 1.0 mg/kg/d (max40 mg/d); Weeks 4 through 7 (maintenance period A): 1.5 mg/kg/d (max60 mg/kg/d); Weeks 8 through 11 (maintenance period B): 2.0 mg/kg/d (max80 mg/d). Data were simulated for a total of 200 virtual patients aged 1 to 16 years and weighing 9.91 to 70.15 kg; 100 dataset replicates were generated for each maintenance period.

## 3. Results

### 3.1. Clobazam PopPK model development

The PopPK model was developed with typical parameters for healthy subjects and for patients with LGS estimated separately but within the same model, as estimating the 2 populations together resulted in a poor fit for healthy subjects. Typical KA values for healthy subjects and Q/F values for patients with LGS were fixed at high values to enable appropriate model estimation. Without these adjustments, the estimation of Q/F and V3/F in the patient studies tended towards infinitely small values, suggesting a minimal model for the patient studies. The adjustments were necessary, as dictated by the data through model estimation, for the assumed 2-compartment model and did not affect CL/F and V2/F, the key dosing parameters. Typical KA, V3/F, and apparent clearance of metabolite ($CL_M$) values for patients with LGS from the observational study were adjusted by fixing the values, estimating the model, and examining the goodness-of-fit diagnostics until an appropriate value was obtained that enabled adequate characterization of the PK of the clobazam and *N*-CLB data in these subjects. This approach became necessary given the nature of the PK data from the observational study. None of these adjustments affected key dosing parameters (CL/F and V2/F).

#### 3.1.1. Covariate analysis: weight, age, and ontogeny

The comparative distribution of the 2 key covariates, age and weight, before and after data synthesis were similar. The median (range) weights before and after data synthesis were 28.55 kg (9.50–133.40 kg) and 26.00 kg (9.50–133.40 kg), respectively; the median (range) ages before and after data synthesis were 10.05 years (0.58–49.20 years) and 9.1 years (0.49–49.20 years), respectively. Weight was modeled on CL/F, V2/F, and PM (the scalar quantity estimated for the derivation of FM fraction of drug metabolized); $CL_M$ was centered on a reference weight of 70 kg (Anderson and Holford, 2011). To avoid the problem of correlation between weight and age, the exponent for weight was fixed at 0.75 for CL/F and 1.0 for V2/F, and estimated for PM and $CL_M$. Age was modeled on V2/F as a multiplicative power function, centered on the median age of 9.10 years.

To improve goodness-of-fit, weight and age were modeled on KA. To account for ontogeny, age models for CYP3A4 and CYP2C19 (Johnson et al., 2006) were incorporated into the CL/F and $CL_M$ models,

**Table 2**
Summary of NONMEM Parameters for the Clobazam PopPK Model[a].

| Parameter [units] | Parameter estimate | RSE, % | 95% CI[b] |
|---|---|---|---|
| **Fixed Effects** | | | |
| $CL/F_{TV,HV}$ [L/h][c] | 5.45 | 20.4 | (3.27, 7.62) |
| $V2/F_{TV,HV}$ [L] | 59.8 | 15.5 | (41.6, 78.0) |
| $KA_{TV,HV}$ [/h] | 15.0 | – | – |
| $Q/F_{TV,HV}$ [L/h] | 10.0 | 11.8 | (7.69, 12.3) |
| $V3/F_{TV,HV}$ [L] | 62.1 | 9.10 | (51.0, 73.2) |
| $CL/F_{TV,PT}$ [L/h] | 8.40 | 10.9 | (6.60, 10.2) |
| $V2/F_{TV,PT}$ [L] | 35.2 | 7.50 | (30.0, 40.4) |
| $KA_{TV,PT}$ [/h] | 0.147 | 4.90 | (0.133, 0.161) |
| $Q/F_{TV,PT}$ [L/h] | 140 | – | – |
| $V3/F_{TV,PT}$ [L] | 1.08 | – | – |
| $CL/F_{WT}$ | 0.750 | – | – |
| $CL/F_{AGE}$ | −0.448 | 20.9 | (−0.631, −0.265) |
| $V2/F_{WT}$ | 1.00 | – | – |
| $V2/F_{AGE}$ | −0.285 | 36.8 | (−0.491, −0.079) |
| $V2/F_{IND}$ | −0.513 | 13.9 | (−0.653, −0.373) |
| $KA_{IND1}$ | 10.0 | – | – |
| $KA_{WT}$ | −0.221 | – | – |
| $KA_{AGE}$ | 0.316 | 17.9 | (0.205, 0.427) |
| $PM_{TV,HV}$ | −4.34 | 1.50 | (−4.47, −4.22) |
| $CL_{M,TV,HV}$ [L/h] | 0.0707 | 7.20 | (0.061, −0.081) |
| $PM_{TV,PT}$ | 19.9 | 14.9 | (14.1, 25.7) |
| $CL_{M,TV,PT}$ [L/h] | 1.77 | 16.3 | (1.21, 2.33) |
| $CL_{M,IND}$ | 1.5 | 0.01 | (1.50, 1.50) |
| $PM_{WT}$ | 0.287 | 19.9 | (0.175, 0.399) |
| $CL_{M,WT}$ | 0.587 | 16.9 | (0.396, 0.782) |
| $CL_{M,AGE}$ | −1.07 | 22.9 | (−1.55, −0.590) |

PopPK, population pharmacokinetics; RSE, relative standard error.
[a] Where $CL_{TV,REF}$, $V2/F_{TV,REF}$, $KA_{TV,REF}$, $Q_{TV,REF}$, and $V3/F_{TV,REF}$ are the typical values of *CL/F* and *V2/F* at the reference value of 70 kg for weight (WT), and 9.10 years for age in the case of V2/F and KA. $V2/F_{IND}$ and $KA_{IND1}$ are fractional changes in V2/F and KA in observational studies subjects and study 301 alone, respectively, and $CL/F_{WT}$, $CL/F_{AGE}$, $V2/F_{WT}$, $V2/F_{AGE}$ are model parameters.
[b] Values are asymptotic confidence intervals.
[c] Covariate effect was estimated relative to a reference (typical) subject weighing 70 kg; age of 9.10 years (median) for age models on V2/F and KA.

**Table 3**
Summary of Interindividual and Residual Variability for the PopPK Model.

| Parameter [units] | Parameter estimate (%[a]) | RSE, % | 95% CI[b] | Shrinkage, % |
|---|---|---|---|---|
| **Interindividual variability (IIV)** | | | | |
| $\omega^2_{CL/F}$ | 0.359 (59.9) | 16.2 | (0.245, 0.473) | 7.4 |
| $\omega_{CL/F}$: $\omega_{V2/F}$ | 0.385 (0.951) | 21.8 | (0.221, 0.549) | – |
| $\omega^2_{V2/F}$ | 0.456 (67.5) | 27.0 | (0.215, 0.697) | 11.9 |
| $\omega^2_{KA}$ | 0.345 (58.7) | 20.7 | (0.205, 0.485) | 34.1 |
| $\omega^2_{Q/F}$ | 0.126 (35.5) | 49.4 | (0.00389, 0.248) | 76.4 |
| $\omega^2_{V3/F}$ | 0.152 (39.0) | 29.0 | (0.0656, 0.238) | 70.0 |
| $\omega^2_{FM}$ | 0.106 (32.6) | 62.3 | (−0.0234, 0.235) | 8.70 |
| $\omega_{FM}$: $\omega_{CL,M}$ | −0.236 (−0.953) | 36.7 | (−0.406, −0.0663) | – |
| $\omega^2_{CL,M}$ | 0.578 (76.0) | 10.4 | (0.460, 0.696) | 4.6 |
| **Residual variability**[c] | | | | |
| CLB (LGS patients) | 0.392 | 4.10 | (0.361, 0.423) | 16.4 |
| CLB (healthy subjects) | 0.229 | 7.20 | (0.196, 0.262) | 5.00 |
| *N*-CLB (healthy subjects) | 0.360 | 4.70 | (0.327, 0.393) | 13.9 |

CLB, clobazam; LGS, Lennox-Gastaut syndrome; *N*-CLB, *N*-desmethylclobazam; PopPK, population pharmacokinetics; RSE, relative standard error.
[a] Coefficient of variation for estimated variances and correlation for estimated covariance.
[b] Values are asymptotic confidence intervals.
[c] Estimated as standard deviations.

respectively. It was necessary to model ontogeny in the CL/F of clobazam and its active metabolite to account for changes in their elimination due to enzyme maturation from infancy to adulthood.

#### 3.1.2. Final clobazam PopPK model

The final PopPK model incorporated age and weight on CL/F and $CL_M$; weight on V2/F, PM (the scalar quantity used in a logistic function to compute FM), and KA; and age on KA and V2/F; V2/F was adjusted for patients with LGS from studies 301 and 401, and KA was adjusted for patients with LGS from study 401. Full model details are included in Supporting Information S1.3.

The parameters of the final PopPK model (Table 2) were similar to those previously reported (Tolbert et al., 2016). Fixed-effect parameters were precisely estimated, with no significant increase in the NONMEM objective function value. Intersubject variability estimates in model parameters (Table 3) were also similar to those reported previously (Tolbert et al., 2016); residual variability estimates were precise, with < 35% shrinkage associated with estimation of variability in parameter estimates, except for intersubject variability in Q/F and V3/F.

#### 3.1.3. Model evaluation and predictive performance

Goodness-of-fit plots show that the structural model adequately described clobazam and *N*-CLB data with no trends in the residuals (Supporting Information S2). The inclusion of the covariates eliminated most of the unexplained variability due to weight and age (not shown). pcVPC of predicted versus observed plasma concentration–time data showed that approximately 95% of observed values between the 5th and 95th percentiles of model predictions; thus the model adequately characterized clobazam and *N*-CLB concentrations (Fig. 2).

### 3.2. Model application

The distributions of clobazam and *N*-CLB in subjects aged < 3 and ≥3 years after 1.5 and 2.0 mg/kg obtained with PopPK model-based simulation are shown in Fig. 3. The ratio of clobazam to *N*-CLB in virtual study subjects aged ≥3 years was 0.14 for the 1.5-mg/kg dose (mean clobazam concentration = 654 ng/mL; mean *N*-CLB concentration = 4780 ng/mL); as expected given the linear PK of clobazam, the same ratio was maintained at the 2.0-mg/kg dose (clobazam = 1083 ng/mL; *N*-CLB = 7570 ng/mL).

The clobazam/*N*-CLB ratio in virtual study subjects aged < 3 years was 0.23 for 1.5 and 2.0 mg/kg. The clobazam/*N*-CLB ratios obtained for subjects aged ≥3 years were 2 to 3 times those reported in a the stiripentol/clobazam/valproate study, in which patients aged ≥3 years receiving clobazam and stiripentol were more likely to be responders (Chiron et al., 2000).

## 4. Discussion

This study describes the development of a PopPK model to predict the dosages of clobazam that are likely to result in efficacious plasma levels of clobazam and *N*-CLB in pediatric patients as young as 6 months of age with DS. The PopPK model utilized a structured approach based on FDA guidance (US Department of Health and Human Services, 1999) and pharmacometric knowledge discovery (Ette et al., 2005; Tolbert et al., 2016), assuming a linear 2-compartment model with first-order absorption and elimination (Tolbert et al., 2016). In addition to incorporating weight using allometric scaling (Anderson and Holford, 2011), the model incorporated CYP isozyme ontogeny using previously developed equations for CYP3A4 and CYP2C19 (Johnson et al., 2006), which are primarily responsible for the metabolism of clobazam and *N*-CLB. This combination of allometric scaling and ontogeny has been shown to produce similar results to those obtained with physiologically based PK modeling using paracetamol as an example (Strougo et al., 2012).

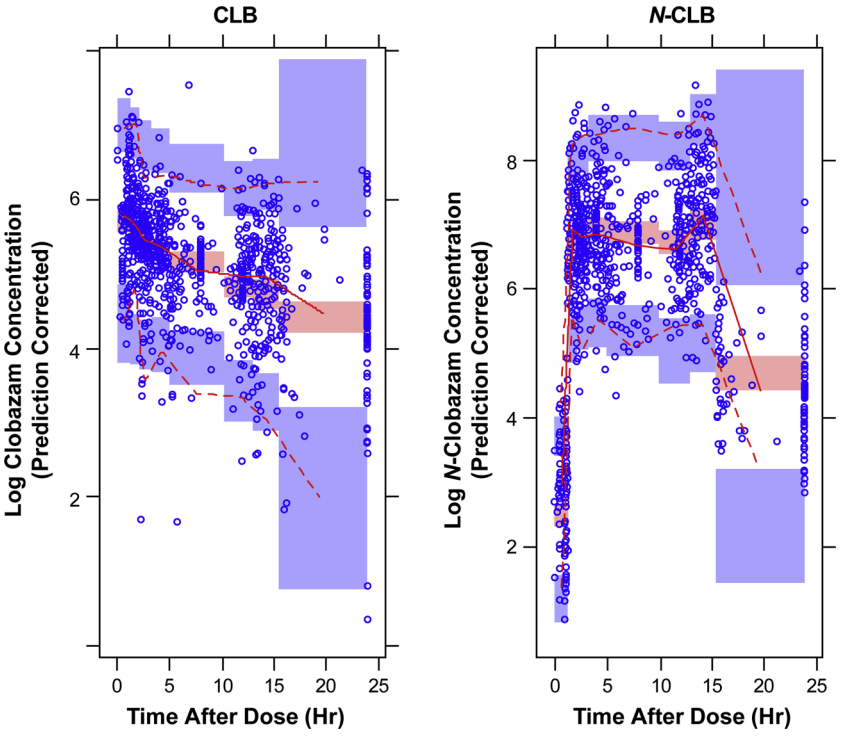


**Fig. 2.** Prediction-corrected visual predictive check (pcVPC): 5%, 50%, and 95% prediction intervals. CLB, clobazam; *N*-CLB, *N*-desmethylclobazam.

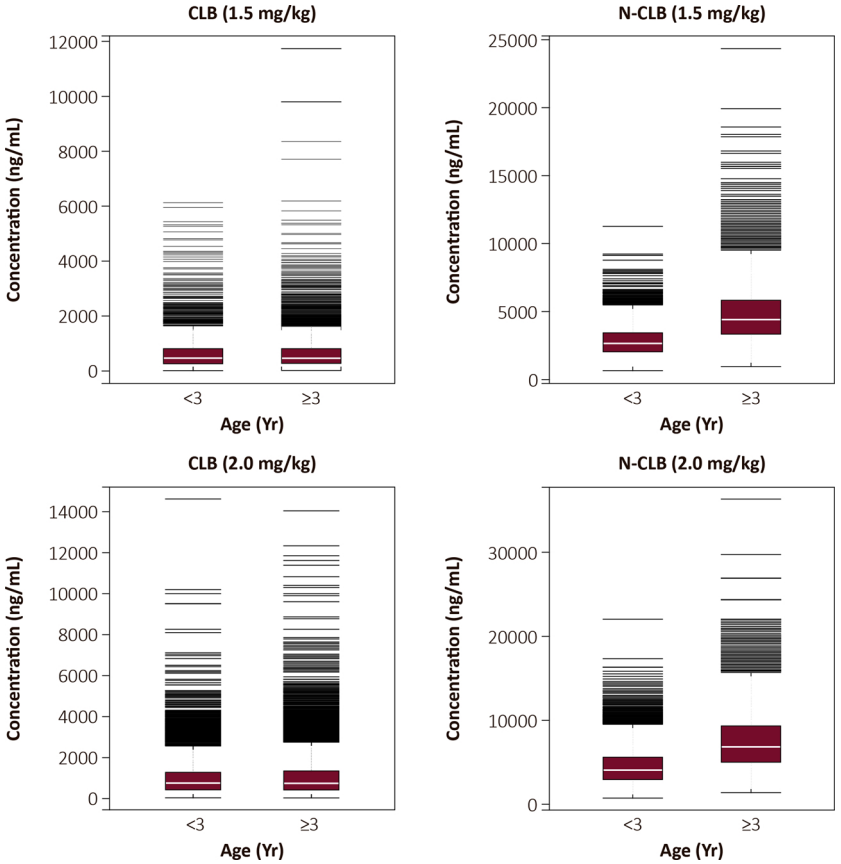


**Fig. 3.** Distributions of steady-state $C_{min}$ obtained with PopPK model-based simulation of clobazam maintenance doses of 1.5 mg/kg and 2.0 mg/kg. CLB, clobazam; $C_{min}$, minimum observed concentration; *N*-CLB, *N*-desmethylclobazam; PopPK, population pharmacokinetics.

The parameters and intersubject and residual variability estimates obtained from the PopPK model were similar to previously reported estimates (Tolbert et al., 2016), and goodness-of-fit evaluation and predictive performance using pcVPC indicated that the final PopPK model adequately characterized the PK of clobazam and *N*-CLB. DS emerges in patients less than 2 years of age, and initially presents as treatment-refractory generalized or hemiconvulsive seizures, with other seizure types emerging in children up to 5 years of age. Because treatment with anti-epileptic drugs must begin so early in life in this patient population, evaluation of age-based response to these drugs is necessary.(Wirrell, 2016) On average, clobazam CL/F increases by approximately 7.85% from age 1 to 2 years. The clobazam/*N*-CLB ratio was 0.23 for virtual study subjects aged < 3 years for both 1.5- and 2.0-mg/kg doses, and 0.14 in virtual subjects aged ≥3 years to enable the comparison of simulated clobazam and *N*-CLB doses with those reported by Chiron et al (2000), who used a similar 3-year age cutoff (Chiron et al., 2000). This result is 2 to 3 times the clobazam/*N*-CLB ratio of 0.07 reported for patients aged > 3 years in the stiripentol/clobazam/valproate combination study by Chiron et al., in which seizure improvement was reported (Chiron et al., 2000). Given the improved seizure control demonstrated in that study, and that clobazam is 3 times as potent as *N*-CLB (Ovation Pharmaceuticals, 2009), the dosing regimens of 1.5 and 2.0 mg/kg/d used in the simulation reported herein can be expected to yield concentrations of clobazam and *N*-CLB that are effective in reducing seizures. As with administration of any anti-epileptic drug in younger patients, dosages should be monitored for tolerability.

A limitation of the study could be the use of clobazam and *N*-CLB data from an observational study in 13 subjects. However, because the predictive performance of the model was shown to be adequate, the impact of the use of the observational data was likely minimal. In the observational study, it was possible that fixing the average KA value for the patients could have made the KA data dependent. However, the approach used in this investigation was such that the data dictated the value to which the KA could be fixed, enabling an adequate characterization of KA in patients with LGS from the observational study (OV-301), as indicated by the diagnostic plots. Fixing the KA value to a published value would have resulted in the inappropriate characterization of the clobazam and *N*-CLB profiles in the observational subjects; and that was evident as model misspecification of the absorption of clobazam in the observational LGS patients (results not shown) in the dataset when we used such an approach.

Given the inherent challenges in conducting clinical trials in pediatric populations with epilepsy, children are often treated using therapies for which efficacy, safety, and/or PK have only been established in adults (Pellock et al., 2012). The problem is further compounded in rare and difficult-to-treat pediatric epilepsies such as DS, for which there are very few approved treatments and very limited clinical trial data on potential therapies (Epidiolex, 2018; Wallace et al., 2016; Wirrell, 2016). The PopPK modeling described in this study was used to determine the dosing regimen for use in a Phase 3 trial of the efficacy and safety of clobazam in patients aged ≥1 to ≤16 years with DS (Lee et al., 2015). While the trial was discontinued because of recruitment challenges (due to the rare and severe nature of DS), the modeling served as an important first step to investigating clobazam in DS, thereby demonstrating a potential place for such modeling in similar patient populations in which the conduction of clinical trials is difficult. In addition, in the absence of controlled studies in pediatric patients with DS, this study may be useful in current treatment decisions.

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## Declaration of Competing Interest

DT is an employee of Lundbeck LLC. EE and H-MC are employees of Anoixis Corporation, which was contracted by Lundbeck to perform the pharmacometric analyses. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2019.106182.

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