# Clinical Pharmacology Review

| | |
|---|---|
| PRODUCT (Generic Name): | Perampanel |
| PRODUCT (Brand Name): | FYCOMPA® |
| sNDA: | 202834/s-014 (sequence 0159)<br>208277/s-002 (sequence 0036) |
| DOSAGE FORM: | Tablet, oral suspension |
| ROUTE of ADMINISTRATION: | Oral |
| INDICATION: | Monotherapy and adjunctive therapy for the treatment of partial-onset seizures and primary generalized tonic clonic seizures in patients 4 years of age and older |
| SUBMISSION DATE: | 03/28/2018 |
| APPLICANT: | Eisai 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

Fycompa® (perampanel) is currently approved in the U.S. for treatment (monotherapy and adjunctive therapy) of partial onset seizures (POS) and adjunctive therapy for the treatment of primary generalized tonic-clonic (PGTC) seizures in patients 12 years of age and older. Supplement 14 / Supplement 2, an efficacy supplement, was submitted under NDA 202,834 / NDA 208277 to pursue an indication for Fycompa for the treatment (monotherapy and adjunctive therapy) of POS and PGTC seizures in patients 2 years of age and older using extrapolation. Specifically, the current submission involves efficacy extrapolation from adult patients to pediatric patients and extrapolation from adjunctive therapy to monotherapy.

1) Extrapolating perampanel adjunctive therapy from adults to children 2 years of age and older for POS:
   In response to DNP's policy for extrapolation of efficacy for adjunctive therapy, the Applicant provided a pharmacokinetic analysis to determine a dosing regimen that would provide similar perampanel exposure (at levels demonstrated to be effective in adults) in pediatric subjects 2 years of age and older to perampanel exposure in adult subjects with POS. Based on review of the data, OCP has concluded that the Applicant has only provided adequate data to support a dosing regimen that would provide similar perampanel exposure in patients down to 4

years of age. The lack of adequate support for extrapolation in the 2 to 4 age group is due to the modest sample size of patients with PK data in this age range (n=4) and the fact that these patients received a maintenance dose level less than 1/3 of the minimum proposed maintenance dose level. Another important consideration was that perampanel pharmacokinetics do not appear to scale with weight as expected, which implies that adults and children should have the same dosing recommendations. Given this unexpected finding and the general paucity of data in this age group, the review team recommends that further pharmacokinetic data in patients age 2 to < 4 years are needed in this population before dosing recommendations are made. A PMR will be issued to address these data.

2) Extrapolating perampanel monotherapy from adjunctive therapy in children for the treatment of POS:
To support use of perampanel as monotherapy for the treatment of POS based on extrapolation, the proposed dosages of a drug, when used as monotherapy, should result in exposures that are similar to those demonstrated to be safe and effective when the drug is used as adjunctive therapy for the treatment of POS. The approved Fycompa label recommends a greater starting dose level (4 mg with concomitant moderate or strong 3A4 inducers versus 2 mg without these inducers). This existing label language for patients age 12 years and older is appropriate for application to the proposed indication in patients age 4 years and older.

The DNP does not currently accept extrapolation of PGTC efficacy for either adjunctive therapy to monotherapy nor adult patients to pediatric patients. Thus, no changes will be made to the PGTC indication.

The Fycompa dosage regimen that OCP recommends for treatment of POS in pediatric patients age 4 years and older is shown in **Table 1**.

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

| **Concomitant Medication Status** | **Initial Dosage** | **Titration Step** | **Minimum and Maximum Maintenance Dosage** |
|---|---|---|---|
| With concomitant use of moderate or strong 3A4 inducers | 4 mg once daily | Increase by 2 mg no more frequently than every week | 12 mg once daily |
| Without concomitant use of moderate or strong 3A4 inducers | 2 mg once daily | Increase by 2 mg no more frequently than every week | 8 to 12 mg once daily |

As the oral suspension and oral tablet have comparable bioavailability, the dose recommendations for the tablet are applicable to the oral suspension.

## 2 RECOMMENDATIONS

The Office of Clinical Pharmacology reviewers have reviewed NDA 202834 Supplement-014 and NDA 208277 Supplement-002 for Fycompa® (perampanel). The Applicant's submission is acceptable from the perspective of the Office of Clinical Pharmacology and we recommend approval for POS patients age 4 years and older provided that an agreement is reached between the Applicant and Agency regarding labeling language. A post-marketing requirement is recommended to collect additional data in POS patients 2 to 4 years of age. No changes are to be made regarding patients with the PGTC indication as neither extrapolation of adult PGTC efficacy to pediatric patients nor extrapolation of adjunctive PGTC efficacy to monotherapy are approaches currently accepted by DNP.

## 3 BACKGROUND

Fycompa® (perampanel) is a non-competitive antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor on post-synaptic neurons. Fycompa is approved in the U.S. as monotherapy or adjunctive therapy for the treatment of POS and as adjunctive therapy for treatment of PGTC seizures in patients with epilepsy 12 years of age and older. In this supplemental NDA, the Applicant seeks an indication for Fycompa as monotherapy and adjunctive therapy for the treatment of POS and PGTC seizures in patients 2 years of age and older based on extrapolation of adult data.

## 4 CLINICAL DEVELOPMENT IN PEDIATRIC PATIENTS

Phase 2 and Phase 3 studies of Fycompa in pediatric subjects include Study 311 and Study 232. Applicant submitted PK and PKPD analysis reports 007r and 015r.

**Study E2007-G000-311 (Phase 3)**: Study 311 is an open-label, multicenter study with an extension phase to evaluate the safety, tolerability, and exposure-efficacy relationship of perampanel oral suspension when administered as an adjunctive therapy for up to 23 weeks (up to 11 weeks titration, up to 12 weeks maintenance) in n=157 pediatric subjects (age 4 to less than 12 years) with inadequately controlled POS or PGTC seizures. Perampanel was administered once daily at bedtime.

Subjects receiving concomitant enzyme-inducing anti-epileptic drugs (EIAEDs) initiated at 4 mg/day and increased the daily dose by 2 mg every 1-2 weeks towards a target of 12 mg/day (with option to increase up to 16 mg/day, depending on tolerability).

Subjects not receiving EIAEDs (as well as all subjects in Japan, regardless of concomitant medication use) initiated at 2 mg/day and increased the daily dose by 2 mg every 1-2 weeks towards a target of 8 mg/day (with option to increase up to 12 mg/day, depending on tolerability). One PK sample was collected at any time during the visit at week 15, the visit at week 19 and the visit at week 23. The study plan also states that a PK sample was to be

collected at the occurrence of serious adverse events, severe unexpected adverse events, and early discontinuation.

**Study E2007-G000-232 (Phase 2)**: Study 232 is an open-label pilot study with an extension phase to evaluate the pharmacokinetics, and to generate preliminary safety, tolerability, and efficacy of perampanel oral suspension when given as an adjunctive therapy for 11 weeks (7 weeks titration, 4 weeks maintenance) in n=50 pediatric subjects from 2 years to less than 12 years of age with epilepsy. Perampanel was administered once daily at bedtime. Subjects were administered 0.015, 0.03, 0.06, 0.09, 0.12, 0.15, and 0.18 mg/kg/day during weeks 0, 1, 2, 3, 4, 5, and 6, respectively.

One PK sample was collected at any time during the visit on Days 8, 36, 64, and 78 (Weeks 1, 5, 9, and 11). The study plan also states that a PK sample was to be collected at serious adverse events, severe unexpected adverse events, and early discontinuation.

**CPMS-E2007-015R-v1**: Report 015R describes population pharmacokinetic and pharmacokinetic / pharmacodynamic analyses of perampanel in pediatric subjects (age 2 to less than 12 years) with inadequately controlled partial-onset seizures or primary generalized tonic-clonic seizures from Study 311 and Study 232.

[*Reviewer comment: PPK report 015R is the updated version of report 007R. Pediatric patients included in report 015R originated from studies 232 and 311. Pediatric patients included in report 007R originated from study 232. In addition, the Applicant based dosing recommendations in this supplement on the results of report 015R. Thus, as report 015R effectively replaces report 007R, report 007R will not be further discussed in this review.*]

## 5 RESULTS OF APPLICANT'S POPULATION PK ANALYSES

The Applicant utilized population PK analyses (report CPMS-E2007-015R-v1) to support the proposed dosing regimen in pediatric patients less than 12 years of age. The simulations in the population PK (PPK) report were conducted with the PPK model which was built using PK data from pediatric patients, adult patients, and adult healthy volunteers.

Population PK Model: The following is a summary of the PPK model. For details regarding the PPK model development, please refer to Appendix A.

The Applicant utilized data from 20 Phase 1 studies in adult healthy volunteers, one Phase 3 study in subjects with PGTC seizures (Study 332), four Phase 3 studies in subjects with POS (Studies 304, 305, 306 and 335), one Phase 3 study in pediatric subjects with POS and PGTC (Study 311) and two Phase 2 studies in subjects with inadequately controlled POS (Study 235) and a Phase 2 study in pediatric subjects with various types of epilepsy (Study 232).

The final model utilizes two compartments, formulation-specific first-order absorption, and was parameterized in terms of Cl/F, Q/F, $V_1$/F, and $V_2$/F. Covariates for clearance

include use of carbamazepine, use of oxcarbazepine/phenytoin, and use of topiramate/phenobarbital. Weight was the only covariate on Q/F, $V_1$/F, and $V_2$/F. Weight was related to $V_1$/F, Q/F and $V_2$/F using allometric scaling based on body weight normalized to 66 kg.

The Applicant determined that weight was not to be covariate in the final model because when including weight as a covariate on clearance via allometric scaling (normalized to 66 kg body weight), the coefficient estimate is nearly zero (coefficient estimate was 0.0285 in run pk-base3-wt-estimatedscaling-output.txt).

The final model parameter estimates are found in **Table 2**.

**Table 2: Parameter Estimates from the Final Population PK Model (pk-final-refined-ctl.txt)**

| | | NONMEM Estimate | |
|---|---|---|---|
| **Parameter** | **Point Estimate** | **%RSE** | **95% CI** |
| ***Apparent clearance: CL/F=$\Theta_1$*$\Theta_{13}$^CBZ*$\Theta_{14}$^OXC/PHEN*$\Theta_{15}$^TOP/FENO*** | | | |
| Basal CL/F ($\Theta_1$; L/h) | 0.590 | 1.17 | 0.576-0.604 |
| Effect of Carbamazepine ($\Theta_{13}$) | 2.99 | 1.13 | 2.92-3.06 |
| Effect of Oxcarbazepine/Phenytoin ($\Theta_{14}$) | 1.99 | 2.74 | 1.88-2.10 |
| Effect of Topiramate/Phenobarbital ($\Theta_{15}$) | 1.20 | 2.93 | 1.13-1.27 |
| ***Apparent central volume of distribution: V1/F= $\Theta_2$*(WGT66)^ $\Theta_{10}$*** | | | |
| *Basal V1/F ($\Theta_2$; L)* | 29.6 | 1.92 | 28.5-30.7 |
| *Effect of Weight ($\Theta_{10}$)* | 0.438 | 19.0 | 0.275-0.601 |
| ***Inter-compartment Clearance: Q/F= $\Theta_3$*(WGT66)^ $\Theta_{11}$*** | | | |
| *Q/F ($\Theta_3$; L/h)* | 7.09 | 3.03 | 6.67-7.51 |
| *Effect of Weight ($\Theta_{11}$)* | 0.744 | 19.8 | 0.456-1.03 |
| ***Apparent peripheral volume of distribution: V2/F= $\Theta_4$*(WGT66)^ $\Theta_{12}$*** | | | |
| *Basal V2/F ($\Theta_4$; L)* | 39.1 | 2.33 | 37.3-40.9 |
| *Effect of Weight ($\Theta_{12}$)* | 1.12 | 10.0 | 0.900-1.34 |
| ***Ka (1/h)*** | | | |
| Ka for tablet fasted ($\Theta_5$; 1/h) | 3.39 | -- | |
| Ka for tablet fed ($\Theta_6$; 1/h) | 0.514 | -- | |
| Ka for suspension fasted ($\Theta_7$; 1/h) | 1.99 | -- | |
| Ka for suspension fed ($\Theta_8$; 1/h) | 0.318 | -- | |
| **ALAG1** | | | |
| ALAG1 ($\Theta_9$; h) | 0.222 | -- | |

[*Reviewer comment: The table above shows the structural PK parameters. The full set of PK parameter estimates can be found in* ***Table 7*** *in the appendix.*]

*Source: cpms-e2007-015r-v1.pdf, page 57 of 379 (sequence 0159)*

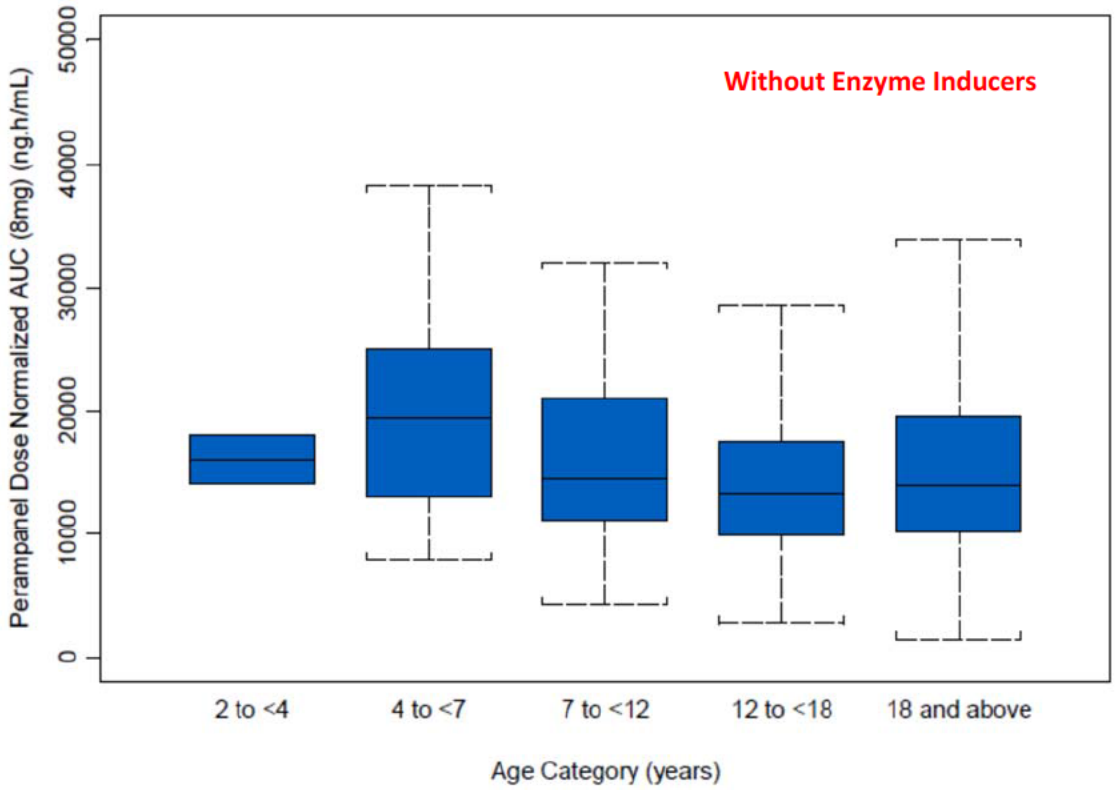
Applicant's PK Simulations to Support Pediatric Dosing:

*Simulation Methodology*: The Applicant utilized two different PK simulation approaches to support their proposed dose recommendations in pediatric patients age 2 to < 12 years of age.

Individual PK Simulations:

For the first PK simulation approach, individual PK parameter estimates and dosing history for all subjects in Phase 2/3 studies were utilized to predict $AUC_{ss}$ (computed as Dose / Cl), $C_{av,ss}$ computed as ($AUC_{ss}$ / 24), and $AUC_{ss}$ dose-normalized to 8 mg. These exposure metrics were simulated for each subject in the Phase 2/3 trials using the same maintenance dose level that was administered in these trials. The comparisons of exposures for the range of maintenance dose levels (normalized to the 8 mg dose level for purposes of comparison) are presented in **Figure 1** (in subjects not receiving concomitating enzyme-inducers in the Phase 2/3 trials) and in **Figure 2** (in subjects receiving concomitating enzyme-inducers in the Phase 2/3 trials)

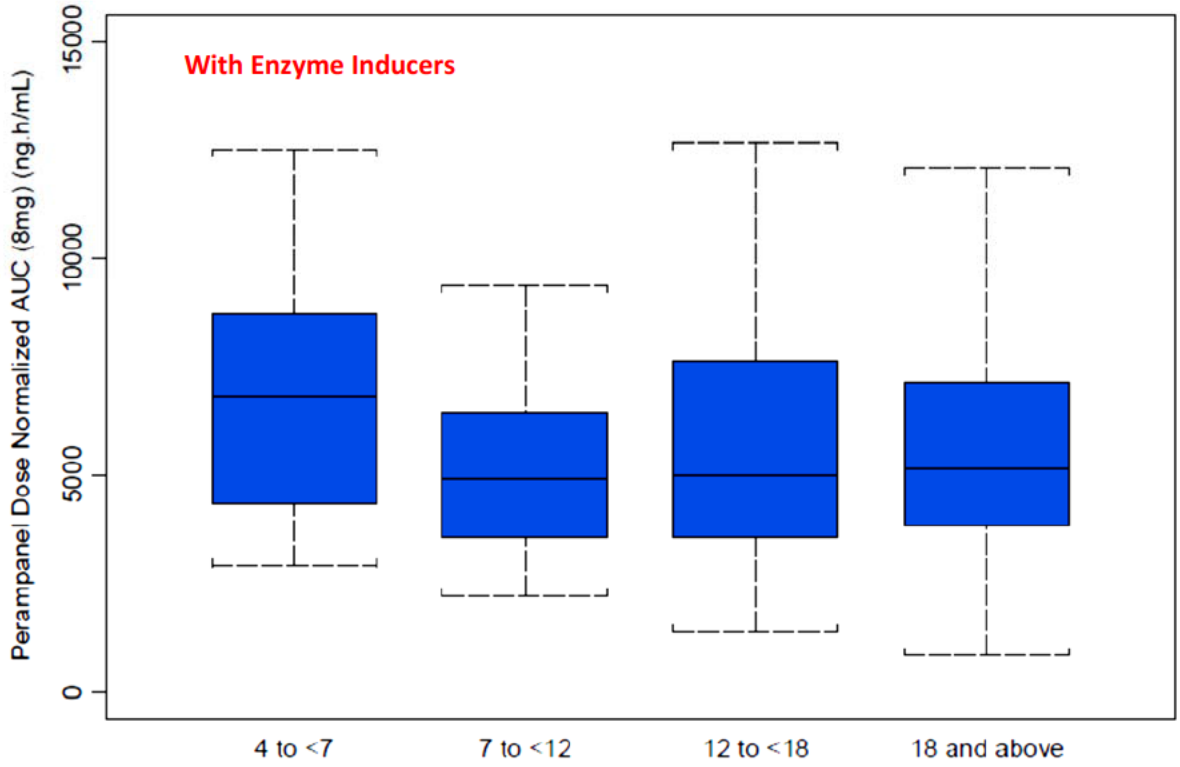
**Figure 1: Applicant's Model-Predicted $AUC_{ss}$ Dose Normalized to 8 mg by Age Group In Patients Not Receiving Enzyme-Inducers**




*Source: cpms-e2007-015r-v1.pdf, page 65 of 379 (sequence 0159)*

[*Reviewer comment: The exposures in **Figure 1** are dose-normalized to 8 mg once daily. Though the n=4 patients age 2 to < 4 years appear to have comparable dose-normalized exposure to adults, the highest maintenance dose in this patient group is 2.5 mg once daily.*]

**Figure 2: Applicant's Model-Predicted $AUC_{ss}$ Dose Normalized to 8 mg by Age Group In Patients Receiving Enzyme-Inducers (CBZ, OXC/PHEN, TOP/PHENO)**




*Source: cpms-e2007-015r-v1.pdf, page 65 of 379 (sequence 0159)*

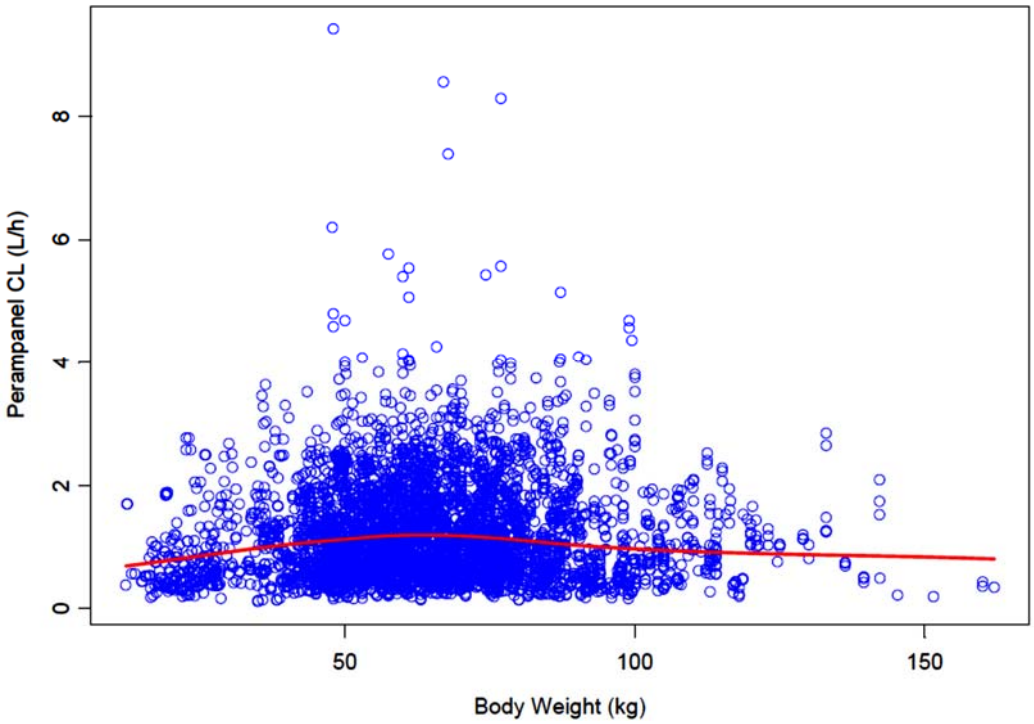
[*Reviewer comment: None of the patients age 2 to < 4 years whom provided PK data received concomitant EIAEDs. Thus, there is no boxplot for pediatric patients age 2 to < 4 in* **Figure** *2.*]

Population PK Simulations:

For the second PK simulation approach, the Applicant utilized the population PK model, described in **Table 2**, to conduct population PK simulations to assess the 8 mg/day maintenance dose level in patients age 2 to < 12- years. As in the first PK simulation approach, pediatric patients were grouped as age 2 to < 4 years, 4 to < 7 years, 7 to < 12 years, and 12 to < 18 years for comparison with adults.

The approved dosing regimen for adolescent patients (age 12 to < 18 years) is identical to the adult dosing regimen. The applicant states that clearance is independent of body weight and generated a plot of predicted perampanel clearance as a function of body weight to support this claim (see **Figure 3**).

**Figure 3: Individual Predicted Perampanel Clearance Versus Body Weight for All Phase 2/3 Patients**




*Source: cpms-e2007-015r-v1.pdf, page 68 of 379 (sequence 0159)*

Based on the data in **Figure 3**, and as well as the final population PK model which did not include weight as a covariate on clearance (e.g. the allometric scaling coefficient estimate was close to zero; 0.0285), the Applicant proposed "flat", non-weight-based dosing in pediatric patients age 2 to < 12. As the population PK model includes an effect of enzyme-inducing concomitant medications as a covariate on perampanel Cl/F, the Applicant performed PK simulations in a scenario with concomitant enzyme inducer medication and another scenario without concomitant enzyme-inducing medication.

The Applicant conducted bioavailability comparisons of the exposures simulated for the proposed 8 mg/day maintenance dose level proposed for each pediatric age group < 12 years of age versus the exposures simulated for the approved 8 mg/day maintenance dose level for adult patients age ≥ 18 years. For reference, the Applicant also included simulations of the approved 8 mg/day maintenance dose level in the age group of 12 to < 18 years. The geometric mean ratios and the corresponding 90% confidence interval of the comparisons of simulated exposures are presented in **Table 3**.

**Table 3: Bioavailability Comparison of Simulated Perampanel $C_{max,ss}$ and $AUC_{ss}$ for a Maintenance Dose of 8 mg once daily Fycompa in the Presence and Absence of Carbamazepine or Oxcarbazepine/Phenytoin**

| CBZ | OXC or FENY | Dose (mg) | Test | Ref | Ratio | Lower 90% CI | Upper 90% CI |
|---|---|---|---|---|---|---|---|
| | | | **Ln(Css,max)** | | | | |
| No | No | 8 | 2 to < 4 yrs | ≥18 yrs | 101 | 92 | 111 |
| No | No | 8 | 4 to < 7 yrs | ≥18 yrs | 91 | 82 | 100 |
| No | No | 8 | 7 to < 12 yrs | ≥18 yrs | 94 | 85 | 104 |
| No | No | 8 | 12 to < 18 yrs | ≥18 yrs | 108 | 98 | 119 |
| No | Yes | 8 | 2 to < 4 yrs | ≥18 yrs | 108.5 | 98.1 | 119.8 |
| No | Yes | 8 | 4 to < 7 yrs | ≥18 yrs | 105.8 | 95.7 | 116.9 |
| No | Yes | 8 | 7 to < 12 yrs | ≥18 yrs | 101.7 | 92.0 | 112.4 |
| No | Yes | 8 | 12 to < 18 yrs | ≥18 yrs | 111.8 | 101.1 | 123.5 |
| Yes | No | 8 | 2 to < 4 yrs | ≥18 yrs | 112.5 | 102.2 | 123.9 |
| Yes | No | 8 | 4 to < 7 yrs | ≥18 yrs | 108.0 | 98.1 | 118.9 |
| Yes | No | 8 | 7 to < 12 yrs | ≥18 yrs | 102.8 | 93.4 | 113.2 |
| Yes | No | 8 | 12 to < 18 yrs | ≥18 yrs | 113.0 | 102.6 | 124.4 |
| | | | **Ln(AUCss)** | | | | |
| No | No | 8 | 2 to < 4 yrs | ≥18 yrs | 101 | 91 | 112 |
| No | No | 8 | 4 to < 7 yrs | ≥18 yrs | 91 | 82 | 100 |
| No | No | 8 | 7 to < 12 yrs | ≥18 yrs | 98 | 89 | 109 |
| No | No | 8 | 12 to < 18 yrs | ≥18 yrs | 111 | 100 | 123 |
| No | Yes | 8 | 2 to < 4 yrs | ≥18 yrs | 98.6 | 87.9 | 110.6 |
| No | Yes | 8 | 4 to < 7 yrs | ≥18 yrs | 99.6 | 88.8 | 111.7 |
| No | Yes | 8 | 7 to < 12 yrs | ≥18 yrs | 99.4 | 88.6 | 111.4 |
| No | Yes | 8 | 12 to < 18 yrs | ≥18 yrs | 108.3 | 96.6 | 121.5 |
| Yes | No | 8 | 2 to < 4 yrs | ≥18 yrs | 98.6 | 87.9 | 110.6 |
| Yes | No | 8 | 4 to < 7 yrs | ≥18 yrs | 99.6 | 88.8 | 111.7 |
| Yes | No | 8 | 7 to < 12 yrs | ≥18 yrs | 99.5 | 88.7 | 111.6 |
| Yes | No | 8 | 12 to < 18 yrs | ≥18 yrs | 108.4 | 96.7 | 121.6 |

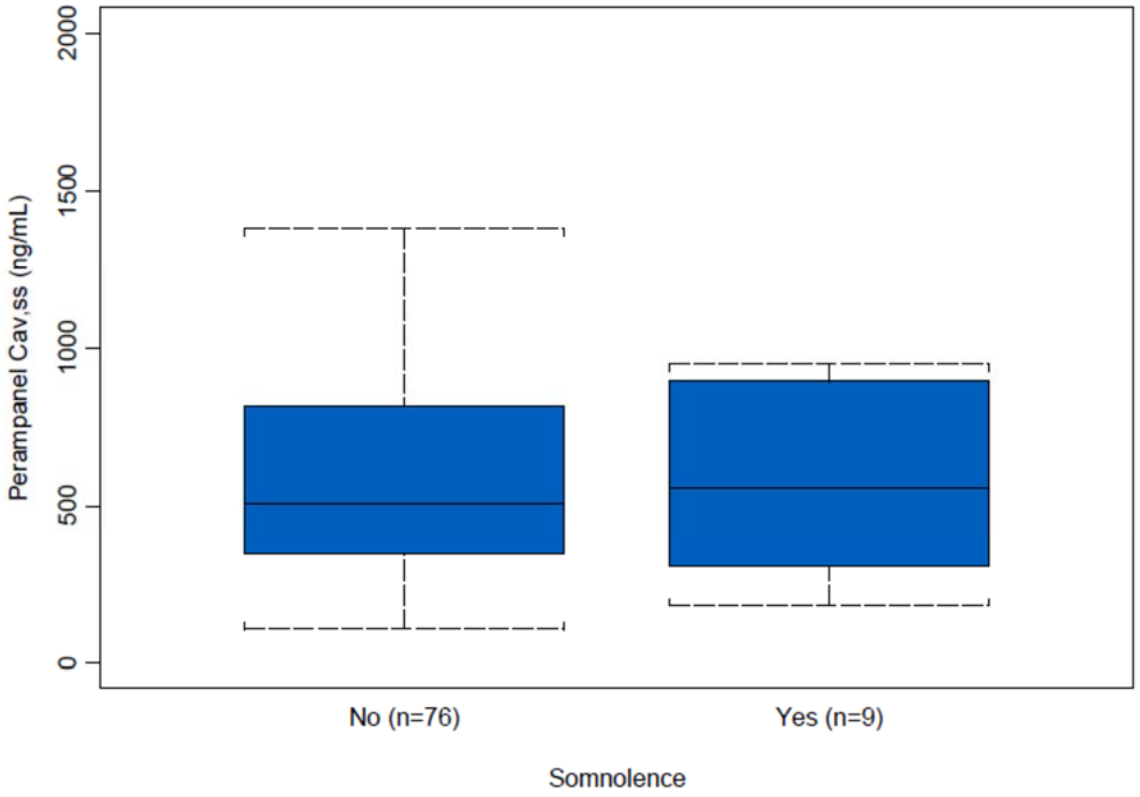
*Source: cpms-e2007-015r-v1.pdf, page 69 of 379 (sequence 0159)*

Based on the aforementioned PK simulations (**Figure 1**, **Figure 2**, and **Table 3**), Applicant concludes that there is a major overlap in exposure across age groups when receiving concomitant enzyme-inducing medication and across age groups when not receiving concomitant enzyme-inducing medication.

Exposure-Response Analyses for Safety:

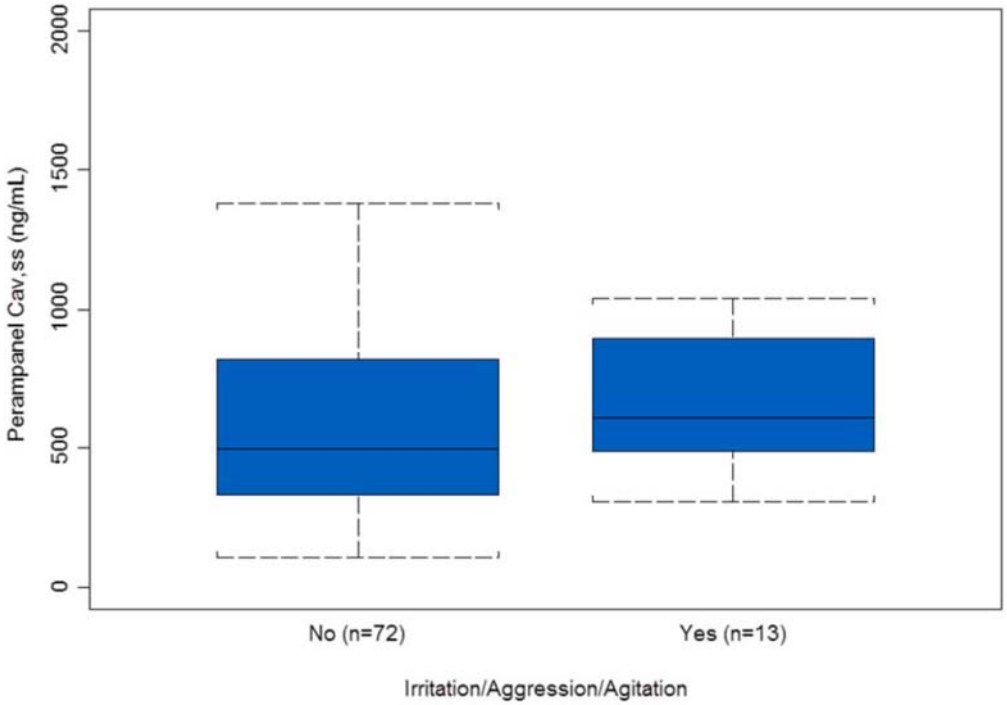
The Applicant performed a graphical exposure-AE analysis based on adverse events reported in Study 311. The Applicant plotted the distribution of predicted $C_{av,ss}$ versus occurrence of treatment emergent AEs (TEAEs) occurring in 5 or more subjects including nasopharyngitis, somnolence, irritability/aggression/agitation, bradyphrenia, gastroenteritis, pyrexia, upper respiratory infection and vomiting. The Applicant noted a possible exposure-AE relationship for only two of the TEAEs, which happened to be two of the most common TEAEs; somnolence (which occurred in 10.6% of patients), and irritability/aggression/agitation (15.3%). Plots of the observed exposures in patients that experienced these adverse events versus observed exposures in patients that did not experience these adverse events are displayed in **Figure 4** and **Figure 5**.

**Figure 4: Distribution of Predicted $C_{av,ss}$ Versus Occurrence of Somnolence in Pediatric Study 311**




*Source: cpms-e2007-015r-v1.pdf, page 96 of 379 (sequence 0159)*

**Figure 5: Distribution of Predicted $C_{av,ss}$ Versus Occurrence of Irritation / Aggression / Agitation in Pediatric Study 311**




*Source: cpms-e2007-015r-v1.pdf, page 95 of 379 (sequence 0159)*

The Applicant applied logistic regression modeling to further assess the relationship between predicted $C_{av,ss}$ and AE occurrence for irritability / aggression / agitation as well as somnolence. The results demonstrate no statistically-significant effect of perampanel exposure on the occurrence of aggression/agitation/irritability or on somnolence was revealed from PK/PD modeling. The Applicant concludes that no significant relationship between any of these AEs and exposure was found. However, the Applicant acknowledges that these results should be viewed with caution due to the limited number of subjects experiencing AEs in Study 311.

[*Reviewer comment: The clinical review team has indicated that there are no safety signals identified in the observed clinical trials.*]

Exposure-Response Analyses for Efficacy:

Report cpms-e2007-015r-v1.pdf also contains the results of the Applicant's exposure-response analyses. Exposure-response analyses were conducted for 28-day average seizure frequency for POS, 28-day average seizure frequency for PGTC subjects, responder analysis for POS, and cognition. All these analyses were conducted using data from pediatric patients age 4 years and older. However, considering that extrapolation of POS efficacy from adult to pediatric patients based on exposure matching is already accepted by the Division, the exposure-response analysis for POS efficacy does not warrant further review. The exposure-response analysis for PGTC efficacy is not applicable as there is

currently no policy regarding extrapolation of PGTC efficacy from adult to pediatric patients.

The Applicant's proposed dosing regimen for POS patients age 2 to < 12 years of age is shown in **Table 4**.

**Table 4: Applicant's Proposed Fycompa Dosage Schedule for Pediatric Patients Aged 2 to 17 Years Old**

| Concomitant Medication Status | Initial Dosage | Titration Step | Minimum and Maximum Maintenance Dosage |
|---|---|---|---|
| With concomitant use of moderate or strong 3A4 inducers | 4 mg once daily | Increase by 2 mg no more frequently than every week | 12 mg once daily |
| Without concomitant use of moderate or strong 3A4 inducers | 2 mg once daily | Increase by 2 mg no more frequently than every week | 8 to 12 mg once daily |

[*Reviewer comment: The lack of weight effect on clearance is an unexpected finding considering the age range of patients.*

*Based on the available PK data and drug-interaction assessments from PK analyses, it is acceptable to apply the dose adjustment in patients receiving concomitant moderate and strong enzyme-inducing medication approved in the current label to pediatric patients age 4 to < 12 years.*

*However, for patients 2 to < 4 years, PK data were available from n=4 patients. In addition, the weight-based dosing administered to these n=4 patients (in Study 232) resulted in maintenance dose levels that were less than 1/3 of the minimum proposed maintenance dose of 8 mg once daily (1.75, 2.25, 2.25, and 2.50 mg once daily in the n=4 patients).*

*Also, the Applicant did not provide PK simulations to assess the adequacy of the titration regimen.*

*For these reasons, the reviewer conducted independent analyses to assess the dosing regimen (see Section 6 for details).*]

## 6 REVIEWER'S ANALYSES

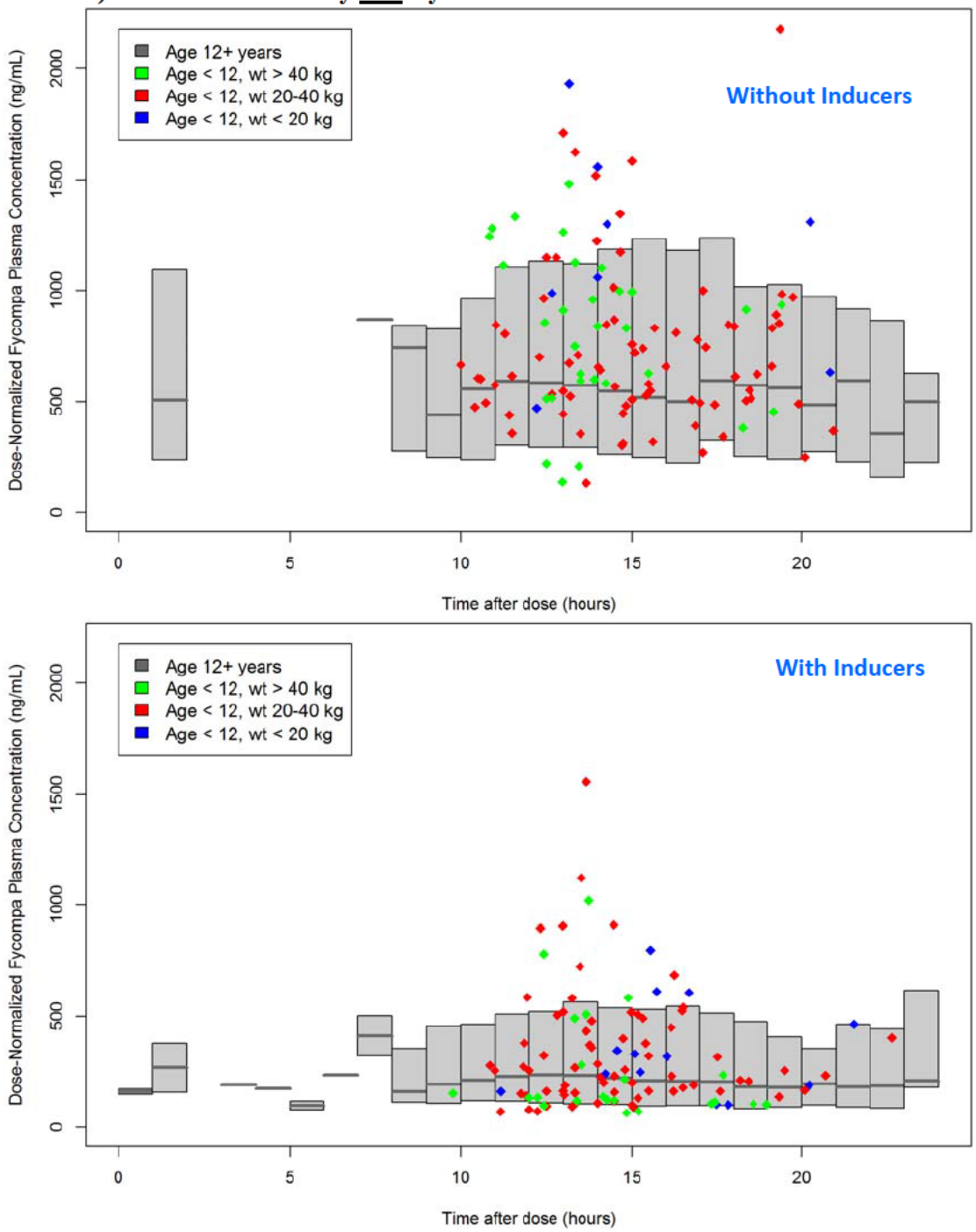
The lack of a weight effect on clearance is unexpected considering the age range of subjects that contributed PK data is 2 to 74 years. Also, the sample size for patients age 2 to < 4 years is small (n=4) and these n=4 patients received a maintenance dose level (1.75 to 2.5 mg once daily) that is less than 1/3 of the minimum proposed maintenance dose (8 mg once daily). For these reasons, the reviewer conducted independent analyses of the Applicant's PK data to further assess the proposed dosing regimen.

Maintenance Dose:

A graphical analysis was conducted to compare the observed PK data from pediatric patients in Study 311 and Study 232 with observed adult PK data. As patients received a range of dose levels, the PK data for adults and pediatric patients were dose-normalized to 8 mg. Dose-normalization to 8 mg is acceptable as, according to the current Fycompa label, the PK of perampanel is known to be dose-proportional after multiple-dose administration of 1-12 mg once daily and the maintenance dose levels for patients included in the population PK analyses were within this range.

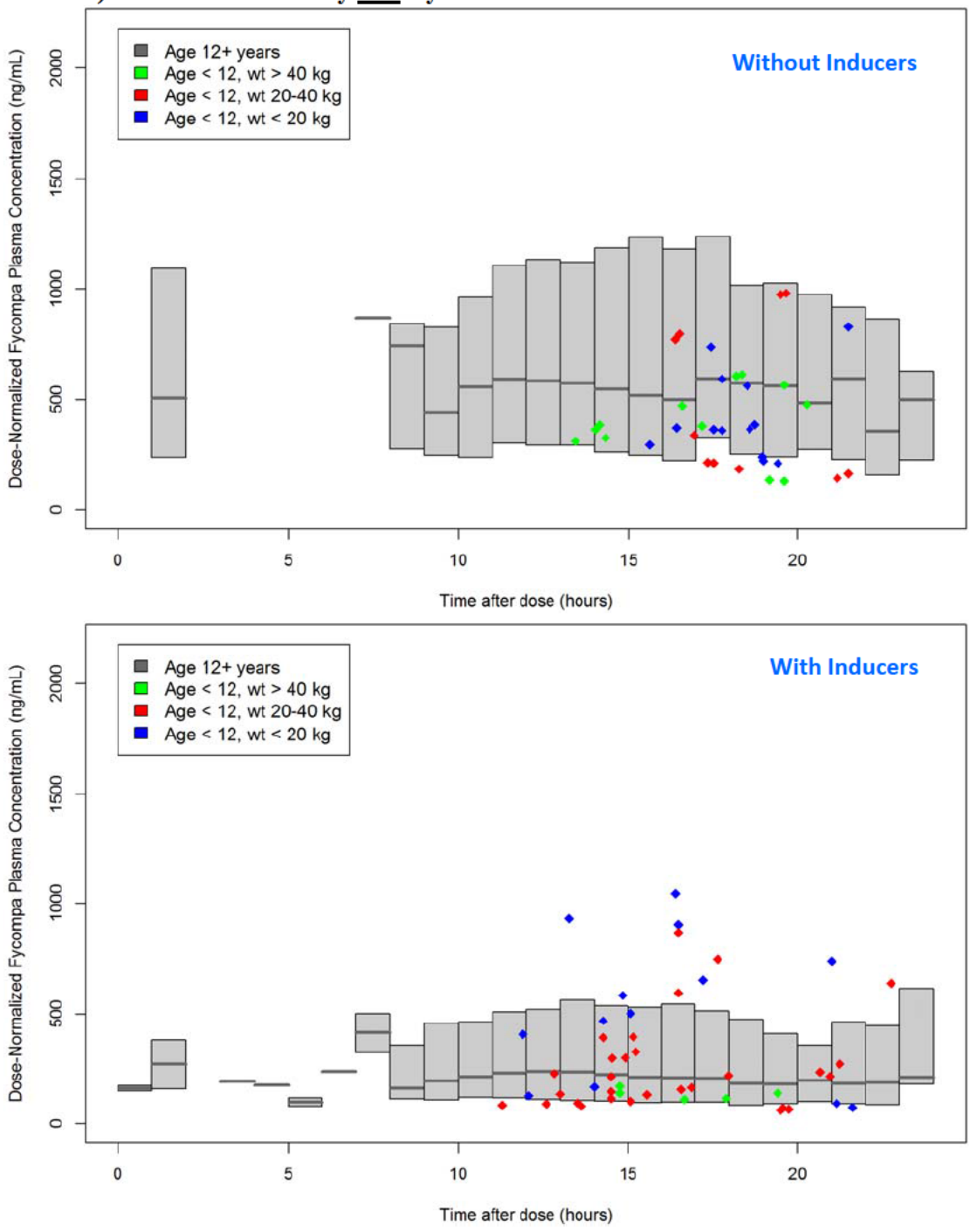
Patients receiving at least one concomitant medication that is a moderate or severe inducer of CYP3A4 (carbamazepine, carbamazepine, oxcarbazepine / phenytoin, topiramate / phenobarbital, or a combination thereof) were plotted separately from patients who received none of these inducers. In addition, perampanel PK was plotted as a function of time after last dose due to all the PK samples being acquired at steady-state and the 105-hour duration half-life. The comparisons the observed dose-normalized exposures between adult patients and pediatric patients in Phase 2/3 are shown in **Figure 6** and **Figure 7**.

**Figure 6: Observed Steady-State Perampanel Concentration Dose-Normalized to 8 mg from Phase 2/3 Studies in Adolescent and Adult Patients (304, 305, 306, 332, 235, and 355) and Pediatric Study 311 By Inducer Status**




*The green, red, and blue dots represent the observed perampanel plasma concentration values measured at the given time with respect to the previous dose administered in pediatric patients age < 12 years that weigh > 40 kg, 20 to 40 kg, and < 20 kg, respectively. The top and bottom of the grey box represent the 10th and 90th percentile of the observed exposures for patients age ≥ 12 years within a 1-hour time window. The dark grey horizontal line segment within each light grey box is the median observed exposure for patients age ≥ 12 years within the 1-hour time window.*

**Figure 7: Observed Steady-State Perampanel Concentration Dose-Normalized to 8 mg from Phase 2/3 Studies in Adult and Adolescent Patients (304, 305, 306, 332, 235, and 355) and Pediatric Study 232 By Inducer Status**




*The green, red, and blue dots represent the observed perampanel plasma concentration values measured at the given time with respect to the previous dose administered in pediatric patients age < 12 years that weigh > 40 kg, 20 to 40 kg, and < 20 kg, respectively. The top and bottom of the grey box represent the 10th and 90th percentile of the observed exposures for patients age ≥ 12 years within a 1-hour time window. The dark grey horizontal line segment within each light grey box is the median observed exposure for patients age ≥ 12 years within the 1-hour time window.*

Overall, the observed PK data from patients age 2 to < 12 years of age from Study 232 as well as 311 are generally within the range of concentrations in patients age > 12 years (as shown in **Figure 6** and **Figure 7**). Though it is an unexpected finding, the observed data suggest that adding weight as a covariate on clearance does not appear to improve the model fit (e.g. objective function increases when weight is put on clearance, allometric scaling coefficient estimate is close to zero) and that weight-based dosing doesn't appear to be necessary in patients age ≥ 4 years.

The sample size of patients age 2 to < 4 years with PK data is small (n=4). All n=4 patients were receiving concomitant inducers. In addition, these n=4 patients were receiving a maintenance dose that is less than 1/3 of the lowest proposed maintenance dose (e.g. less than 1/3 of 8 mg/day). Furthermore, use of PK modeling from older patients to predict exposures in patients age 2 to 3 years may not be a reliable approach to inform dose selection in this group due to the unexpected lack of weight effect on clearance. Even though an effect of weight on clearance is not evident in the current data set, we expect that at some point, a reduction in clearance will manifest that will result in a clinically-relevant exposure increase in young children. The risk of extending the proposed dosing regimen to younger patients (i.e., < 4 years) is that these patients may be overexposed if body size becomes an important factor at lower body weights.

**Overall, the proposed maintenance dose levels in pediatric patients age 4 years to < 12 years are likely to provide perampanel exposures no less than the exposures for patients age ≥ 12 years receiving the approved maintenance dose levels.**

The safety of the proposed dosing regimen is discussed in the next section regarding the initial dose and titration.

Initial Dose and Titration: The reviewer utilized the Applicant's population PK model to simulate the PK profile starting at the initial Fycompa dose and throughout titration. The approved initial dose is 4 mg once daily for patients receiving concomitant medications that are moderate to strong CYP3A4 inducers and 2 mg once daily for patients not receiving such concomitant medications. The approved dose increase during titration is +2 mg once daily no more frequently than at weekly intervals regardless of concomitant medication use.

The titration from 4 mg with inducer effects present and titration from 2 mg without inducer effects present were simulated in a typical adult patient up to a maximum dose of 12 mg once daily.

**Figure 8: Predicted PK Profile Over 9 Weeks From Initiation and Titration Through Steady-State for a 70-kg Adult Not Receiving Enzyme Inducers**

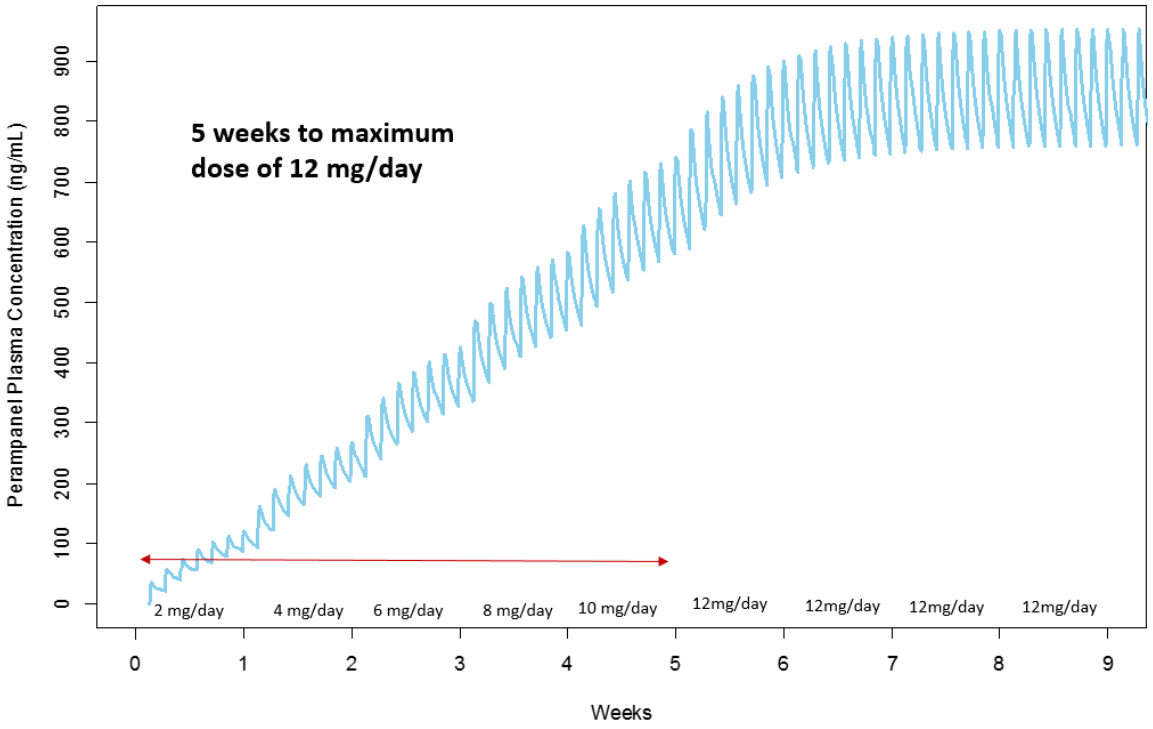
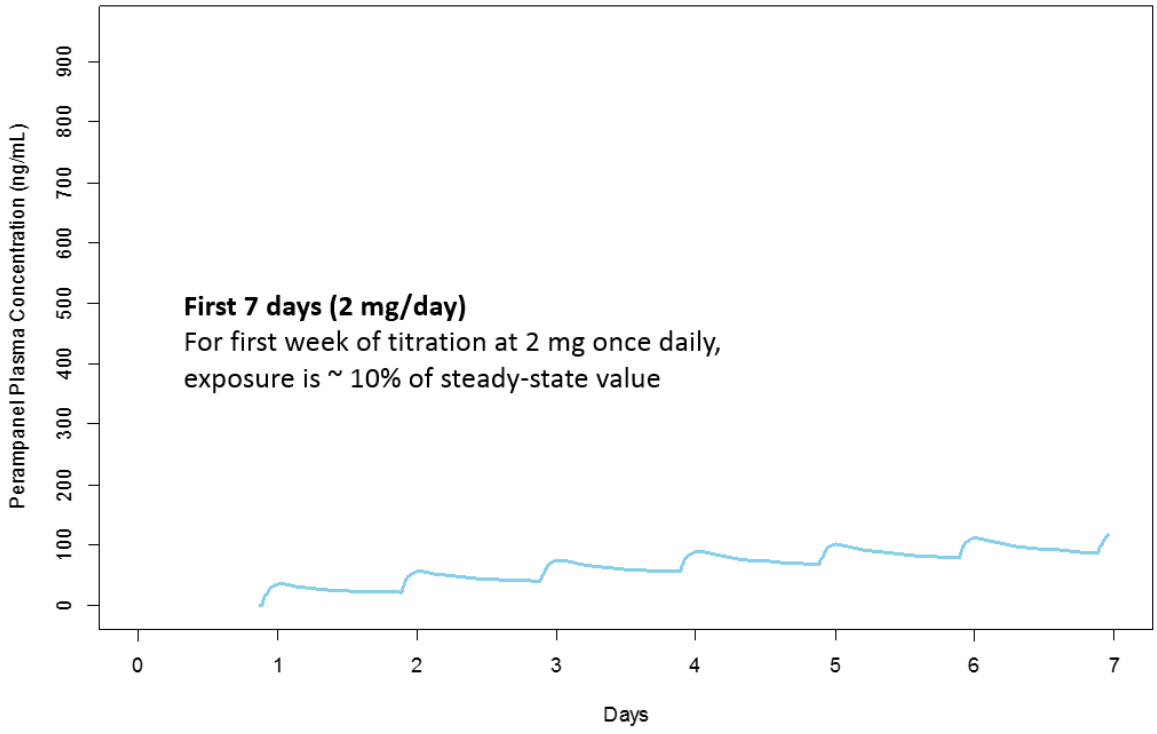
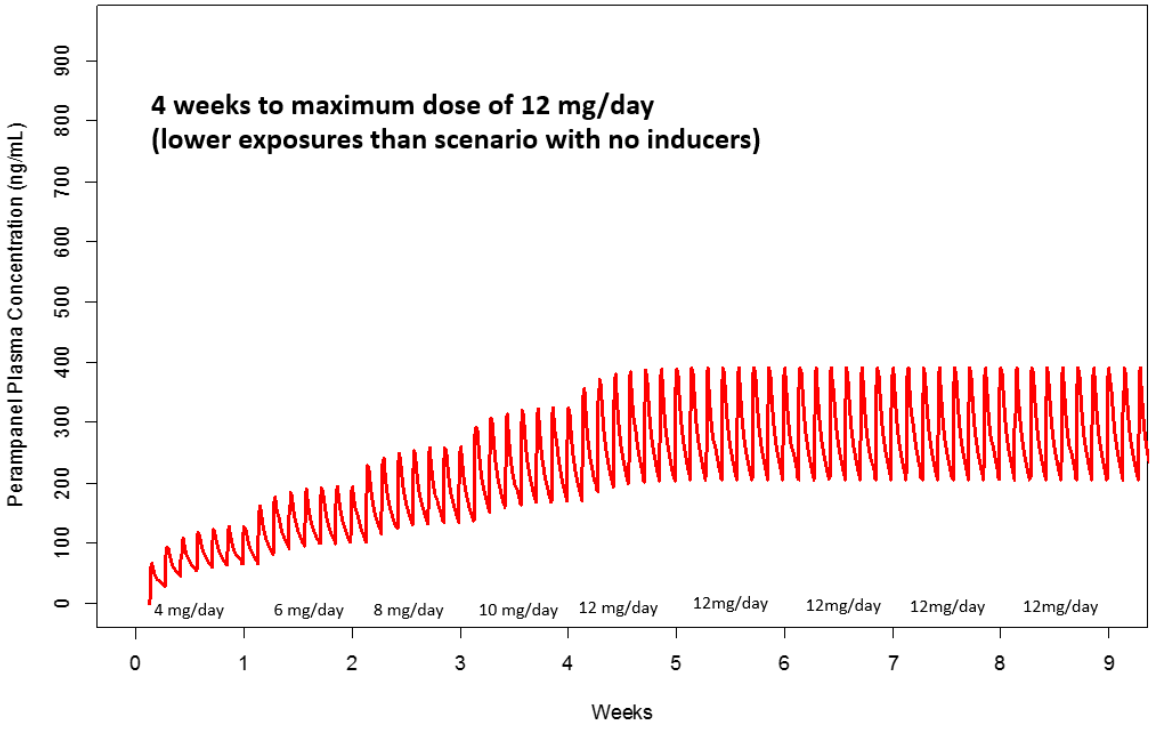



**Figure 9: Predicted PK Profile Over 7 Days from Initiation and Titration Through Steady-State for a 70-kg Adult Not Receiving Enzyme Inducers**



Based on **Figure 8** and **Figure 9**, after one full week of titration the exposure is approximately 10% of the steady-state exposure level. For patients receiving moderate or strong CYP3A4 enzyme inducers, the titration is even slower and results in a lower steady-state exposure (see **Figure 10**).

**Figure 10: Predicted PK Profile Over 9 Weeks from Initiation and Titration Through Steady-State for a 70-kg Adult Receiving Enzyme Inducers**




These simulations suggest a slow progression of perampanel concentrations toward steady-state levels. Even if there truly is a body weight effect on clearance that for some unknown reason is not evident in the available data, the low concentrations following the initial dose and gradual increase to steady-state provide comfort that titration will facilitate a reasonable progression toward an appropriate maintenance dose in the pediatric population.

In addition, the clinical review team has indicated that there are no safety signals identified in the observed clinical trials. **Overall, due to the lack of a safety signal and the modest rate of progression towards steady-state (e.g. ~10% of steady-state levels achieved after 1 week), the Applicant's proposal to apply the titration regimen currently approved in adults and adolescents to patients age ≥ 4 years is acceptable**.

## 7 ANALYTICAL SECTION

**Study E2007-G000-232 (Phase 2):** Perampanel concentrations from blood samples obtained in Study E2007-G000-232 were determined by a dried blood spot (DBS) liquid chromatography with tandem mass spectrometry (DBS LC-MS/MS) analytical method. In order to compare PK across studies, blood perampanel concentrations were converted to plasma perampanel concentrations using the blood:plasma ratio of 0.88 (based on cross validation of analytical assay in human plasma vs blood). The DBS method utilized the same detection instrumentation tandem mass spectrometry as the plasma assay method used for previous studies in adolescents and adults.

The lower limit of quantitation was 1.00 ng/mL and the upper limit of quantitation was 500.00 ng/mL. Accuracy and precision of QC samples were ≤15% (and ≤20% at LLQ), and calibration curves for the LC-MS/MS bioanalytical assay were within acceptable limits. Summary of bioanalytical methods used in the study E2007-G000-232 is provided in **Table 5**.

**Table 5: Summary of Bioanalytical Methods used in Study E2007-G000-232**

| | Project No. | Calibration Range (ng/mL) | QCs (ng/mL) | Inter-Run Precision (%CV) | Inter-Run Accuracy (%RE) |
|---|---|---|---|---|---|
| **Method Validation** | EIS/PER/10002 | 1.00 to 500.00 | 1.00, 3.00, 250.00, 400.00 | 3.93 to 9.09 | -2.00 to -0.30 |
| **Assay Performance** | EIS_PER_11004 | 1.00 to 500.00 | 1.00, 3.00, 250.00, 400.00 | 5.15 to 5.82 | -8.65 to 9.83 |

[*Reviewer comment: OCP previously questioned on the appropriateness of blood-to-plasma ratio value applied in the dried-blood-spot PK analyses. However, removing Study 232 from the PPK analyses has a negligible effect on the PPK parameter estimates.* ***As such, any potential inaccuracy in PK concentration measurement resulting from use of the DBS assay in Study 232 is not likely to have a relevant effect on the final PPK model.*** *See Appendix B for details.*]

**Study E2007-G000-311 (Phase 3)**: Plasma perampanel concentrations obtained in study E2007-G000-311 were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) analytical method.

The lower limit of quantitation was 1.00 ng/mL and the upper limit of quantitation was 500.00 ng/mL. Accuracy and precision of QC samples were ≤15% (and ≤20% at LLQ), and calibration curves for the LC-MS/MS bioanalytical assay were within acceptable limits. Summary of bioanalytical methods used in the study E2007-G000-311 is provided in **Table 6**.

**Table 6: Summary of Bioanalytical Methods used in Study E2007-G000-311**

| | Project No. | Calibration Range (ng/mL) | QCs (ng/mL) | Inter-Run Precision (%CV) | Inter-Run Accuracy (%RE) |
|---|---|---|---|---|---|
| **Method Validation** | EIS-R2850 | 1.00 to 500.00 | 1.00, 3.00, 50.00, 380.00 | 3.6 to 10.2 | -10.2 to -3.6 |
| **Assay Performance** | E2007-G000-311 | 1.00 to 500.00 | 3.00, 50.00, 380.00 | 3.1 to 6.6 | 0.0 to 2.4 |

Key label edits:

1. The Applicant's proposed lower age limit for the POS indication of ≥ 2 years has been changed to ≥ 4 years.
2. All proposed changes for the PGTC indication were removed.

The approved label will reflect the final language that were agreed upon with the Applicant.

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**:

**Pediatric and adult PPK Model for POS, PGTC (Report cpms-e2007-015r-v1.pdf, sequence 0159)**

Applicant developed a population PK model to characterize the pharmacokinetics of perampanel in adult and pediatric patients age 2 to < 12 years with epilepsy as well as healthy adults, assess the relationship between perampanel concentration with demographics and other covariates, and compare the PK with adolescents and adults patients with POS or PGTC. The PPK model was applied to address dose selection in pediatric patients age 2 to < 12 years.

**Summary of PK Data**:

There were 24123 measurable perampanel concentrations from n=2265 patients available for PK analyses. Subjects received 0.5 to 12 mg.

Studies: There were 20 Phase 1 studies in healthy subjects (001, 002, 003, 004, 005,006, 008, 009, 010, 013, 015, 016, 023, 024, 026, 028a, 029, 030, 037, 048a), 1 Phase 3 study in subjects with PGTC seizures (Study 332), 4 Phase 3 studies in subjects with partial-onset seizures (Studies 304, 305, 306 and 335), 1 Phase 3 study in subjects with POS and PGTC (Study 311) and 2 Phase 2 studies in subjects with inadequately controlled partial-onset seizures (Study 235) and in subjects with various types of epilepsy (Study 232).

Applicant utilized PK data from n=4 subjects age 2 to < 4 years; n=39 subjects age 4 to < 7 years, n=84 subjects age 7 to <12 years (for a total of 127 patients age 2 to < 12 years), n=226 age 12 to < 18 years, and n=1912 age 18 and older.

**Population PK Model**:

The structural model was a 2-compartment model with first order absorption and absorption lag time. PK parameters included Cl/F, V/F, and 4 unique $k_a$ (absorption rate constant) terms for tablet in the fasted state, tablet in the fed state, suspension in the fasted state, and suspension in the fed state.

Allometric Scaling: Allometric scaling was applied to $V_1/F$, Q/F, and $V_2/F$ with weight normalized to 66 kg.
Inter-individual variability: exponential
Residual variability: additive proportional error model

Final model parameters are shown in **Table 7**.

**Table 7: PK Parameter Estimates for Population PK Model for (pk-final-refined-ctl.txt)**

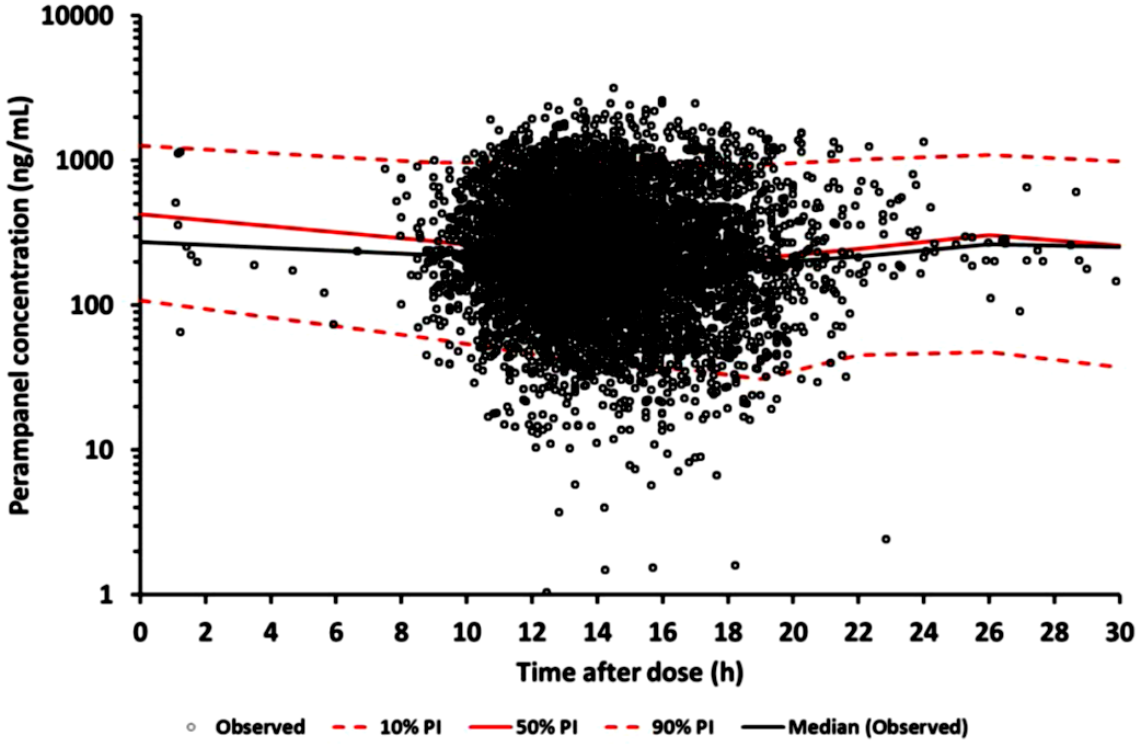
| | | NONMEM Estimate | |
|---|---|---|---|
| **Parameter** | **Point Estimate** | **%RSE** | **95% CI** |
| ***Apparent clearance: CL/F=$\Theta_1$* $\Theta_{13}$^CBZ* $\Theta_{14}$^OXC/PHEN* $\Theta_{15}$^TOP/FENO*** | | | |
| Basal CL/F ($\Theta_1$; L/h) | 0.590 | 1.17 | 0.576-0.604 |
| Effect of Carbamazepine ($\Theta_{13}$) | 2.99 | 1.13 | 2.92-3.06 |
| Effect of Oxcarbazepine/Phenytoin ($\Theta_{14}$) | 1.99 | 2.74 | 1.88-2.10 |
| Effect of Topiramate/Phenobarbital ($\Theta_{15}$) | 1.20 | 2.93 | 1.13-1.27 |
| ***Apparent central volume of distribution: V1/F= $\Theta_2$*(WGT66)^ $\Theta_{10}$*** | | | |
| *Basal V1/F ($\Theta_2$; L)* | 29.6 | 1.92 | 28.5-30.7 |
| *Effect of Weight ($\Theta_{10}$)* | 0.438 | 19.0 | 0.275-0.601 |
| ***Inter-compartment Clearance: Q/F= $\Theta_3$*(WGT66)^ $\Theta_{11}$*** | | | |
| *Q/F ($\Theta_3$; L/h)* | 7.09 | 3.03 | 6.67-7.51 |
| *Effect of Weight ($\Theta_{11}$)* | 0.744 | 19.8 | 0.456-1.03 |
| ***Apparent peripheral volume of distribution: V2/F= $\Theta_4$*(WGT66)^ $\Theta_{12}$*** | | | |
| *Basal V2/F ($\Theta_4$; L)* | 39.1 | 2.33 | 37.3-40.9 |
| *Effect of Weight ($\Theta_{12}$)* | 1.12 | 10.0 | 0.900-1.34 |
| ***Ka (1/h)*** | | | |
| Ka for tablet fasted ($\Theta_5$; 1/h) | 3.39 | -- | |
| Ka for tablet fed ($\Theta_6$; 1/h) | 0.514 | -- | |
| Ka for suspension fasted ($\Theta_7$; 1/h) | 1.99 | -- | |
| Ka for suspension fed ($\Theta_8$; 1/h) | 0.318 | -- | |
| **ALAG1** | | | |
| ALAG1 ($\Theta_9$; h) | 0.222 | -- | |
| ***Inter-individual variability(%CV)*** | | | |
| CL/F | 47.3 | 3.14 | |
| V1/F | 32.1 | 0.103 | |
| Q/F | 46.2 | 7.56 | |
| V2/F | 44.2 | 6.41 | |
| Ka | 84.1 | -- | |
| **Inter-occasion variability (%CV)** | | | |
| CL/F | 19.3 | 1.55 | |
| **Residual variability (%CV)** | | | |
| Proportional | 14.4 | 0.374 | |
| Additive | 0.355 | 4.85 | |
| Proportional (TAD≤1h) | 36.7 | 2.79 | |
| Additive (TAD≤1h) | 10.8 | 3.52 | |

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100;
CL/F = apparent clearance; V1/F = apparent central volume of distribution; Q/F=inter-compartment clearance; Ka = first order absorption rate constant; V2/F = apparent peripheral volume of distribution; ALAG1 = duration of zero order absorption; h = hour; WGT = body weight; CI = confidence interval; %CV = Square root of variance *100.

*Source: cpms-e2007-015r-v1.pdf, page 57 of 379 (sequence 0159)*

Key model diagnostics are presented in **Figure 11**.

**Figure 11: VPC Plot for Phase 2 and 3 PK Data**




*Source: cpms-e2007-015r-v1.pdf, page 59 of 379 (sequence 0159)*

[*Reviewer comment: The VPC for the Phase 1 data (figure not shown here) demonstrates that the model adequately represents the central tendency of the population PK data. The low concentration values are modestly over-predicted.*

*The VPC for the Phase 2 and 3 data demonstrate that the model appears to modestly over-predict the central tendency of the population PK data. PK data from the Phase 2 and Phase 3 studies have the PK samples acquired mainly between 8 hours post-dose and 20 hours post-dose. As such, it is not clear how well the model performs from 0-8 hours post-dose and between 20-30 hours post-dose.*

***Though the model presents modest error in the central tendency, the model is adequate for assessing the general change in perampanel PK values over time in PK simulations (see section 6 for details).***]

**Appendix B**:

**Assessment of Effect of Removing Study 232 on PPK Parameter Estimates**

Unlike study 311, Study 232 analyzed dried blood spots (DBS) to measure perampanel plasma concentration. OCP previously notified the Applicant regarding concerns of the accuracy of this method. OCP previously conveyed the following comment to the Applicant regarding the DBS method:

> "1: Does the Division agree that Study 311 will fulfill the PK analysis and long-term open label safety requirements to support an indication for the treatment of POS in patients 4 years and older that relies upon extrapolation, as outlined in the 12 Nov 2015 General Advice letter?
>
> *Final Response:*
>
> We agree. We recommend you also perform a PK analysis similar to what you proposed but use a dataset that excludes the PK data obtained from Study 232. This is because the concentrations from Study 232 were derived from dry-blood spot sampling, which was different from the methods used for all the other studies where plasma concentrations were directly measured, and there is some uncertainty about the converting factor from blood to plasma concentration., Thus, the PK data to be collected from Study 311 will form the main basis to support extrapolation."

*Source: Written Responses to a Type C interaction for NDA 202834 signed on 05/16/2016, page 4 of 7.*

OCP provided the following reviewer's note in the clinical pharmacology review of NDA 202834 signed on 05/18/2016 (the associated clinical pharmacology review for the aforementioned Type C interaction):

> "The converting factor from blood to plasma concentrations was calculated as 0.88 from an in vitro experiment cross-validating the plasma assay and DBS assay. The value was different from the blood-to-plasma ratio (0.55 – 0.59) determined from another in vitro study. The reason for such discrepancy is still unclear. If the value of 0.55-0.59 is used to convert blood concentrations from Study 232, the derived plasma concentrations will be higher than those calculated with the factor of 0.88 (please see the back-up slides for illustration). Such difference may affect the population PK results and predicted exposure of perampanel in patients aged 4 to 12 years old. It could potentially affect the dosing regimen in these patients targeted to result in similar exposure to those in adults to support extrapolation"

Based on the concerns previously laid out by OCP regarding the effect of the DBS assay method on the PPK analyses (and ultimately dose selection), the reviewer assessed the effect of removing study 232 on PPK parameter estimates. The final PPK model was run using a dataset excluding study 232 and the parameter estimates were compared with the estimates from the final run where study 232 is included. A comparison of the PK parameter estimates computed under these two scenarios is presented in **Table 8**.

**Table 8: Comparison of PPK Parameter Estimates in the Full PK Dataset and When Removing Study 232**

| Theta # | PK Parameter | Estimate With All Studies Present | Estimate when Study 232 is Removed | % Difference from "All Studies Present" |
|---|---|---|---|---|
| 1 | CL | 0.59 | 0.588 | -0.3 % |
| 2 | V1 | 29.6 | 29.5 | -0.3 % |
| 3 | Q | 7.09 | 7.11 | 0.3 % |
| 4 | V2 | 39.1 | 39.1 | 0 % |
| 10 | Wt on V1 | 0.438 | 0.467 | 6.6 % |
| 11 | Wt on Q | 0.744 | 0.719 | -3.4 % |
| 12 | Wt on V2 | 1.12 | 1.12 | 0 % |
| 13 | CBZ on CL | 2.99 | 2.99 | 0 % |
| 14 | OXC/FENY on CL | 1.99 | 1.98 | -0.5 % |
| 15 | FENO/TOP on CL | 1.2 | 1.2 | 0 % |

*The absorption lag and absorption rate constant values for tablet, suspension, fasted, and fed status (thetas 5 through 9) were fixed and thus left out of this comparison. CBZ = carbamazepine, OXC = oxcarbazepine, FENY = phenytoin, FENO = phenobarbital, TOP = topiramate.*

Overall, the effect of removing Study 232 from the PPK analyses has a negligible effect on the PPK parameter estimates. **As such, any PK measurement inaccuracy resulting from use of the DBS assay in Study 232 does not appear to affect the performance of the final PPK model.**

---

**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

---

/s/
---

MICHAEL A BEWERNITZ
09/24/2018

DAWEI LI
09/25/2018

YUXIN MEN
09/25/2018

KEVIN M KRUDYS
09/25/2018