Clinical Pharmacology Review

PRODUCT (Generic Name):	Pregabalin
PRODUCT (Brand Name):	LYRICA®
NDA:	021446/SUPPL-35 (sequence 0408) 022488/SUPPL-13 (sequence 0076)
DOSAGE FORM:	Capsule / oral solution
ROUTE of ADMINISTRATION:	Oral
INDICATION:	Adjunctive therapy for the treatment of partial-onset seizures in patients 4 years of age and older
SUBMISSION DATE:	11/03/2017
APPLICANT:	Pfizer Inc.
OCP REVIEWERS:	Dawei Li, Ph.D., Michael Bewernitz, Ph.D., Kevin Krudys, Ph.D., Angela Men, M.D., Ph.D.
OCP DIVISION:	DPM/DCP I

1 EXECUTIVE SUMMARY

Lyrica (pregabalin) is currently approved in the U.S. for the treatment of partial-onset seizures (POS) as an adjunctive therapy in adult patients. Supplement 035/013, an efficacy supplement, was submitted to pursue an indication for Lyrica for the adjunctive treatment of partial onset seizures in patients 4 years of age and older using extrapolation. Specifically, the current submission involves efficacy extrapolation from adult patients to pediatric patients.

In response to DNP's General Advice Letter regarding extrapolation of efficacy for adjunctive therapy, the Applicant conducted pharmacokinetic modeling and simulation to determine a dosing regimen that would provide similar pregabalin exposure in pediatric patients 4 years of age and older to pregabalin exposure levels demonstrated to be effective in adult patients with POS. The Applicant's proposed dosing for pediatric patients, which OCP finds acceptable, is presented in the table below.

Table 1: Lyrica Dosage Schedule for Pediatric Patients Aged 4 to 17 Years Old

(b) (4)

2 RECOMMENDATIONS

The Office of Clinical Pharmacology reviewers have reviewed NDA 021,446 Supplement-035 for Lyrica (pregabalin). The Applicant's submission is acceptable from the perspective of the Office of Clinical Pharmacology and we recommend approval provided that an agreement is reached between the Applicant and Agency regarding labeling language.

3 BACKGROUND

Pregabalin is an anti-nociceptive, anticonvulsant agent current approved as adjunctive therapy for adult patients with partial onset seizures. Though the mechanism of action is unknown, Lyrica is thought to act at alpha2-delta site (an auxillary subunit of voltage-gated calcium channels). The maintenance dose is 150 to 600 mg/day as BID or TID in adults. The initiation dose in adults is 150 mg/day BID or TID.

4 GENERAL ADVICE FOR PEDIATRIC EXTRAPOLATION

On November 12, 2015 DNP sent a General Advice Letter to the Applicant indicating that it was acceptable to extrapolate to pediatric patients 4 years of age and older the effectiveness of drugs approved for the treatment of partial onset seizures (POS) in adults. This determination was based on the similarity of POS in pediatric patients 4 years of age and older and adults as well as analyses of multiple antiepileptic drugs, conducted by the FDA, that demonstrated a similar exposure-response relationship in pediatric and adult patients with POS.

The following will be required to rely upon extrapolation to support an indication for the treatment of POS in subjects 4 years and older:

- An approved indication for the treatment of POS in adults.
- A pharmacokinetic (PK) analysis to determine a dosing regimen that provides similar drug exposure (at levels demonstrated to be effective in adults) in pediatric subjects 4 years of age and older compared with adult subjects with POS. This analysis will require pharmacokinetic data from both the adult and pediatric (4 years of age and older) populations.
- Long-term open-label safety study(ies) in pediatric subjects 4 years of age and older.

5 CLINICAL DEVELOPMENT IN PEDIATRIC PATIENTS

Studies to support the current submission include a Phase 1 PK study in pediatric POS patients (A0081074) and a Phase 3 efficacy trial in pediatric POS patients (A0081041).

A0081074 (Phase 1): Phase 1 study A0081074 is a placebo-controlled, single ascending dose, multiple-ascending dose study in n=65 patients with POS age 1 month to 16 years. Patients were randomized to receive placebo, 2.5, 5, 10, or 15 mg/kg/day (max 150, 300, 600, or 900 mg/day, respectively) administered BID for 7.5 days (7 days BID administration and a single administration on the morning of Day 8). Patients in the placebo arm received their first and only Lyrica administration on Day 8 after 7 days of receiving placebo. With respect to the Day 8 administration, PK was sampled pre-dose and at 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose.

A0081041 (Phase 3): Phase 3 trial A0081041 is a double-blind, placebo-controlled, parallel trial to assess efficacy in n=295 patients with POS age 4 to 16 years. Patients were randomized to 12 weeks of either placebo, low-dose Lyrica, or high-dose Lyrica. The low dose Lyrica arm administered 3.5 mg/kg/day to patients < 30 kg and 2.5 mg/kg/day for patients ≥ 30 kg, maximum 150 mg/day, without titration/escalation. The high dose Lyrica arm administered 14 mg/kg/day for patients < 30 kg and 10 mg/kg/day for patients ≥ 30 kg, maximum 600 mg/day, with a 2-week escalation period. The starting dose in the high dose Lyrica arm is the same dose as is applied in the low-dose arm. The total daily dose was split evenly and administered BID. Sparse PK were collected (1 sample at Visit 7, two samples at Visit 9). The primary endpoint of this study was the evaluation of the frequency of partial onset seizures standardized to a 28-day duration.

[*Reviewer comment: Only the high dose arm achieved a statistically-significant improvement in seizure rate compared to placebo in Phase 3 trial A008041. However, the dose-response data demonstrate a comparable change from baseline seizure rate at the low dose in pediatric patients versus the low dose in adults. In addition, the high dose arms in pediatric patients appear to demonstrate comparable change from baseline seizure reduction to the high dose arms in adult patients. Furthermore, the pediatric patients demonstrate an apparent improvement in seizure frequency compared to baseline in the placebo arm that is not apparent in adults. The reason for this apparent improvement in the placebo arm in pediatric patients is not known.*

This efficacy trial was initiated prior to DNP issuing the General Advice Letter indicating the acceptability of extrapolating efficacy for adjunctive therapy from adults to pediatric patients. Since the Applicant has provided adequate PK information to support extrapolation of efficacy from adult patients to pediatric patients, the efficacy assessments in A0081041 are considered supportive information.

Please refer to section 7 for details.]

A pooled population PK analysis was performed where PK data from pediatric patients (study A0081074 and trial A0081041) were integrated into a previously-developed adult PPK model. The adult data included in the modeling came from healthy adult subjects, adult subjects with impaired renal function, and adult subjects with POS. Using the combined adult and pediatric population PK model, Applicant conducted PK simulations

to arrive at pediatric doses expected to match exposures in adults receiving approved doses.

PMAR-EQDD-A008s-sNDA-538: This report describes the population PK analyses where the pediatric PK data were merged into the previously-developed adult population PK model. The report also presents the PK simulations used to inform the pediatric dose selection described in the current submission. Finally, this report also describes exposure-response analyses of seizure-frequency data obtained from Phase 3 trial A0081041.

[*Reviewer comment: This current submission is based on PK matching and extrapolation. The exposure-response analyses were not reviewed.*]

6 RESULTS OF APPLICANT'S POPULATION PK ANALYSES

The Applicant conducted population PK (PPK) modeling and simulation to inform the Lyrica dosing regimen in pediatric patients. The PPK model is briefly described below. A detailed summary of the PK model can be found in the appendix.

Adult and Pediatric Population PK Model: The adult PPK model was previously reviewed by OCP and found to be acceptable. The Applicant updated the adult PPK model by including the PK data from pediatric patients (study A0081074 and trial A0081041). A summary of key information about the population PK model is summarized below (please refer to the appendix for details).

The final model utilized one-compartment, first-order oral absorption with lag time, first-order elimination, and was parameterized in terms Cl/F (apparent clearance), V/F (apparent volume of distribution), three k_a (first order absorption rate constant) terms (one for fasted, fed, and unknown food states; estimated as a faction of k_{el}), and two T_{lag} terms (for fasted and unknown food state, estimated from adult PK data). Covariates for apparent clearance include body weight, creatinine clearance, and sex. Covariates for apparent volume of distribution include body weight and sex. Weight was normalized to 70 kg and related to CL/F and V/F using allometric scaling. Creatinine clearance was normalized by body-surface area (BSA) and related to CL/F using a so-called “hockey stick model”. In the “hockey stick model”, CL/F is proportional to creatinine clearance up to a breakpoint creatinine clearance value. For creatinine clearance values at and above the breakpoint, CL/F remains constant.

Between-subject variability (BSV) was estimated for CL/F, V/F, and k_a for the combined adult and pediatric populations except for a separate $k_{a,fed}$ BSV term (for which only adult data are available).

The final model parameter estimates are found in the table below.

Table 2: Parameter Estimates from the Final Population PK Model (Run 8) and Previous Adult Population PK Model (PMAR-00087)

	PMAR-00087 [3]	CLcr in Absolute unit [mL/min]				CLcr normalized to 1.73 m^2 [mL/min/1.73 m^2]			
		Run 24 (AS664635)		Run 25 (AS664641)		Run 16 (AS664637)		Run 8 (AS664216)	
Model	Final	Base		Final Covariate		Base		Final Covariate	
OFV (ΔOFV[a])	-	-2519.939		-2749.262	(-229.32)	-2576.222	(-56.28)	-2803.456	(-283.52)
Parameter	Estimate	Estimate	RSE [%]	Estimate	RSE [%]	Estimate	RSE [%]	Estimate	RSE [%]
CL/F[b] [L/h] (θ_1)	4.89	5.38	1.26	5.26	0.983	4.78	1.47	4.96	1.78
BWT on CL/F (θ_{10})	-	-	-	0.116	22.5	0.534	4.41	0.522	4.72
Sex on CL/F (θ_{13})	-	-	-	-	-	-	-	0.915	2.00
CLcr breakpoint[c] (θ_5)	105	122	1.84	117	0.304	96.9	1.91	96.4	1.91
V/F [L] (θ_2)	43.8	40.3	1.96	40.3	1.59	39.6	1.65	39.8	1.62
Sex on V/F (θ_7)	0.798	0.845	2.84	0.850	2.89	0.846	2.60	0.832	2.48
BWT on V/F (θ_8)	0.573	0.690	4.94	0.722	4.70	0.711	4.52	0.704	4.59
k_a Fasted[d] [h^{-1}] (θ_3)	8.55	11.1	15.1	9.76	11.6	9.99	15.6	10.0	16.2
Food: Fed[e] [h^{-1}] (θ_6)	1.15	0.498	0.981	0.596	1.39	0.614	3.01	0.708	2.39
Food: Unknown[e] [h^{-1}] (θ_9)	-	1.19	5.07	1.52	3.18	1.17	3.89	1.22	3.26
Tlag [h] (θ_4)	0.170	0.321	0.769	0.318	1.55	0.321	0.769	0.318	1.52
Food: Fed[f] (θ_{20})	-	-	-	0.427	10.6	-	-	0.427	10.5
Inter-Individual Variability [%]									
CL/F (ω_1)	19.1	21.9	18.7	21.7	17.9	20.8	18.6	20.2	18.7
V/F (ω_2)	12.4	14.8	26.6	15.1	29.3	13.0	23.6	12.8	21.7
k_a (ω_3)	182	117	14.3	113	16.4	117	14.1	117	13.9
k_{aFed} (ω_4)	-	41.7	50.8	47.3	48.7	59.2	116	57.9	74.4
Tlag (ω_5)	1.51	-	-	-	-	-	-	-	-
Proportional Error [%]									
Phase 1 Adults (σ_1)	14.8	17.5	10.9	16.6	10.2	17.5	11.0	16.6	10.1
Phase 3 Adults (σ_2)	24.5	28.2	7.52	28.5	7.30	28.8	7.55	28.9	7.49
Phase 1 Pediatrics (A0081074) (σ_7)	-	30.1	23.4	29.1	23.1	29.6	22.7	29.8	22.7
Phase 3 Pediatrics (A0081041) (σ_5)	-	36.5	23.2	35.9	20.9	35.0	20.3	35.0	21.0
Additive Error [μg/mL]									
Phase 1 Adults (σ_3)	0.0190	0.0205	67.2	0.0214	67.3	0.0205	64.9	0.0214	66.8
Phase 3 Adults (σ_4)	0.455	0.0605	68.5	0.0565	46.6	0.0496	202	0.0466	77.3
Phase 3 Pediatrics (A0081041) (σ_6)	-	0.733	58.9	0.706	62.6	0.680	68.8	0.682	67.6

Source: sequence 0408, PMAR-EQDD-A008s-sNDA-538.pdf, page 69-70 of 269

Applicant's PK Simulations to Inform Pediatric Maintenance Dose Selection: Applicant conducted PK simulations in virtual adult patients and virtual pediatric patients to derive pediatric dosing for initial dosing and maintenance dosing.

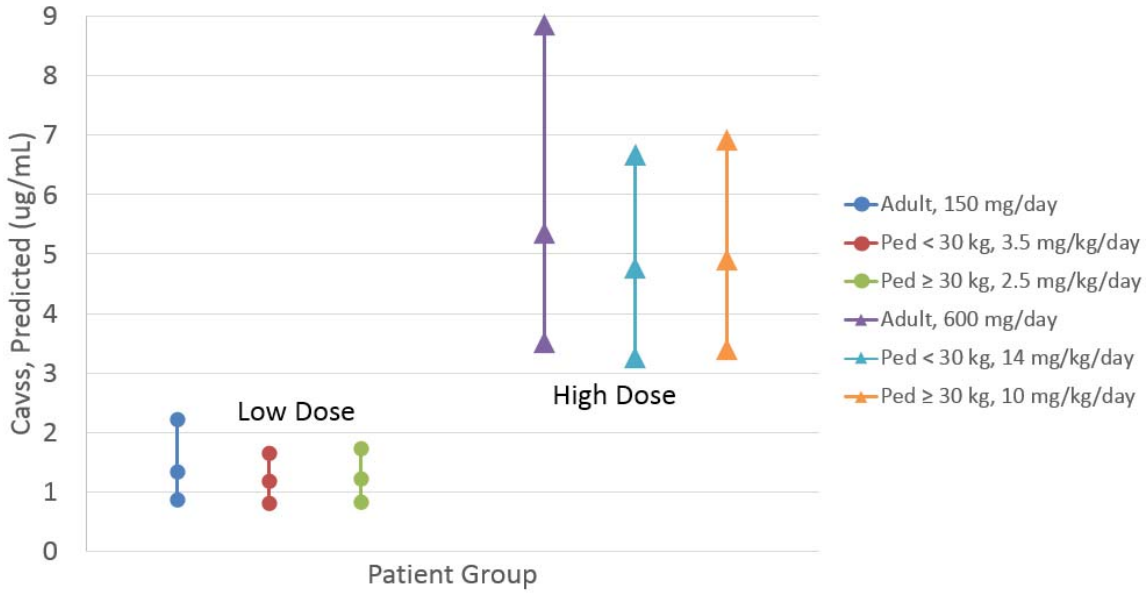
Initiation and Titration Dose Target: Applicant utilized the adult initiation dose of 150 mg/day as the target for selecting the pediatric initiation dose.

Maintenance Dose Target: Applicant utilized the approved low and high maintenance dose levels in adults of 150 mg/day and 600 mg/day as the targets for selecting pediatric maintenance dose. Simulations were conducted with both BID as well as TID administration of the total daily dose.

Simulation Methodology: The simulation dataset for pediatric patients was created by sampling pediatric patients with replacement from the pool of 331 pediatric patients age 4 to 16 years in studies A0081041 and A0081074 to a sample size of 1000 pediatric patients. The simulation dataset for adult patients was created by sampling without replacement from the pool of 1040 adult patients age ≥ 17 years from Phase 3 studies (1008-009, 1008-011, and 1008-034) to a sample size of 1000 adult patients. The individual PK parameters for the 1000 pediatric patient dataset and the 1000 adult patients data were used to simulate the PK profiles in both populations.

The following plot shows the comparison of the simulated average concentration within a dosing interval at steady-state ($C_{av,ss}$) for the proposed pediatric dosing regimen compared with the approved adult regimen.

Figure 1: Simulated $C_{av,ss}$ For the Proposed Pediatric Dosing and the Approved Adult Dosing Administered as BID



Each vertical line represents $C_{av,ss}$ distribution for a given population and dose. The points are 5th, 50th, and 95th percentile. The data in this table are found in Tables 18 and 19 on pages 81 and 82 of 269 in pmar-eqdd-a008s-snda-538.pdf (sequence 0408).

[*Reviewer comment: The $C_{av,ss}$ profile achieved from BID dosing was comparable to that achieved from TID dosing. A table containing the exposure metrics can be found in the appendix.*]

Based on the PK simulations, Applicant concludes that in the pediatric age group of 4 to 16 years,

- subjects weighing ≥ 30 kg and receiving 2.5 or 10 mg/kg/day BID or TID should achieve similar pregabalin exposures to those in adults receiving 150 or 600 mg/day BID or TID of pregabalin, respectively.
- subjects weighing < 30 kg and receiving 3.5 or 14 mg/kg/day BID or TID (40% higher dose than patients weighing ≥ 30 kg) should achieve similar pregabalin exposures to those in adults receiving 150 or 600 mg/day BID or TID of pregabalin, respectively.

The lowest body weight recorded in a pediatric patient that provided PK data (in Phase 3 trial A0081041) was 11.0 kg. OCP and DNP agree that the label can include patients weighing at least 11.0 kg for the proposed indication in patients ≥ 4 years of age.

Overall, **the Applicant's proposed pediatric maintenance doses are acceptable from an OCP perspective for pediatric patients weighing no less than 11.0 kg**.

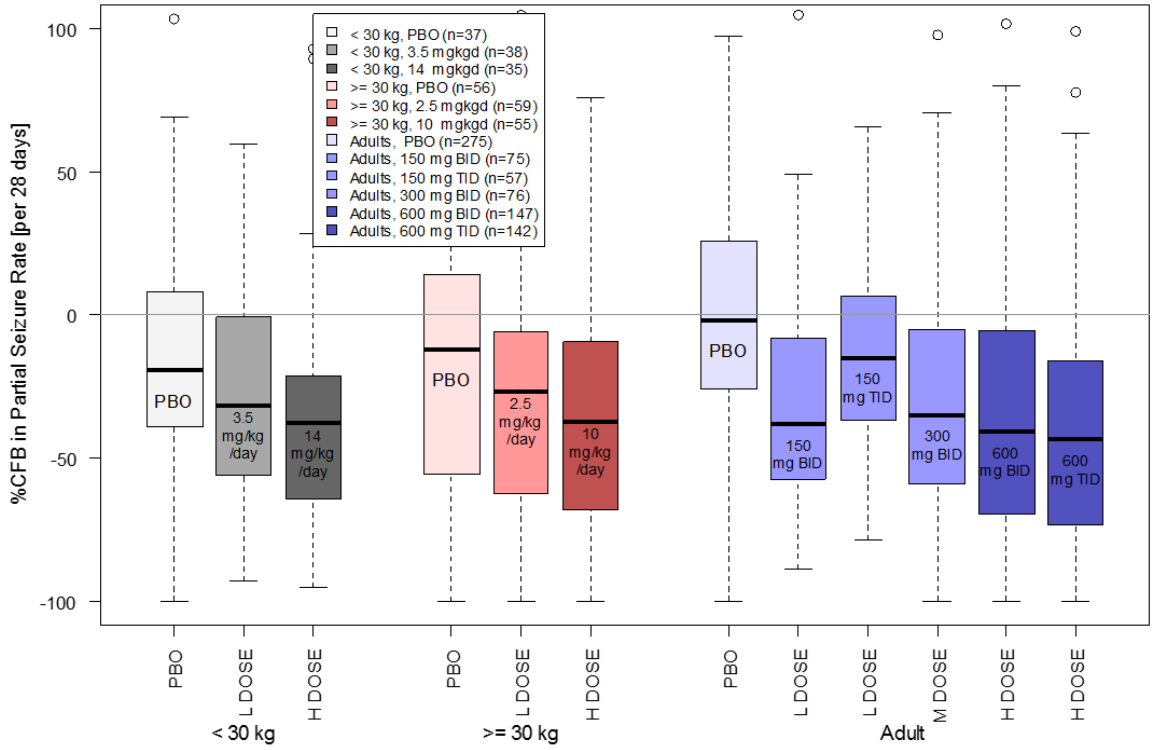
Pediatric Initiation Dose Selection: The proposed initiation dose for pediatric patients is equal to the low maintenance dose, 3.5 mg/kg/day for patients weighing < 30 kg and 2.5 mg/kg/day for patients weighing ≥ 30 kg, (b) (4) . The total daily dose can be administered BID or TID. If increasing to the high dose, increases are to be performed based on response and tolerability of a period of 2 weeks.

This is the same initiation regimen that was utilized in Phase 3 trial A0081041. Based on discussions with the Clinical team, there are no clinically relevant safety concerns identified that would preclude use of this initiation regimen. Overall, **the proposed pediatric initiation doses are acceptable from an OCP perspective.**

7 REVIEWER'S ANALYSIS

In clinical trial A0081041 the high dose arm achieved statistically-significant reduction in seizure rate compared to placebo arm (-19.9%, p=0.0185). However, the low dose did not achieve statistically significant reduction in efficacy compared with placebo arm (effect size -9.93%, p=0.2577). The reviewer conducted exploratory analyses to assess the dose-response relationship of the Phase 3 data to further assess the performance of the low-dose arm. The change from baseline seizure rate was computed for each arm for each group of pediatric patients as well as each group of adult patients. The following plot shows the distribution of change form baseline seizure rate by treatment arm in adult and pediatric trials.

Figure 2: Change from Baseline Seizure Rate By Treatment Arm for Pediatric Patients in Trial A0081041 and Adult Patients in Trials 1008-009, 1008-011, and 1008-034



Pediatric patients received the total daily dose administered as BID.

Pediatric patients demonstrated a change from baseline seizure rate reduction while receiving placebo. The median seizure reduction is greatest in patients < 30 kg. Pediatric patients weighing ≥ 30 kg demonstrate a median reduction in seizure frequency of smaller magnitude than patients weighing < 30 kg. Adult patients presented a median seizure reduction that is closer to zero than for pediatric patients. The reason for the apparent improvement of seizure rate for placebo in pediatric patients versus adults is unknown.

However, the plot demonstrates that the low dose arms for pediatric patients (3.5 and 2.5 mg/kg/day) have comparable change from baseline seizure rate as the low dose arms for adult patients (150-300 mg/day). In addition, the high dose arms for pediatric patients (14 and 10 mg/kg/day) demonstrate a change from baseline seizure rate that is consistent with high dose arms in adult patients (e.g. 600 mg/day). Considering the comparable seizure reduction between the adult and pediatric groups in the treatment arms, it is possible that the lack of statistically significant efficacy for the low-dose arm may be due, in part, to the improvement of the pediatric patients who received placebo.

Overall, the dose-efficacy relationship provides additional support for the Applicant's proposed dose regimen.

Key label edits: The statement "*The use of LYRICA in pediatric patients 4 to 16 years of age with compromised renal function has not been studied*", (b) (4) has been moved to section 2.7.

Michael Bewernitz, Ph.D.

Reviewer, Division of Pharmacometrics (DPM)

Dawei Li, Ph.D.

Reviewer, Division of Clinical Pharmacology 1 (DCP1)

Kevin Krudys, Ph.D.

Team Leader, DPM

Concurrence:

Angela Men, M.D., Ph.D._____

Team Leader, DCP1

cc: HFD-120 NDA# 022416/s-009

HFD-860 Mehul Mehta, Ramana Uppoor, Angela Men, Dawei Li

Appendix A:

Population PK Model Review

Applicant developed a population PK model to characterize the pharmacokinetics of pregabalin in combined datasets from pediatric patients with epilepsy, adult patients with epilepsy, and healthy adult volunteers. An existing prior adult population PK model was updated to include the pediatric PK data. The adult population PK model was previously reviewed and determined to be acceptable by OCP (please refer to the clinical pharmacology review of NDA 021446 signed on 03/22/2004 for details).

Additional aims were to assess the relationship between pregabalin concentration with demographics and other covariates and conduct PK simulations for informing dose selection in pediatric patients.

Summary of PK Data:

There were 5258 measurable pregabalin plasma concentration samples from 979 patients (255 pediatric patients ≤ 16 years of age, 724 adult subjects) available for PK analyses.

Trials: Applicant incorporated PK data from pediatric patients with POS ages 0.25-16 years that received pregabalin in Phase 1 Study A0081074 and Phase 3 Study A0081041. PK data from adult patients with POS were included from Phase 3 studies 1008-009, 1008-011, and 1008-034.

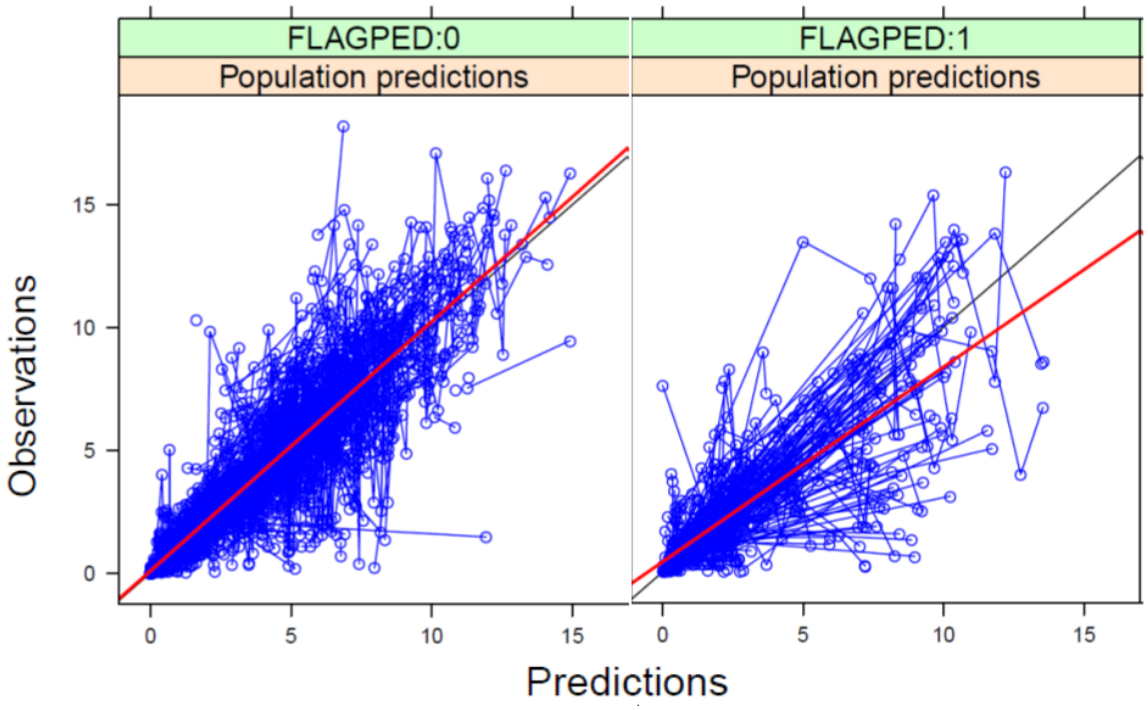
PK Model:

The base structural model was a 1-compartment model with first order absorption, absorption lag, and first-order elimination. PK parameters included Cl/F, V/F, $k_{a,fast}$ (absorption rate order constant [k_a] for the fasted state), $k_{a,fed}$ (k_a for the fed state), $k_{a,unknown}$ (k_a for when fed state is unknown), $T_{lag,fast}$ (absorption lag time [T_{lag}] for the fasted state), and $T_{lag,fed}$ (T_{lag} in the fed state).

Allometric Scaling: Cl/F and V/F had allometric scaling applied using body weight normalized to 70 kg.
Inter-individual variability: Exponential
Residual variability: Additive plus proportional error model
Final Covariate Model: Fed or fasted state is a covariate on T_{lag}. The effect of "fed status" (prandial states of fed, fasted or unknown) on k_a was modelled such that k_a is set to a different portion of k_{el} in each of the 3 prandial states. A "hockey stick" model related CL/F to body-surface area (BSA) normalized creatinine clearance (CRCL). In the "hockey stick" modeling approach, the CL/F increases with increasing BSA-CRCL up to a breakpoint where further increases in BSA-normalized CRCL are not associated with a further increase in CL/F. Sex is a covariate on Cl/F and V/F. The final model parameters are shown in the table 2 in section 6 of this review.

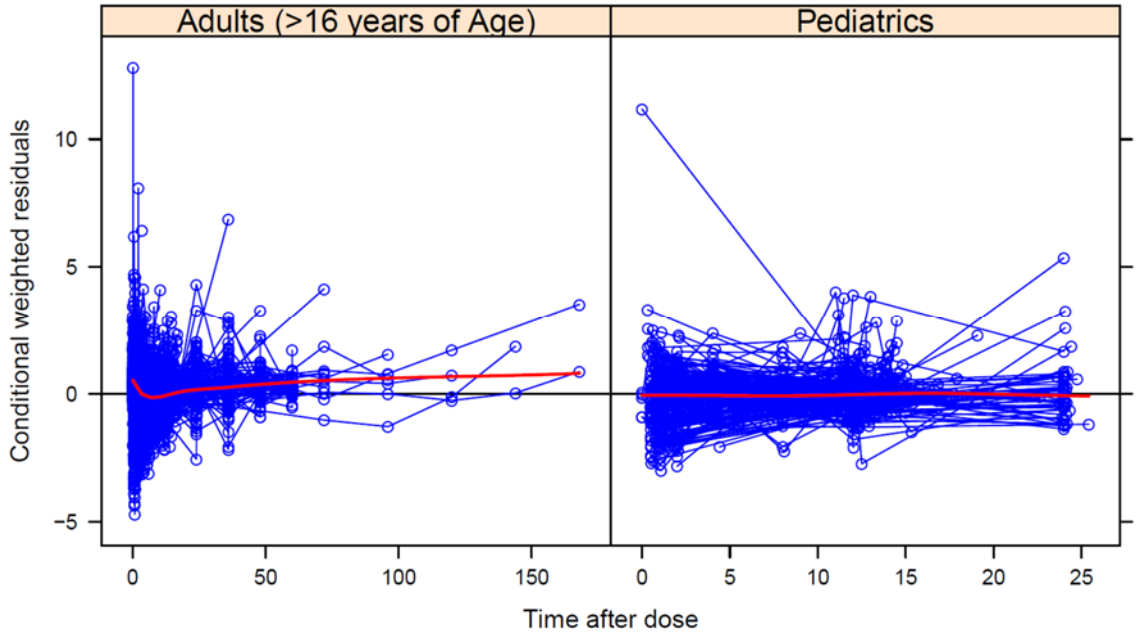
Model diagnostics are presented in the figures below.

Figure 3: Diagnostic Plot Final PK Model (Run 8) for Adult and Pediatric POS Patients and Healthy Volunteers: Absolute Value of Observations Versus Population Prediction



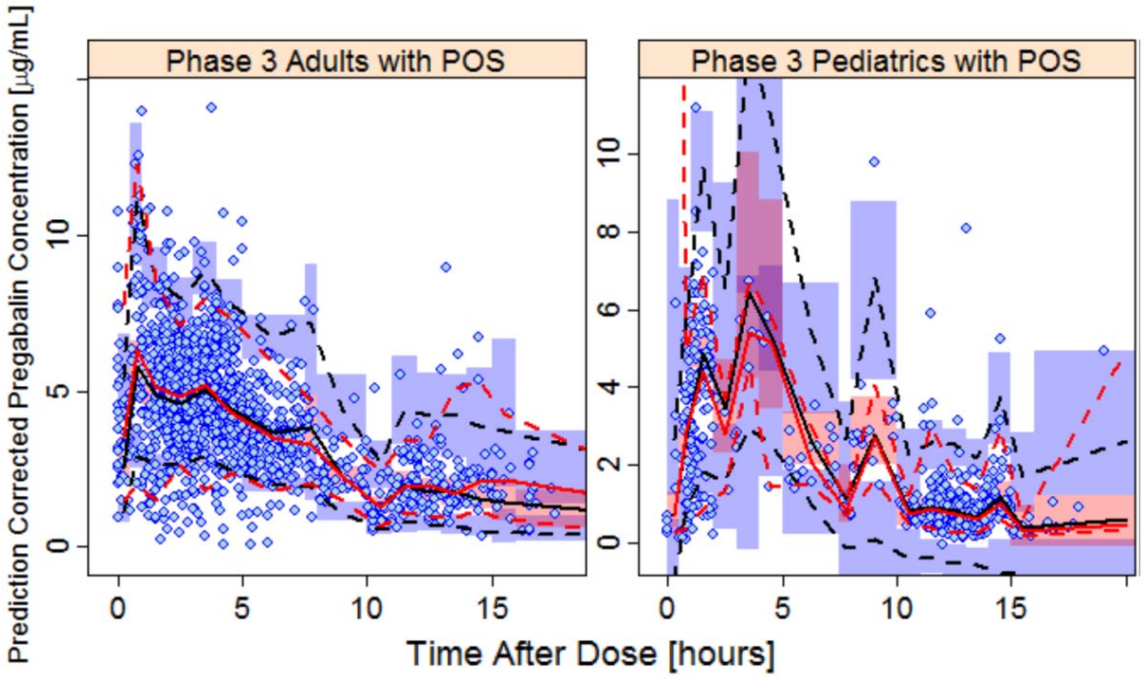
Source: sequence 0408, PMAR-EQDD-A008s-sNDA-538.pdf, page 193, 194 of 269

Figure 4: Diagnostic Plot Final PK Model (Run 8) for Adult and Pediatric POS Patients and Healthy Volunteers: CWRES versus Time



Source: sequence 0408, PMAR-EQDD-A008s-sNDA-538.pdf, page 202 of 269

Figure 5: Visual Predictive Check for Final PK Model for Adult and Pediatric POS Patients



Source: sequence 0408, PMAR-EQDD-A008s-sNDA-538.pdf, page 210 of 269

[*Reviewer comment: The PPK model reviewed in the current submission is a modification to the previously - developed adult population PK model by integration of pediatric PK data into the PK data pool. Overall, the updated model appears to still perform adequately at prediction of adult exposures after integrating the pediatric PK data. As the adult model has already been previously reviewed (see review clinical pharmacology review of NDA 021446 signed on 03/22/2004 for details), the focus of this review is on the performance of the pediatric model.*

The diagnostic plot of conditional weighted residual versus time after dose (Figure 4) shows no apparent prediction bias at any time after dosing. However, the model diagnostic plot of observed value versus population prediction (Figure 3) suggests a trend of increasing over-prediction as exposures increase (e.g. ≥ 8 μg/mL). However, as the PK simulations shown in Figure 1 present a median exposure of ~ 5 μg/mL in all 3 age groups, then a potential over-prediction at exposures ≥ 8 μg/mL is not likely to have a relevant impact on the pediatric dose selection. Overall, within the exposure range expected at clinically-relevant doses in pediatric patients, of interest, ***the performance of PK the model for predicting pediatric exposures is acceptable****.*

Appendix B:

Applicant's Simulated PK Results

The following tables summarize the results of the PK simulations conducted to inform pediatric dose selection.

Table 3: Simulated PK Values For the Proposed Low Dose for Pediatric Patients and the Approved Low Dose for Adult Patients Administered as BID or TID

Dose or Equivalent Dose[a] 150 mg/day		Adults (≥17 years) (n = 1000)			Pediatrics (4 to 16 years)								
					All (n = 1000)			<30 kg (n = 391)			≥30 kg (n = 609)		
Parameter	Frequency	Median	5th Percentile	95th Percentile	Median	5th Percentile	95th Percentile	Median	5th Percentile	95th Percentile	Median	5th Percentile	95th Percentile
$AUC_{ss_{0-\tau}}$	BID	16.1	10.6	26.6	14.7	9.96	20.7	14.3	9.84	20.0	14.8	10.2	20.8
[μg·h/mL]	TID	10.7	7.00	17.6	9.60	6.68	14.3	9.44	6.61	14.2	9.75	6.86	14.3
$C_{av_{ss}}$	BID	1.34	0.880	2.22	1.22	0.830	1.72	1.19	0.820	1.66	1.23	0.849	1.74
[μg/mL]	TID	1.34	0.875	2.20	1.20	0.835	1.79	1.18	0.826	1.78	1.22	0.858	1.79
$C_{max_{ss}}$	BID	2.43	1.60	3.66	2.46	1.83	3.19	2.56	1.86	3.23	2.40	1.81	3.13
[μg/mL]	TID	1.97	1.37	3.03	1.95	1.44	2.62	2.00	1.50	2.62	1.91	1.44	2.60
$C_{min_{ss}}$	BID	0.597	0.273	1.31	0.446	0.184	0.898	0.403	0.158	0.809	0.479	0.210	0.913
[μg/mL]	TID	0.807	0.427	1.56	0.632	0.326	1.17	0.580	0.287	1.12	0.656	0.364	1.19

ePharmacology artifact ID RA13135298. Lines 1–2 substituted.
[a]For Study A0081041, 2.5 mg/kg/day included 2.5 mg/kg/day in subjects ≥30 kg or 3.5 mg/kg/day in subjects <30 kg, with maximum 150 mg/day.
Note: $C_{min_{ss}}$ represents the trough value at 8 hours for TID dosing and 12 hours for BID dosing.
$AUC_{ss_{0-\tau}}$ represents AUC_{ss} 0 to 12 hours for BID dosing and 0 to 8 hours for TID dosing.
Abbreviations: AUC_{ss} = area under the concentration-time curve at steady state; BID = twice daily; $C_{av_{ss}}$ = average pregabalin concentration at steady state; $C_{max_{ss}}$ = maximum pregabalin concentration at steady state; $C_{min_{ss}}$ = minimum pregabalin concentration at steady state; TID = three times daily.

Source: sequence 0408, pmar-eqdd-a008s-snda-538.pdf, Table 18 on pages 81 of 269.

Table 4: Simulated PK Values For the Proposed High Dose for Pediatric Patients and the Approved High Dose for Adult Patients (600 mg/day) Administered as BID or TID

Dose or Equivalent Dose[a] 600 mg/day		Adults (≥17 years) All (n = 1000)			Pediatrics (4 to 16 years) All (n = 1000)			<30 kg (n = 391)			≥30 kg (n = 609)		
Parameter	Frequency	Median	5th Per-centile	95th Per-centile	Median	5th Per-centile	95th Per-centile	Median	5th Per-centile	95th Per-centile	Median	5th Per-centile	95th Per-centile
$AUC_{ss_{0-\tau}}$	BID	64.4	42.2	106	58.7	39.8	82.7	57.3	39.3	79.8	59.2	40.8	83.3
[μg·h/mL]	TID	42.8	28.0	70.3	38.4	26.7	57.1	37.8	26.4	56.9	39.0	27.4	57.3
$C_{av_{ss}}$	BID	5.37	3.52	8.86	4.89	3.32	6.89	4.78	3.28	6.65	4.93	3.40	6.94
[μg/mL]	TID	5.35	3.50	8.79	4.80	3.34	7.14	4.72	3.30	7.11	4.88	3.43	7.17
$C_{max_{ss}}$	BID	9.73	6.42	14.6	9.84	7.32	12.8	10.2	7.42	12.9	9.61	7.23	12.5
[μg/mL]	TID	7.86	5.49	12.1	7.81	5.78	10.5	7.99	5.99	10.5	7.66	5.75	10.4
$C_{min_{ss}}$	BID	2.39	1.09	5.23	1.78	0.737	3.59	1.61	0.634	3.24	1.91	0.840	3.65
[μg/mL]	TID	3.23	1.71	6.23	2.53	1.30	4.66	2.32	1.15	4.50	2.62	1.46	4.77

ePharmacology artifact ID RA13135299. Lines 1–2 substituted.
[a]For Study A0081041, 10 mg/kg/day included 10 mg/kg/day in subjects ≥30 kg or 14 mg/kg/day in subjects <30 kg, with maximum 600 mg/day.
Note: $C_{min_{ss}}$ represents the trough value at 8 hours for TID dosing and 12 hours for BID dosing.
$AUC_{ss_{0-\tau}}$ represents AUC_{ss} 0 to 12 hours for BID dosing and 0 to 8 hours for TID dosing.
Abbreviations: AUC_{ss} = area under the concentration-time curve at steady state; BID = twice daily; $C_{av_{ss}}$ = average pregabalin concentration at steady state; $C_{max_{ss}}$ = maximum pregabalin concentration at steady state; $C_{min_{ss}}$ = minimum pregabalin concentration at steady state; TID = three times daily.

Source: sequence 0408, pmar-eqdd-a008s-snda-538.pdf, Table 19 on pages 82 of 269

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHAEL A BEWERNITZ
05/01/2018

DAWEI LI
05/01/2018

KEVIN M KRUDYS
05/01/2018

YUXIN MEN
05/02/2018