Accepted: 31 October 2017

DOI: 10.1111/ane.12874

ORIGINAL ARTICLE

WILEY Acta Neurologica Scandinavica

Pharmacokinetic/pharmacodynamic analysis of adjunctive perampanel in subjects with partial-onset seizures

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Funding information
The studies described here, as well as the present analysis, were funded by Eisai Inc. Editorial support was funded by Eisai Inc.

For the Tucuxi drug file, only focus on the Total PK population (aged ≥ 12 years) model. Lump together the residual and interoccasion variabilities, taking a global CV of: SQRT(20^2+8.72^2)=21.8%

Objectives: Explore perampanel pharmacokinetics (PK) in all subjects (aged ≥12 years) vs adolescents (aged ≥12 to ≤17 years) with partial-onset seizures (POS) and identify factors explaining between-subject variability in efficacy using a population PK/pharmacodynamic (PD) analysis.

Materials & methods: Population PK analysis was performed using nonlinear mixed-effect modeling with data from phase II/III randomized, double-blind, placebo-controlled studies of adjunctive perampanel in POS. Perampanel exposure was predicted for all subjects and adolescents. Population PK/PD analyses were performed using data from phase III studies to explore the relationship between perampanel exposure and 28-day average seizure frequency and responder probability.

Results: Pooled perampanel PK data from 1318 subjects were described by a one-compartment disposition model. In the absence of antiepileptic drugs (AEDs) affecting perampanel PK, estimated perampanel apparent clearance (CL/F) was 0.668 L/h (all subjects) and 0.682 L/h (adolescent subjects). Co-administration of carbamazepine and oxcarbazepine/phenytoin reduced perampanel exposure. Gender, Asian race (excluding Japanese or Chinese), and increasing alanine aminotransferase lowered perampanel CL/F, but differences were small and not considered clinically relevant. Adolescent outcomes were similar to the total population. Based on PK/PD data from 1748 subjects, percent reduction in 28-day average seizure frequency from baseline and responder probability increased with increasing perampanel exposure; concomitant CYP3A-inducing AEDs lowered perampanel exposure but did not impact the slope for responder probability.

Conclusions: These results are consistent with previous analyses but expand on these through inclusion of a larger number of patients from different ethnic groups, and demonstrate that outcomes were similar between adults and adolescents.

KEYWORDS
antiepileptic drugs, epilepsy, pharmacokinetics, seizures

1 | INTRODUCTION

Comprehensive pharmacokinetic/pharmacodynamic (PK/PD) data can provide key insights to support optimal dosing of antiepileptic drugs (AEDs) and facilitate integration into clinical practice.[1] However, limited PK/PD data are currently available to guide clinicians when optimizing individual AED regimens.[1] Perampanel, a selective, non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist, is approved for adjunctive treatment of partial-onset seizures (POS), with or without secondarily generalized (SG) seizures, and primary generalized tonic-clonic seizures in epilepsy patients aged ≥ 12 years.[2,3] Perampanel was recently approved

for monotherapy use for POS in the United States. The clinical development of perampanel included phase II and phase III international, randomized, double-blind, placebo-controlled studies in subjects with POS (Studies 304 [NCT00699972], 305 [NCT00699582], 306 [NCT00700310], and 235 [NCT01161524]),[4-7] and an Asia-Pacific randomized, double-blind, placebo-controlled study in POS (Study 335 [NCT01618695]).[8]

Perampanel is primarily metabolized via cytochrome P450 3A (CYP3A), with an elimination half-life of approximately 100 hours.[1-3,9] Previous PK/PD analyses of pooled data from phase III studies showed that concomitant CYP3A enzyme-inducing AEDs (EIAEDs; carbamazepine, oxcarbazepine, and phenytoin) reduce perampanel exposure,[1,10] although the slope for the exposure–efficacy relationship remains unchanged.[1] Patients should be closely monitored when concomitant EIAEDs are introduced or withdrawn, and perampanel dose adjustment may be required.[2,3]

Here, we report the most comprehensive population PK and PK/PD evaluation of perampanel in subjects with POS carried out to date. A population-based analysis using data from one phase II and four phase III POS studies was performed to describe the PK of perampanel in all subjects (≥12 years) and adolescents (≥12 to ≤17 years), and identify factors in previously underrepresented groups that may explain between-subject variability (eg, age and ethnicity). Population PK/PD analysis was performed using data from four phase III POS studies to characterize the relationship between 28-day average seizure frequency and perampanel exposure, identify factors affecting this response, and evaluate the probability of a response.

2 | MATERIALS & METHODS

2.1 | Study designs

All studies included a 19-week double-blind phase (6-week titration; 13-week maintenance).[4-8] In the phase III studies, subjects (≥12 years) received once-daily placebo or adjunctive perampanel ≤12 mg.[4-6,8] In the phase II study, adolescents (≥12 to ≤17 years) received placebo or once-daily adjunctive perampanel 8 mg; titration up to 12 mg was possible if tolerated.[7] Subjects were uptitrated by 2 mg/wk to their randomized dose. During maintenance, subjects received the dose achieved during titration. Dose reductions due to intolerability were permitted at the investigator's discretion.

All studies were performed in accordance with the Declaration of Helsinki, European Medicines Agency requirements, the US Code of Federal Regulations, and the ICH-E6 Guideline for Good Clinical Practice. All trial protocols, amendments, and informed consent were reviewed by national regulatory authorities in each country and independent ethics committees or institutional review boards for each site. Written informed consent was provided.[4-8]

2.2 | Subjects

Eligible subjects were aged ≥12 years with refractory POS, with or without SG seizures, despite ≥2 AEDs (≥1 AED for Study 335) within the previous 2 years. Subjects received ongoing treatment with 1-3 concomitant AEDs; only one was permitted to be an EIAED.[4-8] Key exclusion criteria included presence of non-motor simple POS only, primary generalized seizures, diagnosis of Lennox-Gastaut syndrome, or history of status epilepticus in the previous year.[4-8]

The population PK analysis included subjects with sufficient dosing information and ≥1 adequately documented and quantifiable perampanel plasma concentration. The PK/PD analysis included subjects who had received placebo or perampanel, had available PK information, and ≥1 adequately documented baseline and maintenance period seizure frequency.

2.3 | PK assessment

Across studies, dosing time ranged from 00:00 to 23:59 hours, and the last perampanel dose intake was in September 2014 (Study 335); there were no data regarding whether perampanel was taken under fasted or fed conditions. Perampanel plasma concentrations during maintenance were used. Blood samples were collected via venipuncture at visits 6, 7, and 8. In most studies, blood samples were taken at two timepoints, 1-2 hours apart. In Study 335, one blood sample was taken. Plasma concentrations were analyzed by liquid chromatography-mass spectrometry/mass spectrometry.[11]

2.4 | PK model development

Using full PK profiles from 19 phase I studies in 606 healthy subjects, perampanel PK is best described by a two-compartment model with first-order absorption and elimination.[12] However, due to bedtime dosing and daytime clinic visits, steady-state PK was adequately described in phase III studies using a one-compartment disposition model with first-order elimination.[1]

Here, a one-compartment disposition model with first-order linear elimination parameterized for apparent clearance (CL/F) and volume of distribution (V/F) was used. Due to the sparse nature of the data collected during the elimination phase, V/F and its variance were fixed to values (43.5 L and 0.265, respectively) derived from a previous population PK analysis. Interindividual variability and interoccasion variability were assessed on CL/F. Residual variability was assessed by additive, proportional, and combined additive/proportional error structures. The first-order conditional estimation with interaction was used. Covariates investigated for their effects on perampanel PK included demographics (gender, race, age, and weight), renal function marker (creatinine clearance), liver function markers (alanine aminotransferase [ALT] and aspartate aminotransferase), and concomitant AEDs (carbamazepine, oxcarbazepine, phenytoin, valproic acid, lamotrigine, topiramate, levetiracetam, clobazam, phenobarbital, primidone, and zonisamide).

The final PK model was evaluated using a visual predictive check (VPC) and validated using bootstrap resampling. For the VPC, 1000 subjects receiving perampanel 8 mg/d were simulated under four conditions: without EIAEDs, with carbamazepine, with oxcarbazepine/phenytoin, and with topiramate/phenobarbital. Simulated data were

plotted with observed perampanel concentrations (dose-normalized for 8 mg/d).

2.5 | PK/PD model development

Based on individual perampanel CL/F from the final PK model, average perampanel concentration at steady state ($C_{av,ss}$) was derived using $C_{av,ss}$ = (DOSE*1000/Dosing interval)/CL/F, where DOSE is daily dose (mg) during maintenance and dosing interval is 24 hours. For placebo-treated subjects, $C_{av,ss}$ = 0.

For PD determinations, 28-day average seizure frequency at baseline and visits 6, 7, and 8 was calculated. Study 235 was not included in the PK/PD analysis because inclusion criteria for baseline seizure frequency were less demanding, with consequent lower median seizure frequency, suggesting a less severely affected population. Log-transformed percentage change from baseline in 28-day average seizure frequency was used and modeled, as previously described.[13] Response was based on 28-day average seizure frequency and defined as a categorical variable with two modalities: 0, non-responder (<50% decrease from baseline), and 1, responder (≥50% decrease from baseline). Responder probability was analyzed by logistic regression. To calculate the proportion of responses, subjects were divided by placebo and those achieving a perampanel $C_{av,ss}$ of 0-200, 200-400, 400-600, 600-800, 800-1000, 1000-1200, and >1200 ng/mL. Demographics and concomitant AEDs were tested as covariates. The final PK/PD model was evaluated using a VPC and validated using bootstrap resampling.

2.6 | Data analyses

Population PK and PK/PD analyses were performed using nonlinear mixed-effect modeling (NONMEM®) in NONMEM® version 7.2 interfaced with PDx-POP® version 5.0 (ICON Development Solutions, Ellicott City, MD, USA). For Study 335, there were no missing covariates in the PK dataset; however, for the PK/PD dataset, baseline weight was missing for two placebo-treated subjects and replaced by the population median. There were no outlying PK observations for Study 335, but one 28-day average seizure frequency observation was considered an outlier and excluded from the PK/PD dataset. Observations of perampanel concentrations below the limit of quantification were omitted. No adjustments were made for PK/PD data collected from different centers or for multiple comparisons. When comparing the full with the reduced model, the critical value was adjusted according to change in degrees of freedom.

3 | RESULTS

3.1 | PK analysis: subject demographics

The final PK dataset included 6066 perampanel plasma concentrations from 1318 subjects (Study 304, n = 193; Study 305, n = 182; Study 306, n = 394; Study 335, n = 471; Study 235, n = 78). For adolescents, 927 plasma concentrations from 210 subjects were included. Demographics, covariates, and co-administered AEDs were generally well balanced between populations (Table 1).

3.2 | PK analysis: pooled perampanel PK

Consistent with pooled data from phase III studies, pooled perampanel PK data from Studies 304, 305, 306, 335, and 235 were best described by a one-compartment disposition model with linear elimination parameterized for CL/F and V/F. The final population PK model contained the statistically significant effects on perampanel CL/F of ALT, Asian race (not including Japanese and Chinese, which did not significantly affect CL/F), sex, and the concomitant AEDs carbamazepine, oxcarbazepine/phenytoin, and topiramate/phenobarbital (Table 2). In the absence of AEDs affecting perampanel PK, the population estimate of perampanel CL/F was 0.668 and 0.682 L/h in the total and adolescent populations, respectively. For both populations, perampanel CL/F showed a slight decrease with increasing ALT, was lower for females and Asian race, and was higher with co-administration of carbamazepine, oxcarbazepine/phenytoin, and topiramate/phenobarbital (Table 2). To assess the clinical implications of ALT, sex, Asian race, and concomitant topiramate/phenobarbital on perampanel CL/F, a series of simulations (N = 1000 for each) were performed for perampanel 8 mg/d using parameter estimates from the final PK model. These showed considerable overlap in 90% prediction intervals (PIs) for perampanel concentrations at steady state for all covariates tested, thereby obviating the need for dose adjustments (Figures 1A-D).

The VPC showed the majority of observed dose-normalized (8 mg/d) perampanel concentrations were within the 90% PIs, indicating that the perampanel concentration–time course was reasonably well defined by the final model with good predictive performance (Figs. S1 and S2). The success rate of the nonparametric bootstrap was 99.8% for both populations and confidence intervals were generally narrow, indicating that the final PK model was valid, stable, and produced well estimated parameters.

3.3 | PK/PD analysis: subject demographics

The final PK/PD analysis set included 5068 observations from 1748 subjects (Studies 304, 305, and 306, n = 1108; Study 335, n = 640); of these, 1240 (70.9%) received perampanel and 508 (29.1%) received placebo. Demographics and co-administered AEDs were generally consistent between treatment groups (Table 1).

3.4 | PK/PD analysis: percent change in 28-day average seizure frequency from baseline

Following log-transformation of percent change from baseline in 28-day average seizure frequency, the best model to describe the data was the sum of a placebo effect and a perampanel exposure effect. Shrinkage estimates for the placebo effect and perampanel effect parameters were 13.8% and 70.9%, respectively; due to high shrinkage for the perampanel effect, the effects of Japanese and

TABLE 1 Demographics and covariates in the PK and PK/PD analysis populations

	Total PK population (n = 1318)	Adolescent PK population (n = 210)	Total PK/PD population	
			Perampanel (n = 1240)	Placebo (n = 508)
Mean age, years (SD)	32.7 (13.6)	14.6 (1.8)	33.9 (13.2)	34.5 (13.6)
Mean weight, kg (SD)	67.1 (17.9)	55.4 (15.6)	67.4 (17.8)	67.9 (17.7)
Female, n (%)	674 (51.1)	94 (44.8)	243 (19.6)	86 (16.9)
Race, n (%)				
Caucasian	644 (48.9)	106 (50.5)	598 (48.2)	268 (52.8)
Asian[a]	266 (20.2)	41 (19.5)	234 (18.9)	95 (18.7)
Chinese	197 (15.0)	23 (11.0)	196 (15.8)	68 (13.4)
Japanese	173 (13.1)	31 (14.8)	173 (14.0)	58 (11.4)
Black/African American	16 (1.2)	3 (1.4)	14 (1.1)	10 (2.0)
Other	22 (1.7)	6 (2.9)	25 (2.0)	9 (1.8)
Mean ALT, IU/L (SD)	20.7 (15.3)	18.2 (13.9)	–	–
Mean AST, IU/L (SD)	21.4 (9.6)	21.5 (9.2)	–	–
Mean CrCl,[b] mL/min (SD)	118 (29.9)	120 (27.3)	–	–
Perampanel dose, n (%)				
2 mg	153 (11.6)	18 (8.6)	–	–
4 mg	296 (22.5)	33 (15.7)	–	–
6 mg	53 (4.0)	11 (5.2)	–	–
8 mg	487 (37.0)	84 (40.0)	–	–
10 mg	49 (3.7)	17 (8.1)	–	–
12 mg	280 (21.2)	47 (22.4)	–	–
Concomitant AEDs, n (%)				
Inducers				
Carbamazepine	497 (37.7)	55 (26.2)	484 (39.0)	185 (36.4)
Oxcarbazepine	212 (16.1)	35 (16.7)	198 (16.0)	90 (17.7)
Phenytoin	122 (9.3)[c]	16 (7.6)	117 (9.4)	39 (7.7)
Non-inducers				
Valproic acid	462 (35.1)	77 (36.7)	437 (35.2)	179 (35.2)
Levetiracetam	457 (34.7)	81 (38.6)	425 (34.3)	165 (32.5)
Lamotrigine	397 (30.1)	54 (25.7)	381 (30.7)	152 (29.9)
Topiramate	265 (20.1)	39 (18.6)	254 (20.5)	91 (17.9)
Clobazam	141 (10.7)	16 (7.6)	138 (11.1)	48 (9.5)
Zonisamide	102 (7.7)	15 (7.1)	37 (7.9)[d]	12 (7.1)[d]
Phenobarbital	80 (6.1)	7 (3.3)	80 (6.5)	29 (5.7)
Primidone	16 (1.2)	2 (1.0)	16 (1.3)	11 (2.2)

AED, antiepileptic drug; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CrCl, creatinine clearance; PD, pharmacodynamic; PK, pharmacokinetic; SD, standard deviation.

[a]Japanese and Chinese subjects were analyzed as covariates in the PK analysis; thus, Asian race does not include Japanese or Chinese subjects.

[b]When examined as a covariate, CrCl was capped at 160 mL/min as a reasonable value.

[c]Includes one subject who received single-dose rescue phenytoin.

[d]Zonisamide information was available for 471 perampanel-treated subjects and 169 placebo-treated subjects.

TABLE 2 Final population PK parameter estimates for the total PK population (aged ≥ 12 years) and the adolescent PK population (aged ≥ 12 to ≤17 years)

	Total PK population (aged ≥ 12 years)			Adolescent PK population (aged ≥ 12 to ≤17 years)		
Parameter (Units)	Point estimate	% RSE	95% CI	Point estimate	% RSE	95% CI
Basal CL/F in L/h (Θ_{CL})	0.668	2.75	0.632, 0.704	0.682	5.91	0.603, 0.761
ALT effect on CL/F (Θ_{ALT})	−0.0901	24.3	−0.133, −0.0472	−0.107	47.8	−0.207, −0.00684
Gender effect on CL/F (Θ_{SEX})	0.822	2.63	0.780, 0.864	0.839	6.50	0.732, 0.946
Asian effect on CL/F (Θ_{ASIAN})[a]	0.908	3.14	0.852, 0.964	0.766	8.89	0.633, 0.899
Carbamazepine effect on CL/F (Θ_{CARB})	2.95	2.94	2.78, 3.12	2.97	7.10	2.56, 3.38
Oxcarbazepine or phenytoin effect on CL/F ($\Theta_{OXC/FENY}$)	1.99	3.49	1.85, 2.13	1.99	8.89	1.64, 2.34
Topiramate or phenobarbital effect on CL/F ($\Theta_{TOP/FENO}$)	1.21	2.95	1.14, 1.28	1.24	6.74	1.08, 1.40
V/F in L (Θ_V)	43.5 fixed	–	–	43.5 fixed	–	–
Interindividual variability (% CV)						
CL/F	43.5	4.55	–	42.7	11.4	–
V/F	51.5 fixed	–	–	51.5 fixed	–	–
Interoccasion variability (% CV)						
CL/F	20.0	6.77	–	21.6	11.9	–
Residual variability						
Proportional (% CV)	8.72	9.42	–	8.27	26.3	–

% CV, square root of variance * 100; % RSE, percent relative SE of the estimate = SE/parameter estimate * 100; ALT, alanine aminotransferase; CI, confidence interval; CL/F, apparent clearance; PK, pharmacokinetic; SE, standard error; V/F, apparent volume of distribution.

$CL/F = \Theta_{CL} * (ALT/17)^{\Theta ALT} * \Theta_{SEX}{}^{SEX} * \Theta_{ASIAN}{}^{ASIAN} * \Theta_{CARB}{}^{CARB} * \Theta_{OXC/FENY}{}^{OXC/FENY} * \Theta_{TOP/FENO}{}^{TOP/FENO}$.

[a]Japanese and Chinese subjects were analyzed as covariates in the PK analysis; thus, Asian race does not include Japanese or Chinese subjects.

Chinese race, concomitant AEDs, and region were only tested on the placebo effect. The placebo effect was marginally lower with co-administration of clobazam but was unaffected by other AEDs, Japanese or Chinese race, and region (Table S1). The PK/PD relationship was unaffected by time and baseline seizure frequency. Variability in the placebo effect between subjects was mild (10.6% coefficient of variation [CV]).

The effect of perampanel $C_{av,ss}$ on change from baseline in 28-day average seizure frequency showed a decrease of 0.502 on the $\log_e$ scale per 1 μg/mL increase in $C_{av,ss}$. In relation to clinical practice and based on the final PK/PD model, a typical non-Asian male not receiving AEDs affecting perampanel PK was predicted to achieve a reduction in seizure frequency from 10.7 seizures per 28 days at baseline to 5.8 seizures per 28 days during maintenance with perampanel 8 mg/d (predicted $C_{av,ss}$, 575.2 ng/mL; Figure 2). The variability in the slope of perampanel concentration effect between subjects was high (106% CV).

In the presence or absence of AEDs affecting perampanel PK, the model-predicted percentage reduction in 28-day average seizure frequency from baseline increased with increasing perampanel doses in subjects not receiving concomitant clobazam (Figure 3). The model-predicted effect of EIAED co-administration on percent change from baseline in 28-day average seizure frequency was less pronounced than their overall effect on perampanel exposure. The VPC confirmed that the majority of data points were within the 90% PIs, indicating that percentage change from baseline 28-day average seizure frequency was reasonably well defined by the final PK/PD model with good predictive performance. The success rate of the nonparametric bootstrap was 100%; thus, the final PK/PD model was valid and produced well estimated parameters.

3.5 | PK/PD analysis: probability of response

Data for the PK/PD response analysis were the same as described for 28-day average seizure frequency. In this model, the placebo effect was characterized by a constant effect on the logit function. Perampanel $C_{av,ss}$ was a significant predictor for a subject being a responder and best modeled as power of function in relation to perampanel $C_{av,ss}$. Age and concomitant use of clobazam or lamotrigine were also significant predictors of a response.

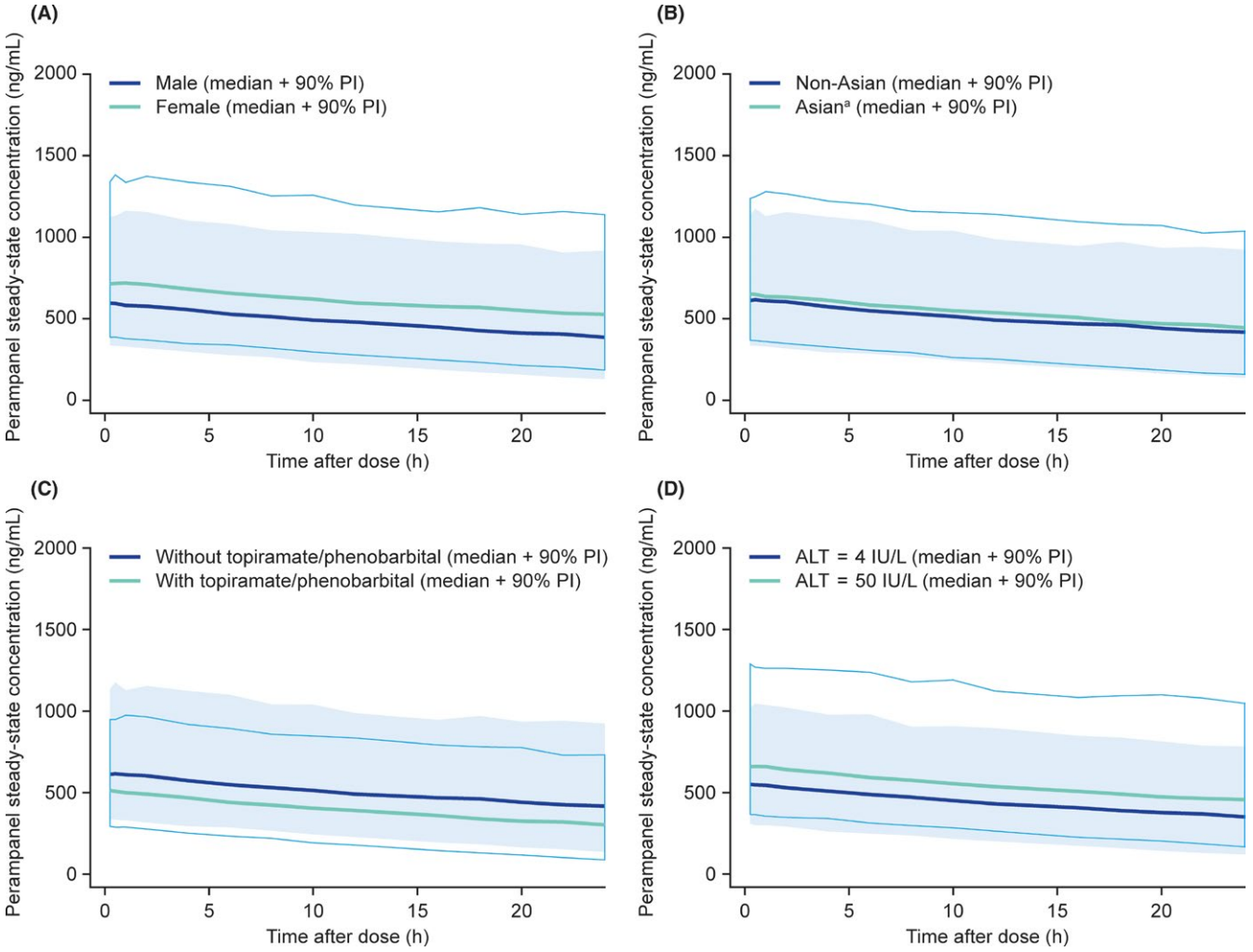

FIGURE 1 Simulated steady-state perampanel 8 mg/d concentration–time profiles for the effect of gender (A), Asian race[a] (B), concomitant topiramate/phenobarbital (C), and ALT (D). ALT, alanine aminotransferase; h, hours; PI, prediction interval; PK, pharmacokinetic. [a]Japanese and Chinese subjects were analyzed as covariates in the PK analysis; thus, Asian race does not include Japanese or Chinese subjects

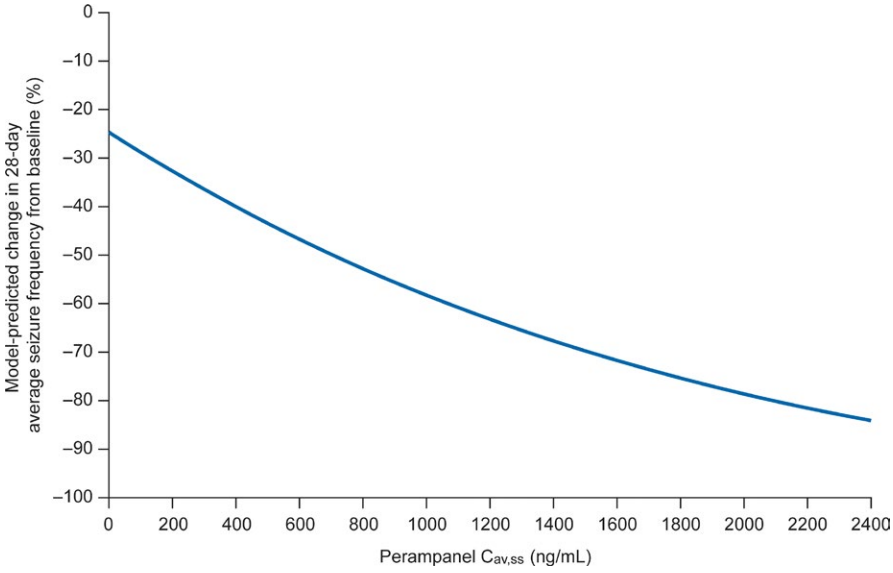

FIGURE 2 Model-predicted PK/PD relationship between 28-day average seizure frequency and perampanel $C_{av,ss}$.[a] $C_{av,ss}$, average concentration at steady state; PD, pharmacodynamic; PK, pharmacokinetic. [a]These data are for subjects who were not receiving concomitant clobazam

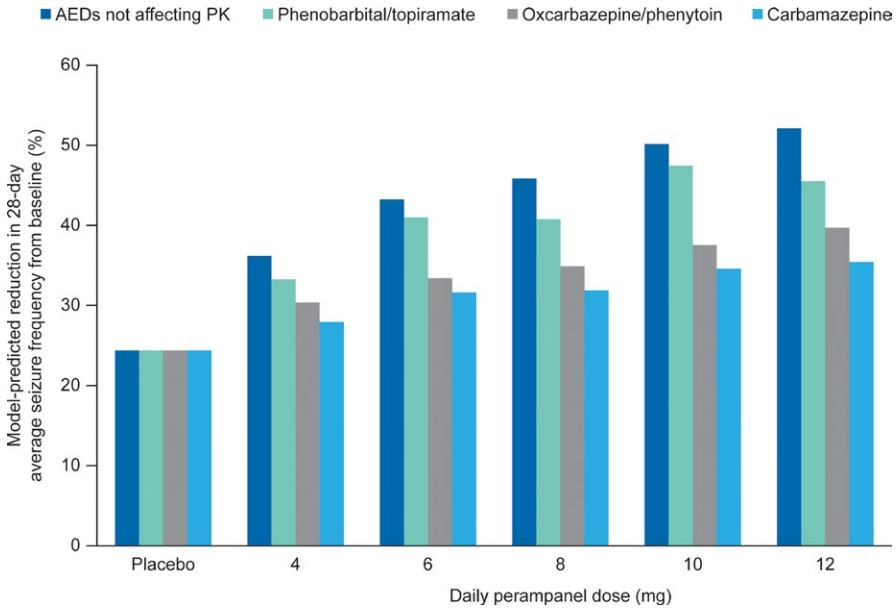

FIGURE 3 Model-predicted percent reduction in 28-day average seizure frequency from baseline in the presence and absence of AEDs affecting perampanel PK[a]. AED, antiepileptic drug; PK, pharmacokinetic. [a]These data are for subjects who were not receiving concomitant clobazam

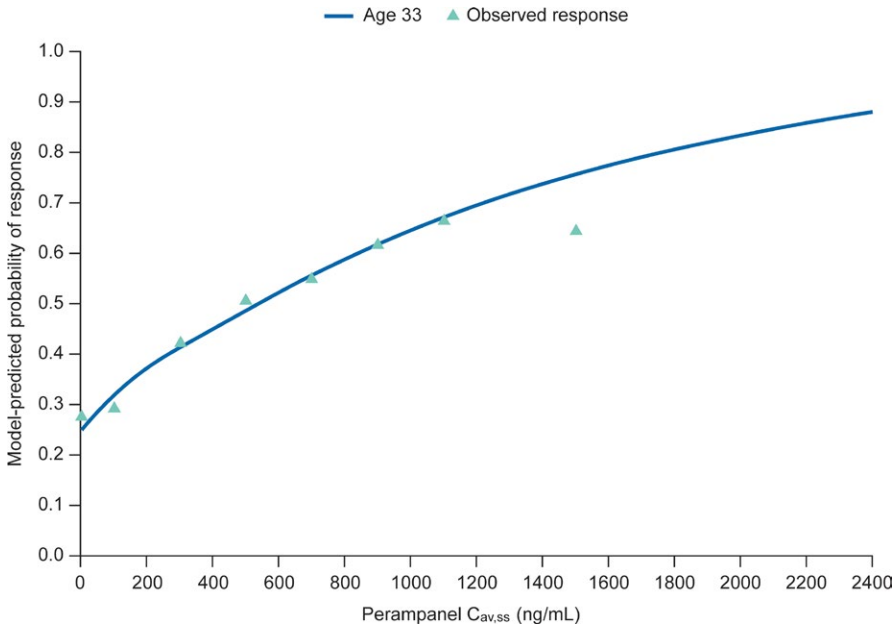

FIGURE 4 Observed and logistics model-predicted response probability[a]. $C_{av,ss}$, average concentration at steady state. [a]These data are for subjects who were not receiving concomitant clobazam or lamotrigine

In the final logistic regression model, responder probability was predicted to increase with increasing perampanel $C_{av,ss}$ in subjects not receiving concomitant clobazam or lamotrigine (Figure 4). There was a small effect of age, with older subjects having a slightly higher probability of being responders; however, this was not considered clinically relevant. The covariates weight, gender, race, baseline seizure frequency, and concomitant use of EIAEDs or non-inducers had no effect on responder probability or on the perampanel exposure effect parameter. Response probability was higher with perampanel 8 mg/d than with placebo in the absence of AEDs affecting perampanel PK and was lower with concomitant carbamazepine or oxcarbazepine/phenytoin compared with the absence of AEDs affecting perampanel PK (Table S2). The success rate of the nonparametric bootstrap was 97.9%, indicating that the final model was valid.

4 | DISCUSSION

Here, a pooled population PK analysis was performed on perampanel steady-state concentration data in all subjects (≥12 years) and adolescent subjects (≥12 to ≤17 years) from phase II and phase III studies. Consistent with pooled data from phase III studies,[1] pooled perampanel PK data were best described by a one-compartment disposition model. In the absence of AEDs affecting perampanel PK, the population estimate of perampanel CL/F was similar in both the total and adolescent populations. Of the extrinsic factors examined, co-administration of carbamazepine and oxcarbazepine/phenytoin increased CL/F threefold and two-fold, respectively, resulting in perampanel exposure being reduced by a similar magnitude. Perampanel CL/F was increased by co-administration of topiramate

or phenobarbital; however, this was considered a mild effect and not clinically important relative to the high variability in perampanel exposure. The small effect of topiramate has also been previously observed in a PK assessment of pooled data from Studies 304, 305, 306, and 332.[14]

Of the covariates examined, gender, Asian race (not including Japanese and Chinese), and increasing ALT significantly lowered perampanel CL/F, although these effects were small and not considered clinically relevant based on overall variability in CL/F. Perampanel CL/F was independent of dose and not significantly affected by body weight, age, and hepatic and renal functions. Perampanel efficacy has been shown to be similar in adolescents and adults; however, somnolence, nasopharyngitis, and aggression occurred more frequently in adolescents compared with the overall population.[15] Here, perampanel population PK parameters and covariate effects in adolescents were similar to the total population. This has also been shown in previous PK analyses,[16] suggesting that perampanel PK is not affected by age, and that dosing in adolescents should follow the same label recommendation as adults (≥12 to <65 years)[2,3,16]; to avoid potential adverse events (AEs) in adolescents, dose titration should be slow and individualized.[15] In terms of co-administration of the EIAEDs carbamazepine, oxcarbazepine, and phenytoin, the results from this population PK analysis are consistent with a previously reported PK analysis of perampanel using pooled data from Studies 304, 305, and 306, in which a two- to three-fold increase in perampanel CL/F was observed.[1]

A pooled PK/PD analysis for seizure frequency and probability of response was performed in subjects involved in four phase III POS studies. Log-transformed percent reduction in 28-day average seizure frequency from baseline was modeled with a placebo effect and a proportional exposure effect. Perampanel administration reduced the frequency of POS, with the decrease proportional to an increase in exposure to perampanel and independent of time. The placebo effect was only found to be lower with co-administration of clobazam. There was a lower reduction in 28-day average seizure frequency with concomitant EIAEDs, which was due to lower exposure to perampanel. The model for responder probability was also the sum of a placebo effect and perampanel exposure effect. The probability of being a responder was predicted to increase with increasing exposure to perampanel (power function). There were no significant effects for any of the other intrinsic (including Japanese and Chinese race) and extrinsic factors on the probability of response. The results of these PK/PD analyses are consistent with a previously reported exposure–efficacy relationship for perampanel using pooled data from Studies 304, 305, and 306, where increasing perampanel exposure was linked to a reduction in seizure frequency per 28 days and an increased probability of response.[1]

In summary, this is the most comprehensive population PK and PK/PD evaluation of perampanel in subjects with POS carried out to date. These data highlight that PK parameters and covariates were similar between all subjects and adolescents, percent reduction in 28-day average seizure frequency from baseline and responder probability increased with increased exposure to perampanel, and concomitant EIAEDs lowered perampanel exposure. These findings are consistent with previous analyses,[1,10] but given the inclusion of PK data from the Asia-Pacific Study 335, we expand on previous analyses across different ethnic groups and increase the relative weight of previously underrepresented groups. In addition, the PK analysis allowed a comparison of perampanel PK in all subjects with adolescents. These data will help to guide clinicians when integrating perampanel into clinical practice, as they demonstrate that there is no effect of a variety of intrinsic factors (including Japanese and Chinese race) on perampanel PK and PK/PD but provide further clarification that concomitant use of EIAEDs may require administration of a higher perampanel dose, depending on subject tolerability and within the approved dose range; special attention should be given to monitoring of psychiatric AEs with higher perampanel doses, as psychiatric AEs have previously been reported with perampanel.[15,17,18] Furthermore, these results highlight that perampanel dosing in adolescents should follow the same label recommendations as for adults.

ACKNOWLEDGMENTS

The authors would like to thank Ziad Hussein and Oneeb Majid of Eisai Ltd., and Yuko Umetsu of Eisai Co., Ltd., for their contributions to the planning and execution of the population modeling. Editorial support, under the direction of the authors, was carried out by Rebecca Furmston of Complete Medical Communications, funded by Eisai Inc.

CONFLICT OF INTERESTS

Osamu Takenaka and Kazunori Saeki are employees of Eisai Co., Ltd. Jim Ferry and Antonio Laurenza are employees of Eisai Inc.

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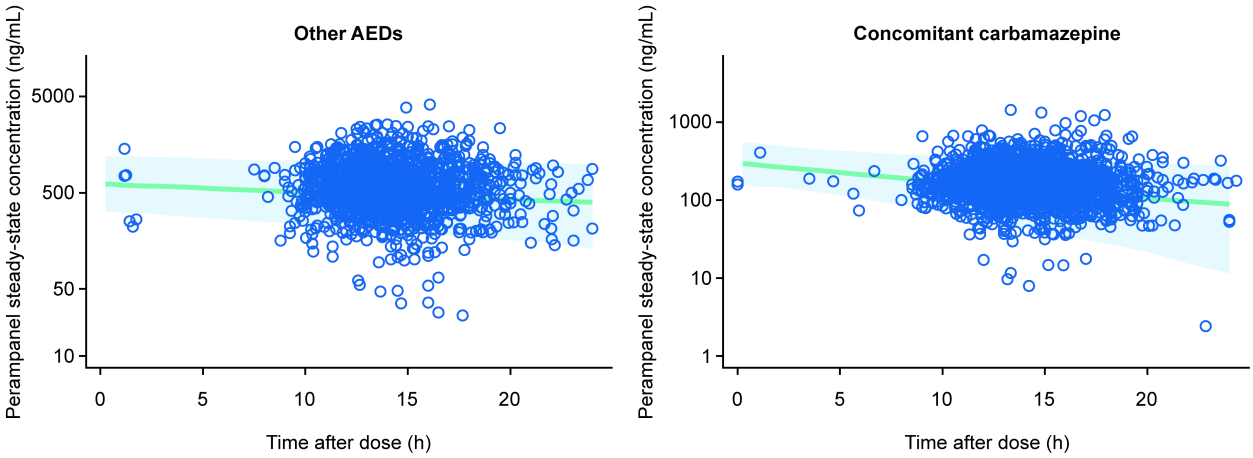
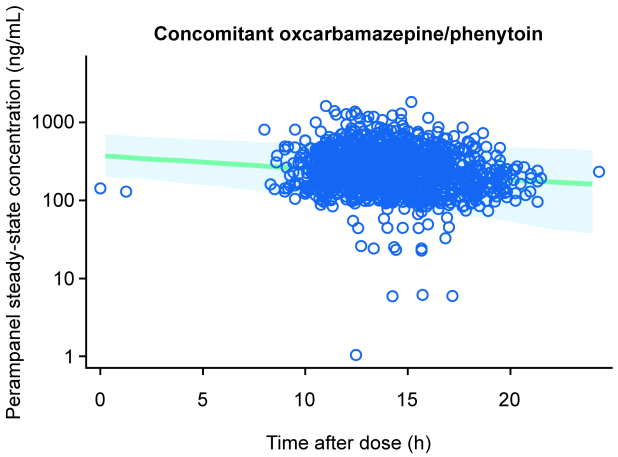
SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Takenaka O, Ferry J, Saeki K, Laurenza A. Pharmacokinetic/pharmacodynamic analysis of adjunctive perampanel in subjects with partial-onset seizures. *Acta Neurol Scand*. 2018;137:400–408. https://doi.org/10.1111/ane.12874


Other AEDs
Perampanel steady-state concentration (ng/mL)
5000
500
50
10
0
5
10
15
20
Time after dose (h)

Concomitant carbamazepine
Perampanel steady-state concentration (ng/mL)
1000
100
10
1
0
5
10
15
20
Time after dose (h)


Concomitant oxcarbamazepine/phenytoin
Perampanel steady-state concentration (ng/mL)
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100
10
1
0
5
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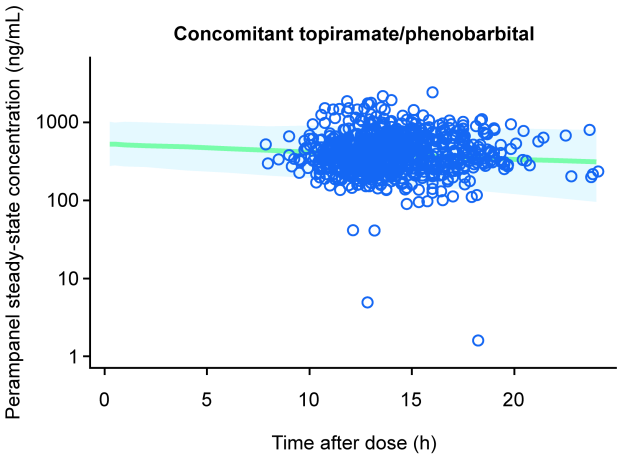
15
20
Time after dose (h)


Concomitant topiramate/phenobarbital
Perampanel steady-state concentration (ng/mL)
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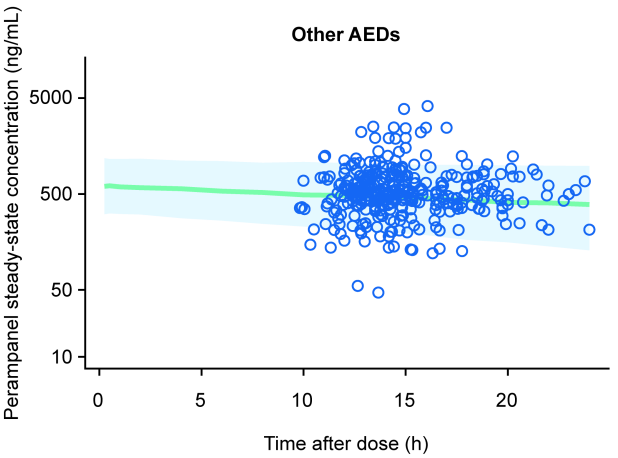
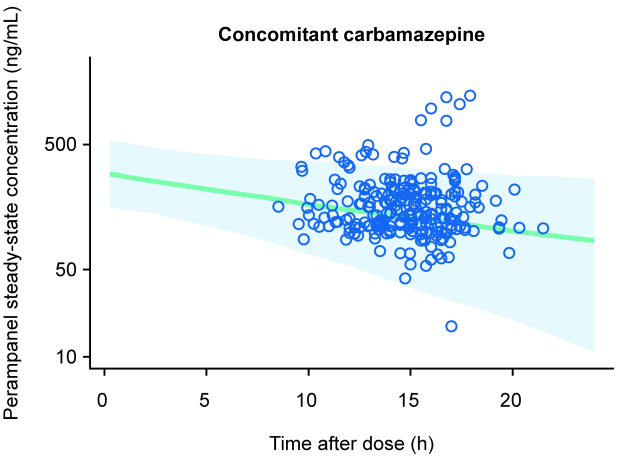
100
10
1
0
5
10
15
20
Time after dose (h)


Other AEDs
Perampanel steady-state concentration (ng/mL)
5000
500
50
10
0
5
10
15
20
Time after dose (h)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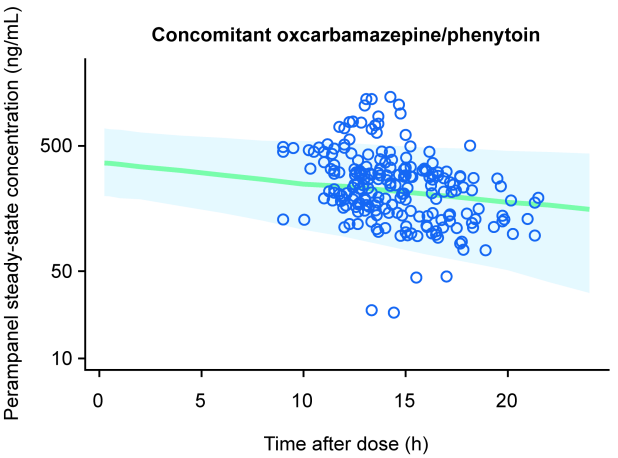
10
0
5
10
15
20
Time after dose (h)


Concomitant oxcarbamazepine/phenytoin
Perampanel steady-state concentration (ng/mL)
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50
10
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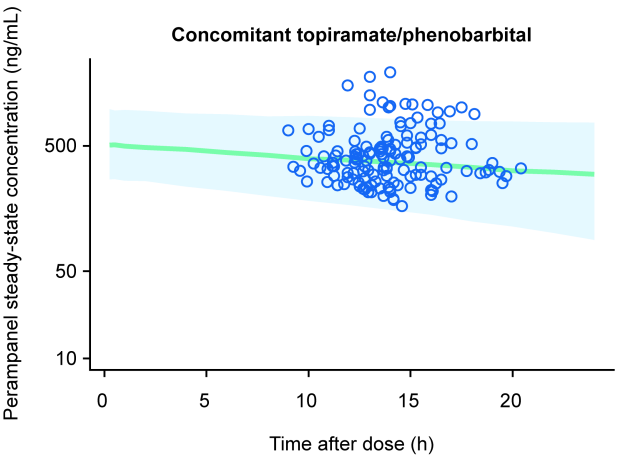
10
15
20
Time after dose (h)


Concomitant topiramate/phenobarbital
Perampanel steady-state concentration (ng/mL)
500
50
10
0
5
10
15
20
Time after dose (h)

Supplementary Table 1 Univariate analysis for the effects of covariates on the placebo effect in the PK/PD model for percent change from baseline in 28-day average seizure frequency

Effects on intercept	OFV	ΔOFV	df	ΔIIV (%)
Base	-1004.372		-	-
Race				
Japanese	-1010.306	↓5.934	1	-
Chinese	-1004.373	↓0.001	1	-
Concomitant AEDs				
Clobazam	-1016.072	↓11.7	1	↓0.001 on intercept ↓0.009 on slope
Phenytoin	-1006.849	↓2.477	1	-
Primidone	-1007.776	↓3.404	1	-
Phenobarbital	-1004.401	↓0.029	1	-
Carbamazepine	-1004.407	↓0.035	1	-
Levetiracetam	-1005.210	↓0.838	1	-
Oxcarbazepine	-1004.506	↓0.134	1	-
Lamotrigine	-1007.468	↓3.096	1	-
Topiramate	-1004.442	↓0.070	1	-
Valproic acid	-1007.468	↓3.096	1	-
Zonisamide	-1004.377	↓0.005	1	-
Region				
Africa	-1004.814	↓0.442	1	-
Asia	-1004.678	↓0.306	1	-
Europe	-1007.921	↓3.549	1	-
North America	-1005.593	↓1.221	1	-
South America	-1004.843	↓0.471	1	-

↓ = decrease.

AED, antiepileptic drug; df, degrees of freedom; OFV, objective function value; PD, pharmacodynamic; PK, pharmacokinetic; ΔOFV, change in objective function value; ΔIIV, change in inter-individual variability for the parameter compared with the model without the effect.

Supplementary Table 2 Model-predicted Cav,ss and responder probability in subjects receiving/not receiving AEDs affecting perampanel PK[a]

Perampanel dose (mg)	Predicted Cav,ss (ng/mL)	Response probability
Placebo	0	0.25
AEDs not affecting PK		
4	296	0.41
6	496	0.49
8	575	0.52
12	780	0.58
Topiramate or phenobarbital		
4	219	0.38
6	430	0.46
8	424	0.46
12	565	0.51
Oxcarbazepine or phenytoin		
4	145	0.34
6	222	0.38
8	261	0.40
12	393	0.45
Carbamazepine		
4	85	0.31
6	176	0.36
8	184	0.36
12	276	0.40

AED, antiepileptic drug; Cav,ss, average concentration at steady state; PK, pharmacokinetic.
[a]These data are for subjects aged 33 years who were not receiving concomitant clobazam or lamotrigine.