Clinical Pharmacology Review

PRODUCT (Generic Name):	Perampanel
PRODUCT (Brand Name):	FYCOMPA®
sNDA:	202-834/s-005
DOSAGE FORM:	Tablet
DOSAGE STRENGTHS:	2, 4, 6, 8, 10, 12 mg
INDICATION:	Adjunctive therapy for primary generalized tonic-clonic seizures in patients of 12 years old and above
SUBMISSION DATE:	08/19/2014
SPONSOR:	Eisai Co.
Clinical Pharmacology REVIEWER:	Xinning Yang, Ph.D.
TEAM LEADER:	Kevin Krudys, Ph.D. (Pharmacometrics) Angela Men, M.D., Ph.D.
OCP DIVISION:	DCP I

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

1.1.1 Is there difference in the pharmacokinetics of perampanel between PGTC and POS patients?

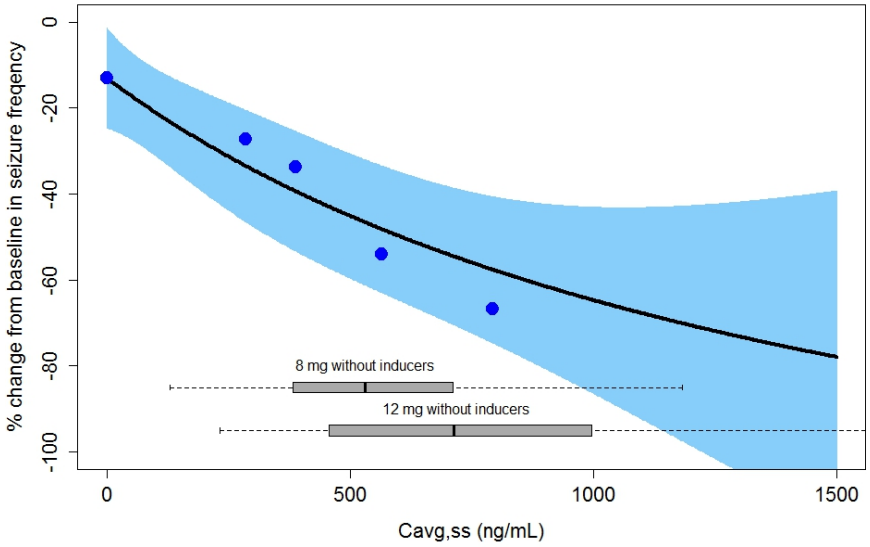
No, seizure type (partial-onset seizure (POS) vs. primary generalized tonic-clonic seizures (PGTC)) was not shown as a significant covariate on pharmacokinetics (PK) of perampanel.

1.1.2 Does the exposure-response relationship for seizure reduction support the proposed dose?

Yes, there was a clear exposure-response relationship for efficacy as measured by the percentage of change from baseline for average seizure frequency during titration and maintenance period (the primary efficacy endpoint).

The model-predicted pharmacokinetic-pharmacodynamic (PK/PD) relationship for perampanel from the reviewer's independent assessment is presented below, showing that the percentage change from baseline in seizure frequency decreases in a concentration-dependent manner in patients with PGTC seizures. The model predicted that a higher dose of 12 mg perampanel (untested during the double-blind phase of the pivotal trial) may provide additional benefit than 8 mg for these patients.

Figure 1. The model-predicted relationship between the percentage reduction from baseline in seizure frequency during titration/maintenance periods and perampanel average concentration at steady state with 95% confidence interval (blue shaded area). (The dots indicate the mean observed responses at four quartiles of perampanel concentrations. The box-whisker plots represent the distribution of perampanel concentration at 8 mg or 12 mg (predicted) doses in patients not taking enzyme-inducing antiepileptic drugs, where the middle dark line is the median. The two ends of the gray zone represent 25% and 75% percentiles. The two ends of the dotted line designate 1.5 times the inter-quantile range (i.e., the width of the box) for each direction.)



As to safety, due to the limited number of patients having hostility/aggression related adverse events (AEs) in the pivotal trial (Study E2007-G000-332) for primary generalized tonic-clonic seizures (PGTC), an exposure-safety analysis for perampanel was not explored. The clinical safety review for this submission primarily focused on the double blind phase of the pivotal trial, concluding that overall the safety findings of perampanel in patients with PGTC were consistent with the data from the original NDA submission for patients with POS. The proportion of patients having hostility/aggression related AEs in this trial (18.5% in perampanel treatment arm) falls between the proportions of patients receiving 8 mg and 12 mg in POS trials (12.3% and 20.4%, respectively). The proportions in placebo groups were similar (4.9% in PGTC trial vs. 5.7% in three POS trials). This was consistent with the previous exposure-safety analysis in POS trials and the expectation that higher perampanel concentrations are associated with more hostility/aggression related AEs. It is noted that the proportion of patients on enzyme-inducing antiepileptic drugs (EIAEDs, i.e., carbamazepine, oxcarbazepine and phenytoin) in perampanel treatment groups was much higher in POS trials (about 60%) than in the PGTC trial (about 14%), so that the perampanel concentrations in patients on the 8-mg dose arms of POS trials were less than the 8-mg group in PGTC trial due to the impact of EIAEDs on perampanel clearance (increased by 2-3 folds in the presence of EIAEDs, i.e., the concentrations of perampanel are reduced by 50-67%), while the

perampanel concentrations in 12-mg dose arms of POS trials were close to those in the 8-mg dose group in PGTC study.

Per the current labeling of FYCOMPA®, the recommended dose range of perampanel is 8 mg to 12 mg once daily for patients with POS not taking baseline EIAEDs. A dose of 12 mg once daily resulted in somewhat greater reductions in seizure rates than the dose of 8 mg once daily, but with a substantial increase in adverse reactions. Individual dosing should be adjusted based on clinical response and tolerability. Similarly, considering that 12 mg may provide additional benefit than 8 mg for PGTC patients as shown by the above exposure-efficacy analysis, and that individual dosing is based on tolerability and response, we think the sponsor's following proposal is acceptable.

In the Absence of Enzyme-Inducing AEDs

The recommended starting dosage of FYCOMPA is 2 mg once daily taken orally at bedtime. Increase dosage by increments of 2 mg no more frequently than at weekly intervals up to a dose of 8 mg once daily taken at bedtime. For subjects who are tolerating the drug well at 8 mg once daily and require further seizure control, some may benefit from a dose increase up to 12 mg once daily. Individual dosing should be adjusted based on clinical response and tolerability.

As to induced patients with PGTC (i.e., on EIAEDs known to inducing perampanel clearance), limited clinical data in the pivotal trial suggested that 8 mg perampanel did not show effectiveness as that demonstrated in non-induced patients. This may be explained by the substantially lower plasma concentrations of perampanel in these patients due to the impact of EIAEDs. Therefore, doses of perampanel in PGTC patients who are taking EIAEDs should be increased. The PK/PD analysis shown above suggested that doses higher than 8 mg may provide additional efficacy for these patients. This prediction assumes similar PK/PD relationships of perampanel for PGTC between induced and non-induced patients. We acknowledge that there is no direct evidence demonstrating that EIAEDs only affect perampanel PK but not its PK/PD relationship and there could be some uncertainty about this assumption. Nevertheless, based on the exposure-response analysis, we considered the sponsor's following proposal acceptable. Given the absence of safety data after multiple dosing, recommending use of doses higher than 12 mg is not appropriate.

In the Presence of Enzyme-Inducing AEDs
The recommended starting dosage of FYCOMPA in the presence of enzyme-inducing AEDs, including phenytoin, carbamazepine, and oxcarbazepine, is 4 mg. Increase dosage by increments of 2 mg no more frequently than at weekly intervals up to a dose of 12 mg once daily taken at bedtime. Patients should be monitored closely for response. The clinical study revealed a substantially reduced effect on seizure rates in these patients. When these enzyme-inducing AEDs are introduced or withdrawn from a patient's treatment regimen, patient should be closely monitored for clinical response and tolerability. Dose adjustment of FYCOMPA may be necessary.

1.2 Recommendations

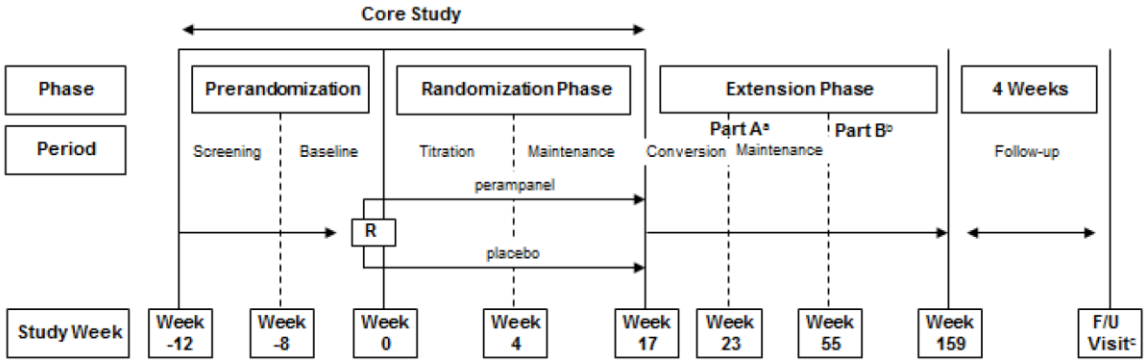
The Office of Clinical Pharmacology reviewers have reviewed the submission and finds NDA 202-834/s005 acceptable from Clinical Pharamcology's perspective provided that an agreement is reached between the Sponsor and the Agency regarding the recommended labeling language.

2 PERTINENT REGULATORY BACKGROUND

Perampanel is an orally active, noncompetitive, α -amino-3-hydroxy-5- methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist. It was approved in the U.S. on October 22, 2012, as adjunctive therapy for the treatment of POS with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. In this efficacy supplement, the sponsor is seeking the approval of perampanel as adjunctive therapy for the treatment of PGTC seizures in patients with epilepsy aged 12 years and older. The sponsor's proposed dosing regimen is as following:

- Starting dose is 2 mg once daily at bedtime in patients not on EIAEDs and (b) (4) mg in patients on EIAEDs (e.g., carbamazepine, oxcarbazepine, phenytoin).
- May increase based on clinical response and tolerability by increments of 2 mg up to a dose of 8 mg once daily at bedtime. For subjects who are tolerating the drug well at 8 mg once daily and require further seizure control, some may benefit from a dose increase up to 12 mg once daily.
- Dose increases should occur no more frequently than at weekly intervals.
- Individual dosing should be adjusted based on clinical response and tolerability.

The sponsor conducted a single pivotal trial (E2007-G000-332) which was designed to evaluate the efficacy, safety, and PK of perampanel in patients with PGTC seizures. This trial was a double-blind, randomized, placebo-controlled, multicenter, parallel-group, adjunctive-therapy study. Males and females 12 years and older who had a diagnosis of PGTC seizures, were receiving 1 to a maximum of 3 AEDs (only 1 inducer AED was allowed, defined as carbamazepine, oxcarbazepine, or phenytoin), and were experiencing ≥ 3 PGTC seizures during the baseline period were included in this trial.



(Source: sponsor's clinical study report for trial E2007-G000-332, page 24)

The pre-randomization phase consisted of 2 periods: screening (up to 4 weeks) and baseline (4- or 8- weeks), during which subjects were assessed for overall eligibility to participate in the study, including seizure activity. Eligible subjects were then

randomized to the perampanel or placebo treatment groups in a 1:1 ratio. During the titration period, subjects initially received perampanel 2 mg per day or matching placebo and were up-titrated weekly in 2-mg increments to a target dose of 8 mg per day or the highest tolerated dose. Subjects entered the maintenance period on the last dose level achieved at the end of the titration period and continued taking this dose once daily for the duration of the maintenance period. Adjustment of the study drug dose level during this period was not recommended; however, according to the investigator's clinical judgment, subjects with inadequate seizure control were allowed to have their dose increased by one 2-mg increment (not exceeding 8 mg) during the maintenance period and subjects who experienced intolerable adverse events (AEs) were allowed to have their dose decreased by one 2-mg increment.

The following table summarizes the percentage change in PGTC seizure frequency per 28 days during the Titration and Maintenance Periods (combined) relative to baseline (pre-randomization) for the Full Analysis Set. The median change was -38.38% in the placebo group and -76.47% in the perampanel group. The median treatment difference from placebo was estimated to be -30.81%. Based on rank ANCOVA, the treatment difference was statistically significant (P<0.0001, please refer to Statistical review for more details).

Table 1. PGTC Seizure Frequency per 28 Days and Percent Change During Treatment Summary – Core Study: Full Analysis Set

	Placebo (N=81)		Perampanel (N=81)	
Analysis Window Statistic	**Actual**	**Percent Change**	**Actual**	**Percent Change**
Prerandomization Phase				
n	81		81	
Mean (SD)	3.17 (2.000)		3.50 (2.620)	
Median	2.50		2.55	
Min, Max	1.0, 11.7		1.4, 18.5	
Treatment Phase (Titration + Maintenance Periods)				
n	81	81	81	81
Mean (SD)	2.87 (4.740)	-5.85 (184.562)	1.90 (3.303)	-56.88 (50.763)
Median	1.57	-38.38	0.71	-76.47
Min, Max	0.0, 39.1	-100.0, 1546.3	0.0, 22.8	-100.0, 184.5
Median Difference to Placebo[a]				-30.81
(95% Confidence Interval)[a]				(-45.490, -15.244)
P value compared to Placebo[b]				<.0001

Max = maximum; Min = minimum; PGTC = primary generalized tonic-clonic; SD = standard deviation.
a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.
b: The *P* value is based on a rank analysis of covariance with treatment and pooled country as factors, and prerandomization seizure frequency as a covariate.

(Source: sponsor's clinical study report for trial E2007-G000-332, page 69)

3 RESULTS OF SPONSOR'S ANALYSIS

Population PK analyses

The population PK analysis for perampanel was based on pooled data collected from all subjects (aged 12 to 58 years) in the pivotal trial for PGTC seizures (Study 332) and in three Phase 3 studies for POS (Studies 304, 305, and 306) where perampanel was also administered as adjunctive therapy. All models were developed in NONMEM version 7.2 interfaced with PDxPop version 5 using first-order conditional estimation with interaction (FOCEI) method.

Protocol Number	Study Design	Treatment Duration in Double-Blind Phase	Dose (mg/day)
E2007-G000-304	Double-Blind, Placebo-Controlled, Dose-Escalation, Parallel-Group in Subjects (≥12 years of age) with Refractory Partial Seizures	19 weeks	Placebo, 8 mg, 12 mg
E2007-G000-305	Double-Blind, Placebo-Controlled, Dose-Escalation, Parallel-Group in Subjects (≥12 years of age) with Refractory Partial Seizures	19 weeks	Placebo, 8 mg, 12 mg
E2007-G000-306	Double-Blind, Placebo-Controlled, Dose-Escalation, Parallel-Group in Subjects (≥12 years of age) with Refractory Partial Seizures	19 weeks	Placebo, 2 mg, 4 mg, 8 mg
E2007-G000-332	Double-blind, Randomized, Placebo-controlled, Multicenter, Parallel-group Study with an Open-label Extension Phase to Evaluate the Efficacy and Safety of Adjunctive Perampanel in Primary Generalized Tonic-Clonic Seizures	17 weeks	Placebo, 2 mg, 4 mg, 6 mg, 8 mg,

(Source: sponsor's population PK study report cpms-e2007-008r-v1-final, page 25)

For Study 332, blood samples were collected at 1 timepoint per designated visits: 6 (week 8), 7 (week 12), and 8 (week 17), follow-up visit, and early discontinuation (if that occurred). For Studies 304, 305, and 306, two blood samples were collected from each subject 1 to 2 hours apart at Visits 6, 7, and 8 (all during maintenance period) and a single blood sample was collected from each subject at Visit 9 (follow-up period) or the early discontinuation visit (if applicable).

For Study 332, a total of 205 perampanel plasma concentrations from 73 subjects were available during the double-blind maintenance period for population PK analysis. Studies 304, 305 and 306 contributed 4467 observations from a total of 770 subjects. The final PK dataset included 4672 observations from a total of 843 subjects. A summary of the demographics for PK population is presented below.

Covariate (unit)	Mean (SD)	Median	Range (Min-Max)
Age (years)	33.9 (13.2)	32	12-74
Weight (kg)	71.2 (18.8)	69	25-160
Alanine transaminase (IU/L)	21.2 (14.4)	17.5	5-184
Aspartate transaminase (IU/L)	21.2 (9.8)	19	9-141
Creatinine Clearance (mL/min)*	120 (28.5)	117	38.6-262
Dose	2mg=140, 4mg=138, 6mg=28, 8mg=377, 10mg=17, 12mg=143		
Sex	Females=440; Males=403		
Race	Caucasian=614; Non-Caucasian=229 (Black/African American=15; Asian=108; Japanese=4; Chinese=79; American Indian/Alaska Native=4; Others=19)		

*Creatinine clearance was capped at 150 mL/min as a reasonable value.

(Source: sponsor's population PK study report cpms-e2007-008r-v1-final, page 4)

A summary of the co-administered AEDs for the PK analysis data set is also presented.

AED	Inducer	No. Subjects	% of Subjects in the PK Population (N=843)
Carbamazepine	Yes	273	32.4
Levetiracetam	No	261	31.0
Lamotrigine	No	289	34.3
Oxcarbazepine	Yes	136	16.1
Topiramate	No	179	21.2
Valproate	No	272	32.3
Clobazam	No	82	9.73
Phenytoin[a]	Yes	73	8.66
Phenobarbital	No	40	4.74
Primidone	No	9	1.07
Zonisamide	No	66	7.83
Inducers*		482	57.2

*Receiving carbamazepine, oxcarbazepine or phenytoin. [a] Includes one subject who received single dose rescue phenytoin

(Source: sponsor's population PK study report cpms-e2007-008r-v1-final, page 5)

The prior analyses in healthy subjects and in subjects with partial seizures or with Parkinson's disease have shown that a two-compartment model described perampanel PK well. However, since the doses of perampanel were administered before bedtime in these Phase 3 trials, and the first samples were taken at the clinic sites during daytime visits, absorption and distribution of perampanel were already complete when the plasma concentrations were collected, preventing fitting a PK model with absorption and distribution phases. Therefore, only a one-compartment PK model with first-order elimination was used to fit the data. Due to the sparse nature of the data during the distribution phase, the apparent volume of distribution (V/F) was fixed. This modeling strategy was used in previous population PK analyses based on pooled data from Studies 304, 305, and 306 (reports Pop PK_cpms-e2007-2011-003 and Pop PK_cpms-e2007-2011-004), which was submitted and reviewed during the original NDA submission.

The effects of the following covariates on perampanel PK were investigated: demographics (gender, race, age, body weight, and seizure type), renal function (creatinine clearance), liver function (alanine aminotransferase (ALT) and aspartate amino transferase (AST)), dose, and concomitant AEDs (carbamazepine, oxcarbazepine, phenytoin, valproic acid, lamotrigine, topiramate, levetiracetam, clobazam, phenobarbital, and zonisamide). Concomitant primidone was not tested as a covariate due to the small number of subjects receiving this AED (1 % of subjects in PK data set).

After construction of a base PK model, univariate analysis was performed to test the effects of demographic and baseline characteristic covariates (not including concomitant AEDs). All the covariates with statistically significant effects on apparent clearance (CL/F) of perampanel were selected and subsequently all the concomitant AEDs were added to the CL/F parameter. This full model was subject to univariate backward deletion. The same modeling approach was used in previous population PK analysis (Reports Pop PK_cpms-e2007-2011-003). The sponsor's final model of perampanel apparent clearance and the estimates for parameters are shown as below.

Table 2. Final Population Pharmacokinetic Parameter Estimates of Perampanel – All Studies (N=843)

Parameter [Units]	Point Estimate	%RSE	95% CI
$CL/F = \Theta_{CL} * (WGT/69)^{\Theta WGT} * \Theta_{SEX}^{SEX} * \Theta_{CARB}^{CARB} * \Theta_{OXC}^{OXC} * \Theta_{TOP}^{TOP} * \Theta_{PHENY}^{PHENY}$			
Basal CL/F in L/h (Θ_{CL})	0.660	3.23	0.618 - 0.702
Weight effect on CL/F (Θ_{WGT})	-0.233	31.9	-0.379 - - 0.0872
Gender effect on CL/F (Θ_{SEX})	0.822	3.36	0.768 – 0.876
Carbamazepine effect on CL/F (Θ_{CARB})	2.75	3.55	2.56-2.94
Oxcarbazepine effect on CL/F (Θ_{OXC})	1.92	4.44	1.75-2.09
Topiramate effect on CL/F (Θ_{TOP})	1.23	3.69	1.14-1.32
Phenytoin effect on CL/F (Θ_{PHENY})	1.74	6.49	1.52-1.96
V/F in L (Θ_V)	31.3	Fixed	--
Inter-individual variability (%CV)			
CL/F	43.2	5.78	
V/F	30.6	Fixed	
Inter-occasion variability (%CV)			
CL/F	20.3	8.57	
Residual variability			
Proportional (%CV)	8.82	7.93	

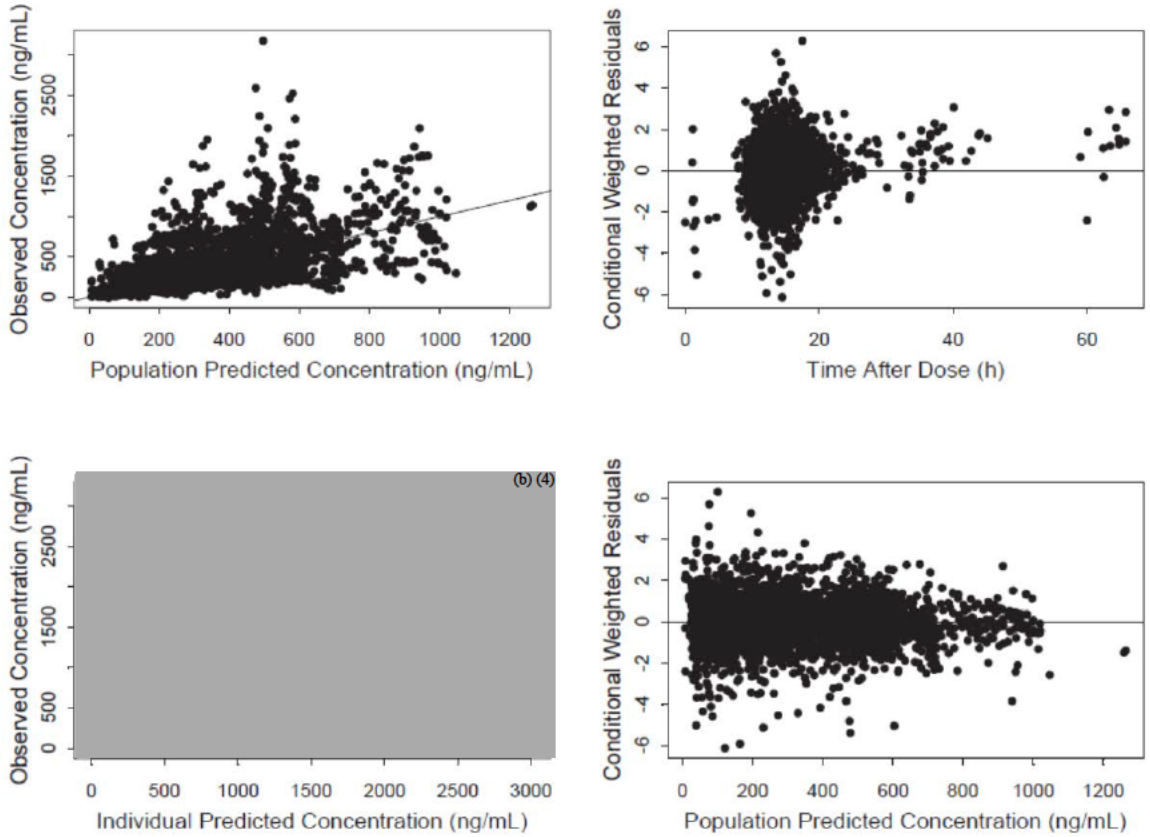
Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CL/F = apparent clearance, V/F = apparent volume of distribution; CI = confidence interval, %CV = Square root of variance *100.

(Source: sponsor's population PK study report cpms-e2007-008r-v1-final, page 6)

The volume parameter (V/F) was fixed to a value of 31.3 L, which is the central volume of distribution (Vc/F) determined from a previous population PK analysis in healthy volunteers based on data rich sampling (Report Pop PK_cpms-e2007-2011-002). Inter-individual variability (IIV) on V/F was also fixed (to 30.6%, the value from the same previous analysis).

The scatter plots of population predicted or individual predicted versus observed concentrations of perampanel were presented below. Scatter plots of CWRES (conditional weighted residuals) versus population predicted concentrations and versus time were also shown.

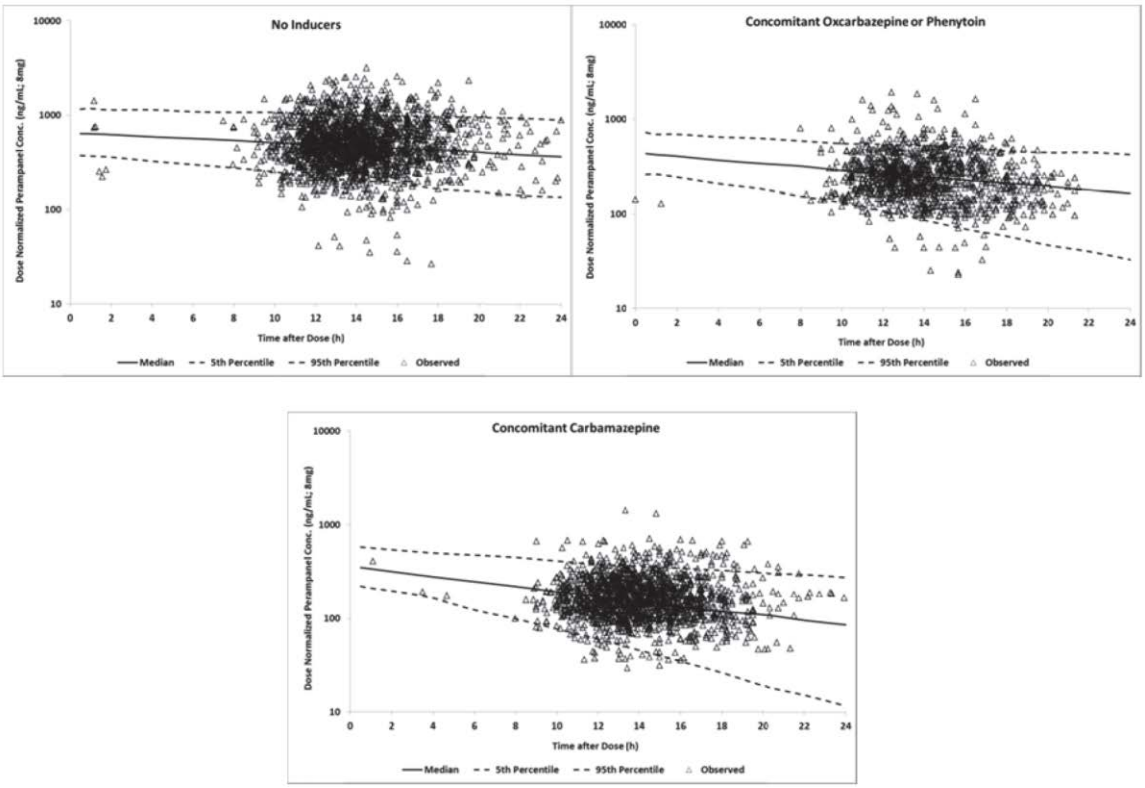
Figure 2. Assessment of Goodness of Fit for the Final PK Model



(Source: sponsor's population PK study report cpms-e2007-008r-v1-final, page 92)

A visual predictive check (VPC) was also performed to evaluate the predictive performance of the final model. Using simulated data, the 90% prediction intervals were determined and plotted together with 8-mg dose normalized observed perampanel concentrations. (*Reviewer's note: The plots are in semi-log scale. There is large variability of the data.)*

Figure 3. Visual Predictive Check Plots for Perampanel PK Model Evaluation following 8 mg Perampanel Daily Administration (Upper left panel: not taking EIAEDs; Upper right panel: taking oxcarbazepine or phenytoin; Lower Panel: taking carbamazepine).



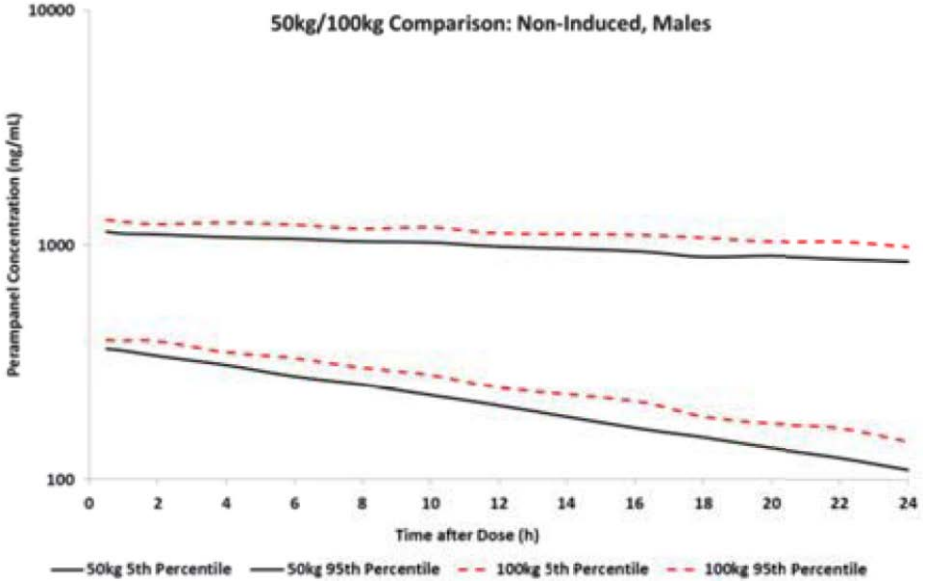
(Source: sponsor's population PK study report cpms-e2007-008r-v1-final, page 45)

In addition, a non-parametric bootstrap for the final model was conducted. The derived 95% confidential intervals for all the parameters were similar to the original estimates from the final model.

The sponsor's final model showed that perampanel apparent clearance (CL/F) was slightly lower in female subjects than in males, so that females will have on average 21.7% higher AUC than males. Though the effect of body weight on perampanel CL/F is statistically significant, there seems no clinically meaningful impact, as shown by simulations of steady state concentration-time profiles of perampanel (n=1000) following 8 mg/day dose in 50 kg vs. 100 kg body weight subjects under non-induced condition.

Reviewer's Comment: The effect of body weight on perampanel CL/F, expressed as an exponent, was estimated as -0.233 by the final model. Usually, CL/F increases with body weight. It remains unclear why the estimated exponent has a negative value. Nevertheless, the number is small and close to zero, suggesting that body weight has a limited effect on perampanel CL/F in this population, as demonstrated by the simulations.

Figure 4. Steady-state 90% Prediction Intervals for Perampanel Concentrations following 8 mg/day perampanel in 50 kg versus 100 mg Body Weight Subjects



(Source: sponsor's population PK study report cpms-e2007-008r-v1-final, page 51)

Regarding co-administered AEDs, CL/F of perampanel was increased to 2.75-, 1.92-, and 1.74-fold with the presence of carbamazepine, oxcarbazepine and phenytoin, respectively, compared to non-induced patients. Also the use of topiramte appeared to increase CL/F of perampanel slightly by 23%. The effect of carbamazepine was consistent with a Phase 1 drug interaction study which showed that perampanel CL/F was increased to 3-fold with co-administration of carbamazepine.

Reviewer's Comment: The estimate for impact of EIAEDs on perampanel clearance is mainly driven by the data from POS trials. A pronounced difference between the three POS trials (304/305/306) and PGTC trial (332) is that the proportion of patients on EIAEDs (defined as carbamazepine, oxcarbazepine, or phenytoin) in POS trials was about 50-60%, much higher than in the PGTC trial (about 22% and 11% for placebo and perampanel treatment groups). Also considering that the number of subjects enrolled in Study 332 was much smaller than the total of the three POS trial, most of the patients on EIAEDs were from POS trials.

The descriptive statistics for predicted perampanel average concentrations at steady-state (Cav,ss) were presented below by dose and by the presence/absence of EIAEDs.

Table 3. Summary Model-Predicted Perampanel Cav,ss (ng/mL) Following Perampanel Daily Dosing by Concomitant Inducer – All Studies

Concomitant Inducer	Dose (mg)	N	Mean	SD	Min	Median	Max	%CV
None	2	174	151.2	73.6	26.1	130.3	405.6	48.6
	4	194	326.9	219.9	56.7	261.2	1215.3	67.3
	6	74	526.3	290.2	169.8	428.6	1612.5	55.1
	8	483	613.1	365.0	115.0	506.0	3028.9	59.5
	10	20	777.8	413.4	322.6	604.2	1729.2	53.2
	12	119	779.0	384.5	217.7	695.4	2007.3	49.4
Carbamazepine	2	128	53.7	22.2	19.4	49.8	136.6	41.3
	4	126	98.4	39.2	32.2	85.4	217.1	39.9
	6	22	170.0	59.6	80.2	160.6	293.1	35.1
	8	330	224.0	121.0	66.0	192.3	1320.7	54.0
	10	16	251.4	81.5	155.3	235.7	387.2	32.4
	12	182	337.3	171.9	125.8	298.2	1056.2	51.0
Oxcarbazepine or Phenytoin	2	109	78.6	33.7	11.4	73.7	200.1	42.9
	4	89	172.3	97.3	39.5	147.8	609.7	56.5
	6	29	235.7	90.8	116.4	233.3	421.6	38.5
	8	234	327.2	226.6	98.9	270.5	1827.4	69.2
	10	20	360.6	95.0	219.1	327.4	614.1	26.3
	12	97	427.7	212.9	133.4	383.1	1193.3	49.8

(Source: sponsor's population PK study report cpms-e2007-008r-v1-final, page 47)

Perampanel CL/F was not significantly affected by age, dose, renal or liver function (estimated with creatinine clearance or circulating liver enzymes, respectively), and other concomitant AEDs. The PK of perampanel was not statistically significantly affected by seizure type (POS vs. PGTC), thus validating the pooling of data from all the pivotal trials.

Reviewer's Comment: Based on this analysis, (b) (4)

We consider this is unnecessary, since it does not provide actionable recommendations to physicians. The current labeling already states that,

A dedicated study has not been conducted to evaluate the pharmacokinetics of perampanel in patients with renal impairment. Population pharmacokinetic analysis was performed on pooled data from patients with partial-onset seizures and receiving FYCOMPA up to 12 mg/day in placebo-controlled clinical trials. Results showed that perampanel apparent clearance was decreased by 27% in patients with mild renal impairment (creatinine clearance 50-80 mL/min) compared to patients with normal renal function (creatinine clearance >80 mL/min), with a corresponding 37% increase in AUC. Considering the substantial overlap in the exposure between normal and mildly impaired patients, no dosage adjustment is necessary for patients with mild renal impairment.

FYCOMPA can be used in patients with moderate renal impairment with close monitoring. A slower titration may be considered based on clinical response and tolerability. Use in patients with severe renal impairment or patients undergoing hemodialysis is not recommended.

The PK dataset contains very limited number of patients with creatinine clearance less than 60 ml/min (the lowest value was 38.6 ml/min), so it is difficult to draw any further conclusion/recommendation for patients with moderate renal impairment.

Exposure-Response Analyses

Exposure-Efficacy Analyses

The final population PK model was used to obtain individual measures of average perampanel concentration at steady state ($C_{av,ss}$ = AUC_{ss}/24 hours; AUC_{ss} = Dose/(CL/F); for subjects on placebo, $C_{av,ss}$ was set to zero) which were then incorporated into the PK/PD datasets to be used in the subsequent exposure-response analyses: a continuous PK/PD model for change in 28-day average PGTC seizure frequency and logistic regression analysis for responder/non-responders. All models were developed in NONMEM version 7.2 interfaced with PDxPop version 5.

The exposure-response analyses were based on data from Study 332 alone. The 28-day average PGTC seizure frequency and response data at each visit (Visits 6, 7, and 8) during the Maintenance Period was used. For Study 332 a total of 151 subjects had 438 observation records including subjects on placebo treatment. Fifteen observations were excluded from the PK/PD analysis due to being outliers or the subjects not having perampanel exposure data available. The final analysis data set for Study 332, 28-day average PGTC seizure frequency and response PK/PD data, had a total of 423 observations from 149 subjects.

Table 4. Summary of Baseline Demographics and Other Covariates included in the Population PK/PD Analysis for PGTC Seizure Frequency - Study 332 Alone (N=149) [The same analysis population was used in the responders/non-responders analysis].

Covariate (unit)	Mean (SD)	Median	Range (Min-Max)
All Subjects (n=149)			
Age (years)	27.9 (11.0)	25	12-70
Weight (kg)	69.7 (21.0)	67	36-154
Baseline Seizure Frequency	3.32 (2.37)	2.50	1.00-18.5
Sex	Females=85; Males=64		
Race	Caucasian=78; Non-Caucasian=71 (Black/African American=4; Asian=19; Japanese=10; Chinese=35; Others=3)		
Placebo (n=77)			
Age (years)	29.0 (11.9)	25	14-70
Weight (kg)	69.8 (19.9)	65.5	40.5-151
Baseline Seizure Frequency	3.20 (2.40)	2.50	1.00-18.5
Sex	Females=44; Males=33		
Race	Caucasian=41; Non-Caucasian=36 (Black/African American=3; Asian=8; Japanese=6; Chinese=18; Others=1)		
Perampanel (n=72)			
Age (years)	26.7 (9.8)	25	12-58
Weight (kg)	69.7 (22.3)	67.3	36-154
Baseline Seizure Frequency	3.40 (2.40)	2.63	1.09-11.7
Sex	Females=41; Males=31		
Race	Caucasians=37; Non-Caucasians=35 (Black/African American=1; Asian=11; Japanese=4; Chinese=17; Others=2)		

(Source: sponsor's population PK study report cpms-e2007-008r-v1-final, page 35)

Table 5. Summary of Selected Co-Administered AED Included in the Population PK/PD Analysis for PGTC Seizure Frequency - Study 332 Alone (N=149)

AED	Inducer	Number of Subjects	% of Subjects in the PK/PD Population
Placebo (n=77)			
Carbamazepine	Yes	9	11.7
Levetiracetam	No	18	23.4
Lamotrigine	No	29	37.7
Oxcarbazepine	Yes	3	3.9
Topiramate	No	7	9.1
Valproate	No	25	32.5
Clobazam	No	4	5.2
Phenytoin	Yes	6	7.8
Phenobarbital	No	2	2.6
Primidone	No	0	0.0
Zonisamide	No	13	16.9
Inducers		18	23.4
Perampanel (n=72)			
Carbamazepine	Yes	4	5.6
Levetiracetam	No	26	36.1
Lamotrigine	No	30	41.7
Oxcarbazepine	Yes	2	2.8
Topiramate	No	17	23.6
Valproate	No	25	34.7
Clobazam	No	3	4.2
Phenytoin*	Yes	4	5.6
Phenobarbital	No	3	4.2
Primidone	No	0	0.0
Zonisamide	No	5	6.9
Inducers		10	6.7

(Source: sponsor's population PK study report cpms-e2007-008r-v1-final, page 36)

(reviewer's note: There is an error for the fraction of inducers in perampanel treated group. It should be 14% instead of 6.7%).

For efficacy measured as seizure frequency, natural log-transformed percentage change from baseline in average seizure frequency over 28 days data was used as the response variable. Average seizure frequency over 28 days at baseline and at Visit 6, 7, and 8 (all during maintenance period) was calculated as:

$$\frac{\text{Total number of seizures in diary from previous visit}}{\text{Number of days from previous visit}} * 28$$

The initial structural model was the sum of a baseline seizure frequency (Bi) (centered around the population median, B), the effect of perampanel exposure at steady state (Cav,ss,i), the effect of time (Time) on seizure frequency and an interaction term between Bi and Cav,ss,i.

$$Y_{obs,i} = \beta_0 + \beta_1 \times C_{av,ss,i} + \beta_2 \times \text{Time} + \beta_3 \times [\log(Bi) - \log(B)] + \beta_4 \times C_{av,ss,i} \times [\log(B_i) - \log(B)] + \varepsilon_{y,I}$$

Between-subject effects (IIV) was explored on all parameters using an additive error model or proportional error model. Different error models were also tested for residual variability. First Order Conditional Estimation (FOCE) was used.

The optimal model included only the intercept parameter β_0 (placebo effect) and the predicted perampanel $C_{av,ss}$ slope effect parameter β_1 as follows:

$$SF,i = \beta_0 + \beta_1 * \text{Cav,ss}$$

where *SF,i* is the predicted log-transformed percentage change from baseline of 28-day average seizure frequency. There was no significant baseline effect, time effect, or interaction between baseline 28-day PGTC seizure frequency and $C_{av,ss}$. IIV was estimated on both β_0 and β_1 according to proportional models and similarly for residual variability. This model was named as the base model.

Covariate analysis was further conducted. The variance estimated (ETAs) for placebo effect from the base model were plotted against covariates of interest (age, weight, gender, race, dose, concomitant AEDs). No relationship between ETA for placebo effect and any of these covariates appeared to exist. Plots of variance estimated (ETAs) for perampanel effect slope against covariates of interest were not assessed due to the high shrinkage (>30%) on ETA value for this parameter. Hence, no covariate was added and the base model described was considered as the final model. The parameter estimates and the Goodness-of-Fit plots for the final model are presented below (*reviewer's note: the variability of perampanel concentration effect between subjects is high, with %CV =74.2.*)

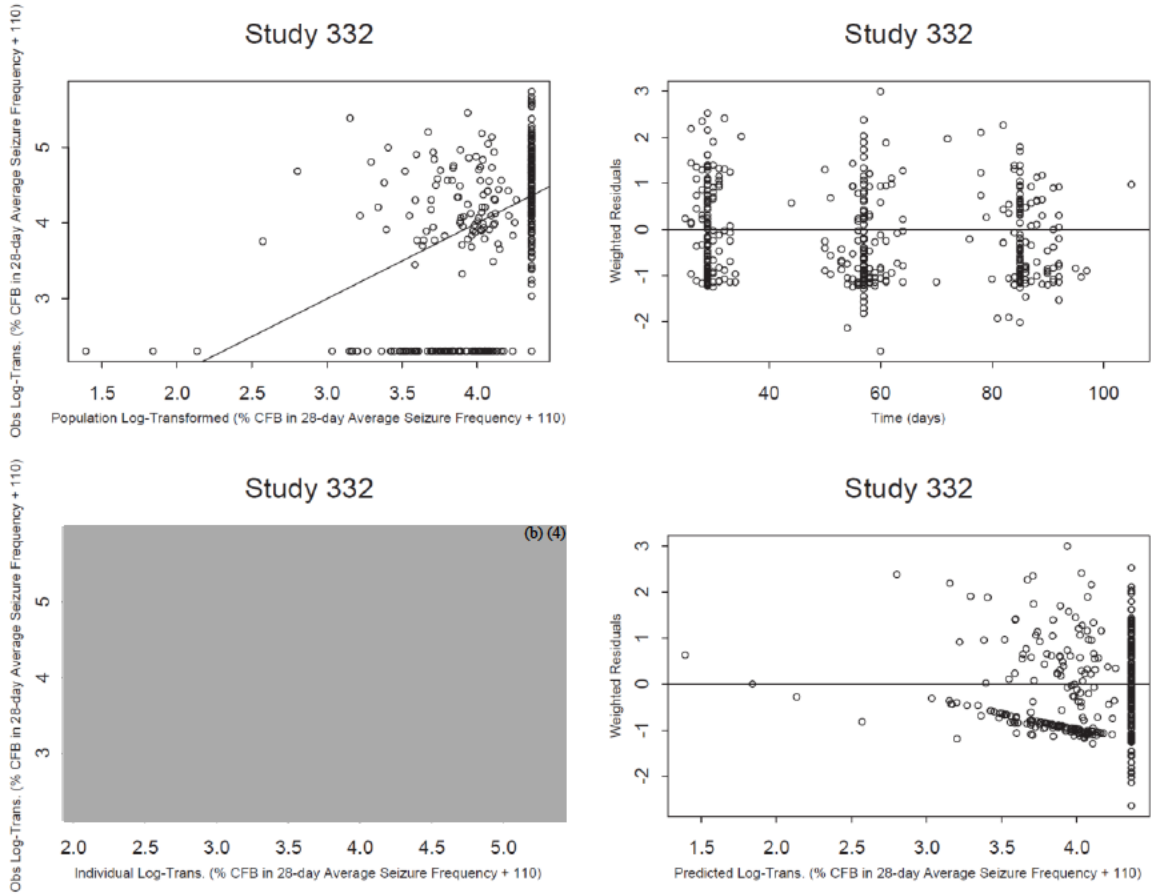
Table 6. Parameter Estimates from Base/Final PK/PD Model for Average PGTC Seizure Frequency – Study 332

Parameter [Units]	Point Estimate	%RSE	95% CI
Placebo effect - β_0	4.36	1.41	4.24-4.48
Perampanel Exposure Effect - β_1	-0.981	31.4	-1.58 – - 0.377
Inter-individual variability (%CV)			
Placebo effect - β_0	8.72	34.6	--
Perampanel Effect - β_1	74.2	39.8	--
Residual variability (%CV)			
Study 332 (proportional)	9.76	12.2	--

%RSE: percent relative standard error of the estimate = SE/parameter estimate * 100, SD=Standard deviation

(Source: sponsor's population PK study report cpms-e2007-008r-v1-final, page 54)

Figure 5. Assessment of Goodness of Fit for the Base/Final 28-Day PGTC Seizure Frequency PK/PD Model – Study 332



(Source: sponsor's population PK study report cpms-e2007-008r-v1-final, page 107)

The model predicts a placebo effect of 31.7% reduction from baseline in 28-day average PGTC seizure frequency. The effect of perampanel on the change from baseline in 28-

day average PGTC seizure frequency is a decrease of 0.981 on the loge scale for an increase of 1 μg/mL in $C_{av,ss}$. For a typical male subject of median body weight (69 kg) not receiving any inducer medication, the seizure frequency per 28 days is predicted to be reduced by 62.3% when treated with 8 mg/day perampanel (predicted $C_{av,ss}$ of 505 ng/mL).

$\log_e$ (% change SF/28days +110) = 4.36 (Placebo effect $\log_e$) -0.981* Cav,ss (in ng/mL)/1000

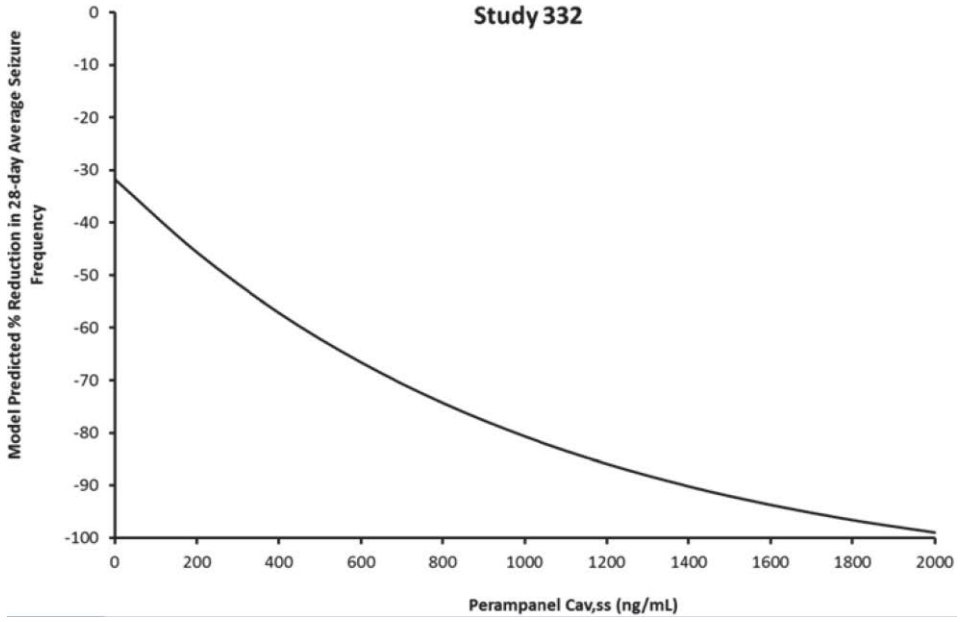
Model-predicted percentage reduction in 28-day average PGTC seizure frequency by dose of perampanel administered for subjects not receiving EIAEDs is presented below. Although in Study 332 the number of subjects receiving EIAEDs which are known to induce perampanel clearance was small (see Table 5), model-predicted results are also presented for oxcarbazepine/phenytoin and carbamazepine for illustration purposes. (*reviewer's note: Herein, an assumption is made that concomitant EIAEDs only affect perampanel PK but not its PK/PD relationship.)*

Table 7. Perampanel Median $C_{av,ss}$ (ng/mL) vs. Model-Predicted % Reduction in PGTC Seizure Frequency in Subjects Receiving / Not Receiving Inducer Co-medication – Study 332

	Median Cav,ss (ng/mL)			% Reduction in Seizure Frequency		
Dose (mg)	No Inducers	Oxcarbazepine or Phenytoin	Carbamazepine	No Inducers	Oxcarbazepine or Phenytoin	Carbamazepine
Placebo	0	0	0	31.7	31.7	31.7
4	253	137	92	48.9	41.6	38.5
6	379	205	138	56.0	46.0	41.6
8	505	273	184	62.3	50.1	44.6

(Source: sponsor's population PK study report cpms-e2007-008r-v1-final, page 111)

Figure 6. Plot of Model-Predicted PK/PD relationship between PGTC Seizure Frequency and Perampanel $C_{av,ss}$ – Study 332



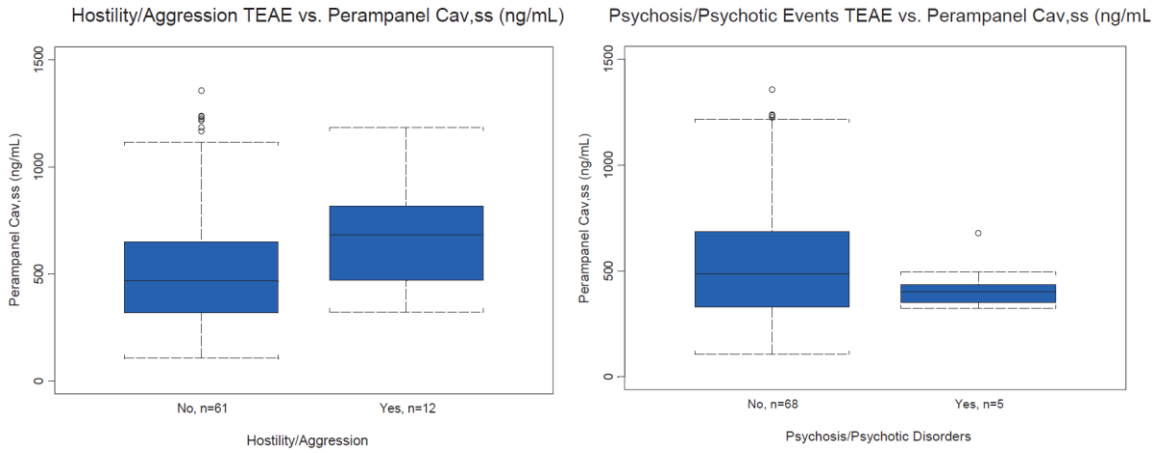
(Source: sponsor's population PK study report cpms-e2007-008r-v1-final, page 56)

The sponsor also conducted an exposure-efficacy analysis for responder (subjects had ≥ 50% decrease in seizure frequency from baseline) / non-responder (subject had < 50% decrease of seizure frequency from baseline) data using logistic regression. Since responder rate is not the primary efficacy endpoint (it is a key secondary endpoint), the details of modeling method and results are not described here (*reviewer's note: responder rate is the primary efficacy endpoint for submission to EMA).*

Exposure-Safety Analyses

The relationship between perampanel $C_{av,ss}$ and occurrence of treatment emergent adverse events (TEAEs) of special interest in Study 332 was first explored graphically. Since the incidence of individual TEAEs using narrow SMQ terms in MedDRA was small, all individual TEAEs of special interest using both the narrow and broad SMQ terms relating to hostility/aggression (irritability, laceration, agitation, abnormal behavior, affect lability, aggression, drowning, paranoia, physical abuse) and those relating to psychosis/psychotic events (hallucination, abnormal behaviour, affect lability, delusion, hallucination-visual, illusion, paranoia, speech disorder, hallucination-auditory) as a group were used for the purpose of the exposure-safety assessment. Fifteen subjects receiving perampanel experienced hostility/aggression related AEs for whom PK exposure data was available for 12 subjects. Six subjects receiving perampanel experienced psychosis/psychotic event related AEs for whom PK exposure data was available for 4 subjects.

Figure 7. Box-whisker Plots of the Relationship between Perampanel Exposure and Occurrence of Hostility/Aggression and Psychosis/Psychotic Events in PGTC subjects Receiving Perampanel.



(Source: sponsor's population PK study report cpms-e2007-008r-v1-final, page 11)

The median perampanel exposure in subjects who experience events related to hostility/aggression were higher than those who did not experience such events, though there was some extent of overlap in the concentrations. No exposure relationship was apparent for psychosis/psychotic events. The potential relationship in perampanel exposure and occurrence of hostility/aggression related TEAEs was attempted via modeling using a logistic regression approach, including both perampanel and placebo

treated subjects (n=151). However, due to high variability in probability of event and overall limited number of AEs, reliable parameter estimates could not be determined.

Reviewer's comment: The observation that hostility/aggression related AEs increased in subjects with higher perampanel concentrations was consistent with the previous observation in patients with POS. This was also demonstrated by exposure-safety analysis previously conducted by the Pharmacometric reviewer, Dr. Joo-Yoen Lee, for POS indication in the original NDA submission. Though the percentage of patients having hostility/aggression related AEs in this study was similar to the patients with POS in the previous pivotal trials (see Table 21 in the Clinical Safety review for more details), the number of AEs related to hostility/aggression in this study were limited and may not be enough to support a robust exposure-safety analysis, since the overall number of subjects in this trial was much smaller than the sum of Studies 304/305/306.

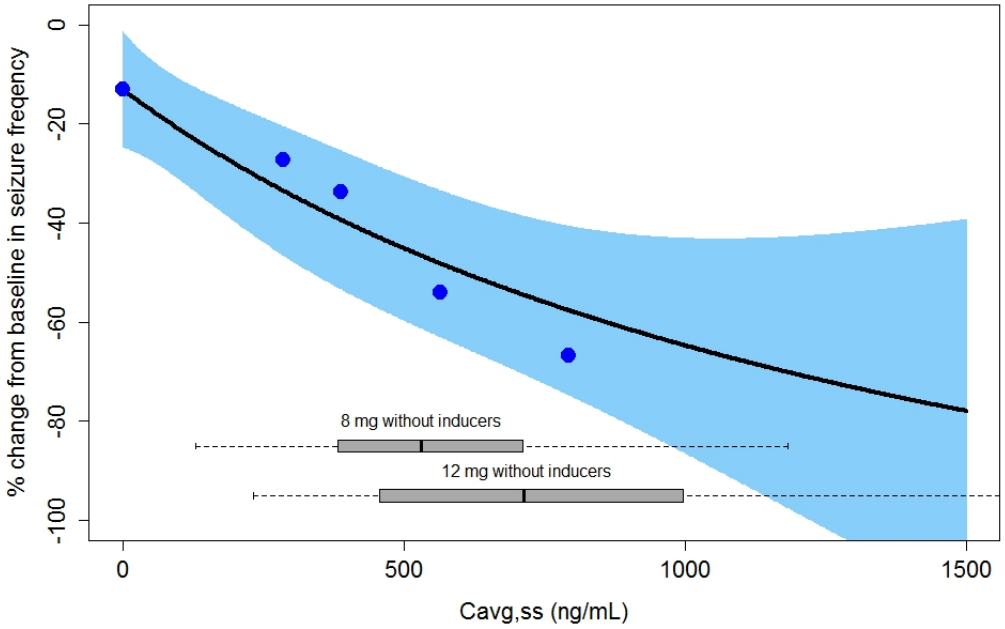
4 REVIEWER'S ANALYSES

The reviewer can reproduce the sponsor's population PK and PK/PD analysis for the percentage of change from baseline for the average seizure frequency. The reviewer further conducted analysis between steady state average concentrations of perampanel and percentage of change from baseline for seizure frequency during the double blind phase. The major differences between the reviewer's independent analysis and sponsor's are: 1) the response variable used by the reviewer is the primary efficacy endpoint which combined the data from titration period with maintenance period instead of maintenance period alone; 2) thus, there was only one response variable for each subject. In contrast, the sponsor's analysis had up to 3 responses for each subject since the data from Visits 6, 7 and 8 were treated individually; 3) the sponsor's analysis used log transformed data with a log-linear model, while the reviewer's analysis used raw data with an E_{max} model, since log-transformation seems not to significantly improve the skewness of the data.

The dose received at the last visit (Visit 8) for each subject was used to derive the $C_{av,ss}$ using the sponsor's final population PK model. Most of the patients received 8 mg, with 11 subjects receiving 6 mg and one subject remaining on 4 mg through the maintenance period. Among the subjects administered 6 mg at Visit 8, the majority of them stayed at 6 mg since Visit 6. Three subjects had their doses down from 8 mg (Visit 6) to 6 mg (Visits 7 and 8) and one subject got 8 mg at Visits 6 and 7. So, the dose received at the last visit seemed largely reflecting the doses administered over the entire maintenance period. Software R version 3.1.2 were used for the analysis.

The model-predicted PK/PD relationship from the reviewer's assessment is presented below, showing similar trend as the sponsor's analysis. The percentage reduction from baseline of seizure frequency decreases in a concentration-dependent manner, which predicts that a higher dose of 12 mg (untested during the double-blind phase of the pivotal trial) may provide additional benefit than 8 mg. In addition, the reviewer also conducted exposure-efficacy analysis only using non-induced patients who accounted for majority of the patients in Study 332. The PK/PD relationship was very similar to the one using all the subjects.

Figure 8. The model-predicted relationship for the percentage reduction from baseline in seizure frequency and perampanel average concentration at steady state with 95% confidence interval (blue shaded area). The dots indicate the mean observed responses at ranked four bins of perampanel concentrations. The box-whisker plots represent the distribution of predicted perampanel concentrations at 8 mg or 12 mg dose in patients not taking inducing AEDs.



(The middle dark line of box-whisker plot is the median. The two ends of the gray zone represent 25% and 75% percentiles. The two ends of the dotted line designate 1.5 times the inter-quantile range (i.e., the width of the box) for each direction.)

The analysis included non-induced and also induced patients. An assumption made here is that concomitant EIAEDs only affect the PK of perampanel but do not alter the PK/PD relationship of perampanel, which was also assumed by the sponsor in their analysis. Since the number of patients taking EIAEDs in this trial was limited (18 in placebo group and 10 in perampanel treatment group), it is difficult to derive a reliable exposure-efficacy relationship for this sub-group. The sponsor's analysis suggested that placebo effect for PGTC was not affected by concomitant AEDs. A literature published by the sponsor showed that the exposure-efficacy relationships for POS indication were similar between induced and non-induced patients (Gidal BE, et al. Epilepsia 2013, 54(8):1490–1497). In addition, an exploratory analysis independently conducted by the Pharmacometric reviewer, Dr. Joo-Yeon Lee, during the original NDA review also suggested that, at similar concentration ranges of perampanel, the reduction in seizure frequency was similar between the two groups, implying that there might not be additional pharmacodynamic interaction by EIAEDs beyond their impact on perampanel PK (see previous Clinical Pharmacology review for the original NDA submission). Given

these observations, we acknowledge that there is no direct evidence demonstrating similar PK/PD relationship of perampanel for PGTC seizure frequency reduction between induced patients and non-induced patients. Due to this assumption uncertainty, there could be some limitations in the application of this exposure-response analysis.

As aforementioned, due to the limited number of patients having hostility/aggression related AEs, an exposure-safety analysis was not explored. The dose of perampanel was capped at 8 mg during the double blind phase of Study 332. While the patients were allowed to have doses up to 12 mg during the extension phase, there was limited number of subjects with modal dose beyond 8 mg (30 subjects, see Table 5 of the Clinical Safety review). The clinical safety review primarily focused on the double blind phase of the pivotal trial, concluding that overall the safety findings in patients with PGTC were consistent with the data from the original NDA submission for patients with POS. The proportion of patients having hostility/aggression related AEs in this trial (18.5% in perampanel treatment arm) falls between the proportions of patients receiving 8 mg and 12 mg in POS trials (12.3% and 20.4%, respectively). The proportions in placebo groups were similar (4.9% in PGTC trial vs. 5.7% in three POS trials).

This was consistent with the previous exposure-safety analysis in POS trials and the expectation that higher perampanel concentrations are associated with more hostility/aggression related AEs. It is noted that the proportion of patients on inducer AEDs in perampanel treatment groups was much higher in POS trials (about 60%) than in the PGTC trial (about 14%), so that the perampanel concentrations in patients in the 8-mg dose arms of POS trials were less than the 8-mg group in PGTC trial due to the impact of EIAEDs on perampanel clearance, while the perampanel concentrations in 12-mg dose arms of POS trials were close to those in the 8-mg dose group in PGTC study.

Per the current labeling of FYCOMPA®, the recommended dose range of perampanel is 8 mg to 12 mg once daily for patients with POS not taking baseline EIAEDs. A dose of 12 mg once daily resulted in somewhat greater reductions in seizure rates than the dose of 8 mg once daily, but with a substantial increase in adverse reactions. Individual dosing should be adjusted based on clinical response and tolerability. Similarly, considering that 12 mg may provide additional benefit than 8 mg as shown by the above exposure-efficacy analysis, and that individual dosing is based on tolerability and response, we think the sponsor's following proposal is acceptable.

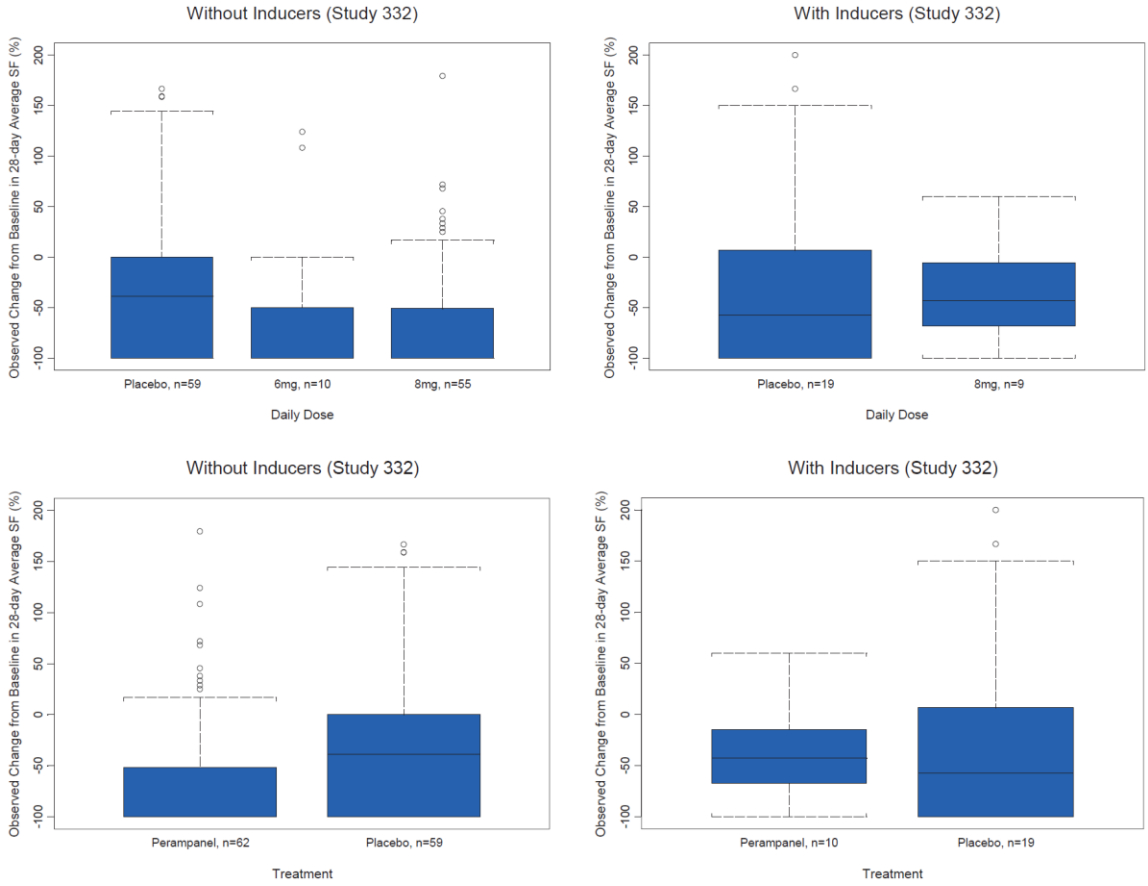
In the Absence of Enzyme-Inducing AEDs

The recommended starting dosage of FYCOMPA is 2 mg once daily taken orally at bedtime. Increase dosage by increments of 2 mg no more frequently than at weekly intervals up to a dose of 8 mg once daily taken at bedtime. For subjects who are tolerating the drug well at 8 mg once daily and require further seizure control, some may benefit from a dose increase up to 12 mg once daily. Individual dosing should be adjusted based on clinical response and tolerability.

As to induced patients (taking EIAEDs) with PGTC, there were very limited clinical data. The boxplots below display the observed percentage change form baseline in 28-day

average PGTC seizure frequency by perampanel dose level and by treatment group for subjects receiving and not receiving concomitant inducing AEDs.

Figure 9. Boxplot of Observed % Change from Baseline in 28-day Average Seizure Frequency During Maintenance Period by Dose/Treatment and Inducers – Study 332



Based on these limited clinical data, it appears that 8-mg perampanel in induced patients did not demonstrate significant effectiveness as that for non-induced patients. One of the possible reasons is that the concentrations of perampanel in induced patients were significantly lower than those in non-induced patients, since EIAEDs can decrease perampanel concentrations by 2-3 folds. Thus, dose higher than 8 mg is needed for those induced patients, which is supported by our PK/PD analysis (Figure 8). The sponsor's proposal is shown below,

In the Presence of Enzyme-Inducing AEDs
The recommended starting dosage of FYCOMPA in the presence of enzyme-inducing AEDs, including phenytoin, carbamazepine, and oxcarbazepine, is 4 mg. Increase dosage by increments of 2 mg no more frequently than at weekly intervals up to a dose of 12 mg once daily taken at bedtime. Patients should be monitored closely for response. The clinical study revealed a substantially reduced effect on seizure rates in these patients. When these enzyme-inducing AEDs are introduced or withdrawn from a patient's

treatment regimen, patient should be closely monitored for clinical response and tolerability. Dose adjustment of FYCOMPA may be necessary.

The sponsor's proposal is considered acceptable. Though doses higher than 12 mg may bring additional efficacy, such doses have never been tested in humans as multiple dosing. Due to concerns about the safety profile of perampanel which already resulted in a box warning in the current labeling, we think recommending use of doses higher than 12 mg not appropriate, given the absence of safety data on doses above 12 mg.

An argument questioning the extrapolation of efficacy for induced patients with PGTC is that, if extrapolation based on PK/PD analysis is allowed here (i.e., doses higher than 8 mg have not been studied in PGTC trial), similar extrapolation should have been implemented for POS indication. Instead of recommending doses up to 12 mg which was the highest dose tested in the pivotal trials for POS (refer to current labeling of FYCOMPA®), doses higher than 12 mg could have been recommended in the labeling, since the PK/PD relationship clearly demonstrated that higher doses would result in greater reduction in seizure frequency for induced patients with POS (see previous Clinical Pharmacology review for the original NDA submission). However, a post-marketing requirement (PMR) was issued when perampanel was approved for POS indication, which required the sponsor conduct an additional efficacy/safety study to test doses higher than 12 mg in POS patients on EIAEDs. Thus, there seems to be some 'inconsistency' in our recommendations, i.e., on one hand (for POS), we adopt an empirical approach relying on observed data from clinical trials; on the other hand (for PGTC), we allow some flexibility by extrapolating from the observed data.

As clarification, we don't think there is 'inconsistency'. Actually, both the decision on the PMR for POS indication and our current recommendation on doses for induced patients with PGTC are supported by PK/PD analyses. As stated in the Office memo for the original NDA submission (for POS indication),
What is clear is that the concentration response relationship is quite similar, whether or not patients are on inducers, but that patients on inducers never reach the concentrations needed for a full effect even with a 12 mg dose. Given the absence of any data on doses above 12 mg, recommending use of higher doses does not appear appropriate.

There seems little doubt that physicians will be tempted to increase the dose of perampanel beyond 12 mg, doses that are essentially unstudied. We are therefore requiring (a post-marketing requirement) a multi-dose safety and effectiveness trial to explore the higher dose-ranges. There is no doubt that this addresses the safety concerns raised by potential use of higher doses than 12 mg, which already has safety concerns sufficient to have led to a Boxed Warning.

Thus, the rationale of requesting the PMR is due to concern about unknown safety problems with higher doses beyond what have been tested. Instead of ignoring the prediction from exposure-response analysis, the PMR actually relied on supportive evidence provided by the PK/PD relationship. Similar logic is applied here, based on which, we consider doses up to 12 mg appropriate for PGTC patients on EIAEDs.

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
nonmem_pk.csv	Population PK dataset	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\ Perampanel_sNDA202834_XY
pk27_05052015.ctl	Control stream for popPK analysis	
pk27_05052015.lst	Population PK output	
NSEIZRSP.csv	PK/PD dataset	
Exposure_Efficacy.R	PK/PD analysis code	
Exposure_Efficacy.jpeg	PK/PD plot	

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

/s/

XINNING YANG
06/02/2015

KEVIN M KRUDYS
06/02/2015

YUXIN MEN
06/02/2015