CLINICAL PHARMACOLOGY REVIEW

NDA:	**202834**
Brand Name:	Fycompa™
Generic Name:	Perampanel
Dosage Form & Strength:	Immediate Release Tablet (2, 4, 6, 8, 10 and 12 mg)
Indication:	Adjunctive therapy for partial-onset seizures in patients aged 12 years and above
Applicant:	Eisai Co.
Submission:	505(b)(1), Standard
Submission Dates:	12/22/2011, 07/13/2012, 08/10/2012, 08/21/2012, 09/05/2012, 09/10/2012, 09/17/2012
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The OCP office level briefing was held on September 20, 2012.

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1. Executive Summary

The sponsor is seeking approval of Fycompa (perampanel) as an adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients aged 12 years and older. Perampanel is a non-competitive AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor antagonist. The proposed formulations are film-coated oral tablets with strengths of 2, 4, 6, 8, 10 and 12 mg. The sponsor's proposed dosing regimen is: Fycompa should be taken once daily before bedtime; start with a dose of 2 mg/day; the dose may be increased based on clinical response and tolerability by an increment of 2 mg/day to a dose of 4 mg to 12 mg/day. The maximum recommended daily dose is 12 mg once daily. Dose increases should occur at weekly intervals and no more frequently than that.

To support the approval of the application, three pivotal, placebo-controlled, Phase 3 trials were conducted in intend-to-treat patient population to demonstrate the safety and efficacy of perampanel. Clinical pharmacology program consists of single- and multiple-dose studies evaluating pharmacokinetic (PK) profiles of perampanel, and examining the metabolic profiles, dose proportionality (Western and Japanese populations), absolute bioavailability (BA), effects of food and evening dosing, potential for drug-drug interactions, and PK in specific populations (elderly and hepatic impairment), and bridging between the to-be-marketed formulations and the clinical formulation used in the pivotal trials. Exposure-Response analysis was performed to evaluate the relationships between exposure of perampanel and efficacy and safety data obtained from the Phase 3 trials. Population PK analyses were performed to evaluate the effects of common covariates (age, gender, weight, race, and renal impairment) on PK of perampanel in healthy subjects and/or in patient population.

1.1 Recommendation

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 1 (OCP/DCP-1) has reviewed the submission and finds NDA 202-834 acceptable from an OCP perspective provided that an agreement is reached between the Sponsor and the Agency regarding the Post-Marketing Requirement (PMR), Post-Marketing Commitment (PMC) and the recommended labeling language.

Comments to be conveyed to the Medical Officers:

1. Based on Dose- and Exposure-Response relationships (efficacy: primary endpoint, % of reduction in seizure frequency during double-blind phase from baseline; safety: % of patients having hostility/aggression), we recommend the following,

1) For patients not on any enzyme-inducing AEDs (defined as carbamazepine, oxcarbazepine, phenytoin, phenobarbital and primidone), perampanel treatment should be initiated from 2 mg/day, and increased by an increment of 2 mg/day every week to a target dose of 8 mg/day. The labeling of FYCOMPA will describe the risk of hostility/aggression and recommend close monitoring of patients during titration period and at higher doses of perampanel. Given that,

dose of perampanel may be further increased to 12 mg/day in some patients, based on individual clinical response and tolerability.

2) For patients already on enzyme-inducing AEDs (any of carbamazepine, oxcarbazepine, phenytoin, phenobarbital and primidone), perampanel treatment should be initiated from 4 mg/day, and increased by an increment of 2 mg/day every week to a maximum dose of 12 mg. If adequate response is not obtained at 12 mg dose, patients should be switched to alternate treatment.

3) For patients on perampanel treatment, when enzyme-inducing AEDs mentioned above are introduced or withdrawn, patients should be closely monitored for their clinical response and tolerability. Dose adjustment of perampanel may be necessary.

4) Concomitant use of other strong CYP3A inducers (e.g., rifampicin and St. John's wort) should be avoided.

Dose- and Exposure-Response analyses showed that, the percentage reduction in seizure frequency during double-blind phase from baseline increased in a dose- and concentration-dependent manner with little difference between 8 mg and 12 mg, while the proportion of patients with hostility/aggression related adverse events increased in the concentration range between 8 mg and 12 mg.

A dedicated study in healthy subjects showed that carbamazepine increased oral clearance of perampanel to 3-fold and correspondingly decreased perampanel AUC to 1/3 of controls. Population PK analysis reported that carbamazepine, oxcarbazepine and phenytoin decreased perampanel AUC to 1/3-1/2 compared to patients not on enzyme-inducing AEDs. Lower efficacy (percentage of reduction in seizure frequency) was reported for patients on enzyme-inducing AEDs as a result of lower exposure of perampanel. Consequently, higher dose of perampanel may be necessary for these patients. The maximum dose of perampanel should not exceed 12 mg, as dose beyond 12 mg has not been tested in patients.

2. The maximum dose of perampanel should not exceed 4 mg for patients with moderate hepatic impairment. We recommend 6 mg as the maximum dose for patients with mild hepatic impairment. Dose should be titrated up every two weeks instead of every week. The total $AUC_{0\text{-}inf}$ of perampanel (free drug and drug bound to plasma protein) in patients with mild and moderate hepatic impairment was 1.49- and 2.55-fold, respectively, of those in healthy matched controls. The $AUC_{0\text{-}inf}$ of free perampanel in patients with mild and moderate hepatic impairment was 1.81- and 3.28-fold, respectively, of those in healthy controls because of the decreased plasma protein binding of perampanel in hepatically impaired patients. The terminal half-life values of perampanel in these patients were prolonged to 2-3 times of those in healthy controls.

3. Perampanel is not recommended for patients with severe renal impairment or patients undergoing hemodialysis. A dedicated study has not been conducted to evaluate the

effect of different degrees of renal impairment on PK of perampanel. Population PK analysis suggested that creatinine clearance is not a significant covariate for perampanel oral clearance. However, the dataset only contained 52 patients with mild renal impairment (CLcr: 50 – 80 mL/min) and 3 patients with moderate renal impairment (CLcr: 30 – 50 mL/min). Thus, the effect of severe renal impairment and end stage of renal disease on perampanel PK is unknown and can not be readily predicted, either. No dose adjustment is needed for patients with mild renal impairment. We recommend use of perampanel with caution in patients with moderate renal impairment and slower titration may be considered.

4. Repeated doses of 12-mg perampanel decreased C_{max} and AUC of levonorgestrel by 42% and 40%, respectively. The effectiveness of levonorgrestel-containing hormonal contraceptives may be impaired. Thus, if 12-mg perampanel is used, additional non-hormonal contraceptive methods should be used.

5. Perampanel should be taken ***at*** bedtime. When perampanel was administered under fasted state, C_{max} was 39-67% higher than that under fed condition (high-fat meal), and T_{max} was achieved earlier by 2-3 hrs. In accordance, the time to reach the maximal decrease of peak saccadic velocity was attained earlier by 1-2 hrs when perampanel was taken under fasted state, indicating earlier onset of sedation effects, compared to that under fed condition. In addition, all the pivotal trials were conducted with perampanel given before bedtime with food.

6. We propose a PMR to request the Sponsor to conduct *in vitro* study(ies) to further characterize the contributions of major CYP enzymes (other than CYP3A4/5) and non-CYP enzymes to perampanel metabolism in liver. Pending the results, further *in vivo* study may be considered. Perampanel is primarily metabolized. Though *in vitro* studies suggested that CYP3A4/5 may be the major enzyme responsible for perampanel metabolism, dedicated drug-drug interaction (DDI) studies in humans showed that CYP3A4/5 plays a limited role in perampanel metabolism and other CYP enzymes and/or non-CYP enzymes may also be involved. Due to the limitations of *in vitro* studies, the contributions of non-CYP3A enzymes to perampanel metabolism have not been adequately characterized. Thus, it is unknown whether any of these enzymes could be the major enzyme(s) responsible for perampanel metabolism. Consequently, the potential for adverse drug interactions cannot be excluded for patients who are on perampanel and concomitant medications that are inhibitors of such an enzyme.

7. We propose a PMC to ask the Sponsor to conduct an *in vitro* study to evaluate the effect of perampanel on CYP2B6 activity at clinically relevant concentrations. An *in vitro* study showed that perampanel at a concentration of 30 μM increased CYP2B6 activity to 2.2 – 3.6 fold of control. The steady-state C_{max} of perampanel at a maintenance dose of 12 mg once daily is projected to be around 2.83 μM, which is about 10-fold lower than the concentration studied. Thus, the effect of perampanel on CYP2B6 activity at this therapeutic concentration is unknown. Bupropion is a sensitive substrate of CYP2B6 and could be used in epilepsy patients. If perampanel increases CYP2B6 activity also at

therapeutic dose level, it has the potential to significantly decrease bupropion plasma concentration and thereafter lead to inadequate efficacy of bupropion.

1.2 Phase IV Commitment

The Sponsor should commit to conducting the following studies as a PMR or PMC:

- PMR: Conduct *in vitro* study(ies) to elucidate the contributions of major CYP isozymes (except CYP3A4/5) and non-CYP metabolic enzymes to perampanel metabolism, e.g., characterization of the enzymes involved in the formation of all identified metabolites of perampanel (including the oxidative metabolite M5).
- PMC: Conduct an *in vitro* study in human liver microsomes to evaluate the effects of a range of concentrations of perampanel (e.g., up to 30 μM and including clinical relevant concentration of ~3 μM) on CYP2B6 activity using a recommended CYP2B6 probe substrate as per the FDA Guidance for Drug-Drug Interactions.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Pharmacokinetics:

The exposure (AUC) of perampanel increased dose-proportionally over the range of 0.2-12 mg after single-dose administration and 1-12 mg after multiple-dose administration. Cmax of perampanel increased in a dose-proportional manner after single-dose administration of 0.2-8 mg and increased less than dose-proportionally beyond dose of 8 mg. The PK of perampanel was time-independent in both healthy subjects and patients. Oral clearance of perampanel was similar between healthy subjects and patients with partial-onset seizures.

Absorption:

The absolute oral bioavailability of perampanel tablets was reported to be 116%. The mass-balance study showed that, after a single oral dose of radiolabeled perampanel, only 3% of radioactivity was recovered in feces within 48 hrs post-dosing. Taken together, these results indicated that oral absorption of perampanel is essentially complete. Perampanel was rapidly absorbed after oral administration, with median T_{max} ranging from 0.5 to 2.5 hrs after single- or multiple-dose administration under fasted condition. High-fat meal reduced perampanel C_{max} by 28-40% and delayed its T_{max} by 2-3 hrs, but had insignificant effect on perampanel AUC.

Distribution:

The apparent volume of distribution (Vd/F) of perampanel in healthy volunteers averaged 77 L (ranging from 51 to 105 L). Plasma protein binding of perampanel was high (95-96%) and independent of perampanel concentrations (20 to 2000 ng/ml). Perampanel mainly bound with albumin and α1-acid glycoprotein and to a much lesser extent with γ-globulin. Saturable binding of perampanel was found for α1-acid glycoprotein. Mild and moderate hepatic impairment decreased the extent of plasma protein binding of perampanel. Blood to plasma ratio of perampanel was 0.55 – 0.59.

Metabolism:
Study showed that perampanel is extensively metabolized. Perampanel was primarily eliminated by oxidative metabolism, followed by glucuronide conjugation for some metabolites. *In vitro* studies suggested that CYP3A4/5 was the major enzyme responsible for perampanel metabolism. However, co-administration with ketoconazole in humans, a strong CYP3A4/5 inhibitor, only resulted in a modest increase (20%) of perampanel AUC, suggesting that CYP3A4/5 play a limited role in perampanel metabolism *in vivo*. Oral clearance of perampanel was greatly increased to 3-fold by carbamazepine which is known as a broad-spectrum enzyme inducer and is able to induce CYP3A4/5 and also other CYP and non-CYP enzymes. These findings suggest the involvement of other CYP enzymes and/or non-CYP enzymes in perampanel metabolism. However, the contributions of these non-CYP3A enzymes to perampanel metabolism have not been fully characterized. Several caveats are noted for the *in vitro* studies performed by the Sponsor using recombinant human CYP isozymes and human liver microsomes. (see Sections 2.2.4.4, and 2.4.1).

Unchanged perampanel accounted for 75-80% of the total drug-related material (total radioactivity) in plasma. No major metabolite with significant amount (> 10% of total drug-related material) was present in systemic circulation.

Elimination:
In the mass-balance study 22% and 48% of the dose were recovered in urine and feces, respectively, within a period of 42 days. Relative to metabolites, parent drug was present in feces only in small amounts. Due to low extraction efficiency (20-30%) of the feces samples, quantitative interpretation of the results could not be made. Little parent drug was detected in urine. Consistently, in a single-dose and a multiple-dose study less than 0.2% of administered dose was recovered as parent drug in urine within 48 hrs or 24 hrs after drug administration, respectively.

Oral clearance (CL/F) of perampanel was approximately 12 mL/min in healthy adults and patients. The terminal half-life ($t_{1/2}$) was 105 hrs on average based on the Phase 1 population PK analysis. After multiple dosing steady-state exposure of perampanel was approached by Day 14 and achieved within 21 days with around 4.3-fold accumulation in perampanel exposure ($AUC_{0\text{-}24hr}$) compared to single dose. Steady-state C_{max} was around 2.5-fold of that after single-dose administration.

Dose-/Exposure-Response relationships:
There were clear dose- and exposure-response relationships for both efficacy and safety of perampanel. The percent reduction in seizure frequency during double-blind phase from baseline (i.e., primary efficacy endpoint) appeared to increase in a dose- and concentration-dependent manner with little difference between 8 mg and 12 mg, while the proportion of patients with hostility/aggression related adverse events increased in the concentration range between 8 mg and 12 mg. The benefit-risk assessment supported a target dose of 8 mg in patients on treatment not including enzyme-inducing AEDs (such as carbamazepine, oxcarbazepine, phenytoin, phenobarbital and primidone). Further dose increase to 12 mg may be considered for some patients, depending on individual clinical

response and tolerability. (see Section 1.3 Extrinsic Factors for dosing recommendations for patients on treatment including enzyme-inducing AEDs)

Statistical analysis of the efficacy data suggested that 4 mg once daily was the minimum effective dose.

Intrinsic factors:

Age, gender, race, weight:

The population PK analyses based on pooled data from the pivotal efficacy trials showed that adolescent patients had slightly higher CL/F (0.787 L/hr) than adult patients (0.73 L/hr for males and 0.605 L/hr for females). Elderly (> 65 years old) had similar CL/F to younger adults. Female healthy subjects had 32% higher exposure (AUC) to perampanel than males. The difference was smaller in patients (19-27% higher AUC in females). CL/F of perampanel slightly decreased with increased fat body mass. These differences are not considered clinically significant. Race had no significant impact on the PK of perampanel.

Renal impairment:

A dedicated study has not been conducted to evaluate the PK of perampanel in patients with renal impairment. Though population PK analysis showed that median CL/F of perampanel was 27% lower in patients with mild renal impairment (CLcr: 50–80 mL/min), corresponding to an increase of 37% in AUC, compared to patients with normal renal function (CLcr > 80 mL/min), there was substantial overlap in exposure between these two groups of patients. In addition, there was no significant correlation between CL/F of perampanel and estimated creatinine clearance (mostly ≥ 50 mL/min). Thus, no dosage adjustment is needed for patients with mild renal impairment. There were only 3 subjects with moderate renal impairment (CLcr: 30–50 mL/min) in the Phase 3 PK dataset, who had 14% lower CL/F than patient with normal renal function. It is recommended that perampanel be used in moderately renal impaired patients with close monitoring. A slower titration may be considered. On the other hand, perampanel is not recommended for patients with severe renal impairment or patients undergoing hemodialysis, as their effects on perampanel PK can not be readily predicted.

Hepatic impairment:

Perampanel PK was evaluated in subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Total (free and plasma protein bound) $AUC_{0\text{-inf}}$ of perampanel was 50% higher in mild hepatic impairment patients and was more than doubled (2.55-fold) in moderate hepatic impairment patients compared to their demographic-matched healthy controls. The terminal $t_{1/2}$ was prolonged from 125 hrs in normal hepatic function subjects to 306 hrs in mild hepatic impaired patients, from 139 hrs to 295 hrs in moderate hepatic impaired patients. Unbound fraction of perampanel in plasma was 27% and 73% higher in mild and moderate hepatic impaired patients compared to their controls, respectively. Thus, the $AUC_{0\text{-inf}}$ values of free perampanel in patients with mild and moderate hepatic impairment were 1.81- and 3.28-fold, respectively, of those in healthy matched controls. Perampanel dose should not exceed 4 mg in moderate hepatic impaired patients and 6 mg should be the maximum

recommended dose for mild hepatic impaired patients. Due to longer $t_{1/2}$ of perampanel, titration of perampanel in these patients should be conducted more slowly with dose increased no more frequently than every two weeks.

Extrinsic factors:
Drug-Drug Interaction (DDI):
In vitro studies:
Perampanel did not inhibit CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, UGT1A1, UGT1A4 or UGT1A6 *in vitro*. It was a weak inhibitor of CYP2C8, UGT1A9 and UGT2B7 (IC_{50} > 30 μM) and is not expected to result in clinically significant DDI. Perampanel was a time-dependent inhibitor of CYP3A4. At a concentration of 30 μM, it increased CYP2B6 activity to 2.2 – 3.6 fold of control.

The effect of perampanel on CYP2B6 activity is unknown at its therapeutic concentration levels (steady state C_{max} predicted to be 1.89 μM for a maintenance dose of 8 mg once daily). Thus, a PMC is proposed for an *in vitro* study to investigate the effect of perampanel on CYP2B6 activity at clinically relevant concentrations to clarify the drug-drug interaction potential between perampanel and CYP2B6 substrates.

Perampanel did not induce CYP1A2. It was a weak inducer of CYP2B6 and is not expected to have clinically significant consequence. Perampanel induced CYP3A4 at concentrations of 3 μM and above, but the inducing effect was weak compared to the positive control, rifampicin. Perampanel may induce UGT1A1 (≥ 3 μM) and to a lesser extent induce UGT1A4 (30 μM).

Perampanel was not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT2, OAT3, OAT4, OCT1, OCT2 or OCT3. It was a weak inhibitor of P-gp, BCRP, OAT1, OAT3, OCT1 and OCT3. Perampanel increased activity of OAT2. Significant *in vivo* consequence involving these transporters is not anticipated.

Effect of co-administered drugs on perampanel:
Co-administration with ketoconazole (a strong inhibitor of CYP3A4) at 400 mg q.d. increased perampanel AUC by 20%, suggesting that CYP3A4/5 may play a limited role in perampanel metabolism. Co-administration with carbamazepine (a strong inducer of CYP3A4 and a broad-spectrum inducer for other CYP and non-CYP enzymes) at 300 mg b.i.d. increased CL/F of perampanel to 3-fold, decreased perampanel AUC by 67% and shortened its $t_{1/2}$ by half (from 56.8 hrs to 25.3 hrs). Results of these studies suggested the potential involvement of other CYP enzymes and/or non-CYP enzymes, besides CYP3A4/5, in the metabolism of perampanel in humans. However, the importance of these enzymes in perampanel metabolism remains unclear and, consequently, possibility of significant drug interactions between perampanel and inhibitors of these enzymes can not be excluded. Thus, a PMR is required to further elucidate the role of non-CYP3A metabolic enzymes in perampanel metabolism with *in vitro* study(ies).

The population PK analysis showed that carbamazepine increased perampanel CL/F to 3-fold of that in patients not receiving enzyme-inducing AEDs, which is consistent with the

results of the dedicated DDI study in healthy subjects. In addition, population PK analysis revealed that phenytoin and oxcarbazepine increased CL/F of perampanel to 2-fold in patients. Thus, with the presence of carbamazepine, oxcarbazepine and phenytoin, the exposure of perampanel was decreased to 1/3 – 1/2 of that in patients not receiving these AEDs. Population PK analysis did not detect inducing effect of phenobarbital (a broad-spectrum enzyme inducer) or primidone (prodrug of phenobarbital) on CL/F of perampanel. However, the result was not conclusive due to the limited number of patients on concomitant phenobarbital or primidone.

The recommended starting dose of perampanel is 2 mg/day for patients on treatment not including enzyme-inducing AEDs (carbamazepine, oxcarbazepine, phenytoin, phenobarbital and primidone). For patients already on treatment with any of these enzyme-inducing AEDs, we recommend a starting dose of 4 mg/day which can be increased to a maximum dose of 12 mg/day. If seizure control is not sufficient at 12-mg dose, switching to other treatment should be considered.

On the other hand, when these enzyme-inducing AEDs are introduced or withdrawn from patients on perampanel, patients should be closely monitored for their clinical response and tolerability. Dose adjustment of perampanel may be necessary.

Other strong CYP3A inducers (e.g., rifampicin, St. John's wort) should be avoided for concomitant use with perampanel.

Population PK analysis found that topiramate increased perampanel CL/F by 23-29%. However, such effect is not clinically meaningful. Other AEDs (clobazam, clonazepam, lamotrigine, levetiracetam, valproate, zonisamide) did not alter CL/F of perampanel.

Daily dosing of oral contraceptive (ethinylestradiol 30 μg and levonorgestrel 150 μg) did not affect perampanel PK.

Effect of perampanel on co-administered drugs:
Repeated 6-mg perampanel doses decreased AUC of midazolam (a probe CYP3A4 substrate) by 13%, indicating that perampanel was a weak CYP3A inducer and had minimal effect on CYP3A4 substrates. Repeated 4-mg doses did not alter the PK of levodopa.

Repeated doses of 12 mg perampanel reduced $AUC_{0\text{-}24hr}$ and C_{max} of single-dose levonorgrestrel by 40% and 42%, respectively. At 12-mg dose level, perampanel decreased C_{max} of single-dose ethinylestradial by 18% but not affected its $AUC_{0\text{-}24hr}$, suggesting that at this dose level perampanel did not significantly induce CYP3A. Repeated doses of 4 mg or 8 mg perampanel did not significantly affect AUC and C_{max} of ethinylestradial or levonogrestrel, with 8-mg perampanel slightly reducing $AUC_{0\text{-}24hr}$ and $AUC_{0\text{-}inf}$ of single-dose levonogrestrel by 9% and 12%, respectively. The significant decrease in exposure of levonorgestrel in the presence of 12 mg once daily dose of perampanel may impair its effectiveness as contraceptive. Thus, when 12 mg dose of perampanel is given, non-hormonal forms of contraception should be used.

Population PK analysis showed that perampanel did not have clinically significant effects on other AEDs (carbamazepine, clobazam, clonazepam, lamotrigine, levetiracetam, phenobarbital, phenytoin, topiramate, valproic acid, and zonisamide). Perampanel decreased oxcarbazepine clearance by 26%. The clinical relevance of this effect is unknown, as the pharmacological activity of oxcarbazepine is primarily exerted through its major metabolite, 10-monohydroxy metabolite (MHD), which was not measured by the sponsor.

Food effect:
All the pivotal clinical trials were conducted under fed condition (i.e., perampanel was administered with food before bedtime). Two Phase 1 food-effect studies showed that, compared to administration of drug under fed condition with high-fat meal, C_{max} of perampanel was 39% or 67% higher when administered under fasted state, while AUC remained similar. In addition, median T_{max} of perampanel was shortened by 2-3 hrs to approximately 1 hr under fasted state. Peak saccadic velocity (PSV), an objective assessment of sedation, was measured in these studies. The maximal decrease of PSV from baseline was similar when perampanel (single dose of 1 mg or 6 mg) was administered under fasted state compared to fed condition. However, the time to reach the maximal decrease of PSV was achieved earlier by 1-2 hrs when perampanel was administered under fasted state, indicating early onset of sedation effect. Considering the clinical trial design and the observed correlation between T_{max} for plasma concentration and T_{max} for sedative effect (i.e, PSV) of perampanel, we recommend that perampanel be taken ***at*** bedtime regardless of food intake.

PK Comparison of TBM vs. Clinical Formulations in Pivotal Trials:
All the pivotal trials were conducted with Formulation C of perampanel tablet in 2-mg strength, whereas Formulations C (2 and 4 mg) and Formulation D (6, 8, 10 and 12 mg) are the proposed commercial formulations. Two BE studies using the lowest (6 mg) and the highest (12 mg) strengths of Formulation D demonstrated that this formulation was bioequivalent to Formulation C on the basis of point estimates for geometric mean ratios and the corresponding 90% confidence intervals (CIs) which fell within the 80-125% BE acceptance criteria. Biowaiver was granted for the intermediate 8-mg and 10-mg strengths of Formulation D based on comparisons of *in vitro* dissolution data. In addition, one BE study demonstrated dose strength bioequivalence between 2-mg and 4-mg strengths of Formulation C.

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2. Question Based Review

2.1 General Attributes

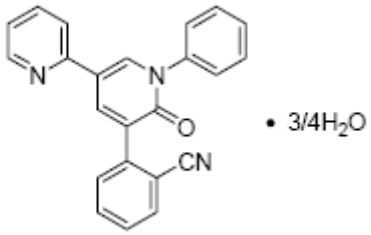
2.1.1 What are therapeutic indication(s) and the proposed mechanisms of action?

Fycompa (perampanel, E2007) is proposed as an adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

The precise mechanism by which perampanel exerts its antiepileptic effects in humans remains to be fully elucidated. The presumed mechanism of action of perampanel is acting as a non-competitive antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor. *In vitro*, perampanel inhibited AMPA-induced (but not NMDA-induced) increase in intracellular calcium. In animals, perampanel significantly prolonged seizure latency in an AMPA-induced seizure model.

2.1.2 What are the highlights of physico-chemical properties of the drug substance?

Perampnael (E2007), the active ingredient of Fycompa, is chemically known as 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl) benzonitrile hydrate (4:3). Its molecular formula is $C_{23}H_{15}N_3O \bullet 3/4H_2O$ and the molecular weight is 362.90 (3/4 hydrate) or [redacted] (b) (4) Perampanel is white to yellowish white powder that is freely soluble in N-methylpyrrolidone, sparingly soluble in acetonitrile and acetone, slightly soluble in methanol, ethanol and ethyl acetate, very slightly soluble in 1-octanol and diethyl ether and practically insoluble in heptane and water. The structure for perampanel is provided below.



2.1.3 What are the proposed dosage(s) and route(s) of administration?

Fycompa tablets are available as round, bi-convex, film coated oral tablets in multiple strengths, as presented in Table 1 below.

Table 1. Description of Commercial Tablet Formulations of Perampanel

Dosage Strength	2 mg	4 mg	6 mg	8 mg	10 mg	12 mg
Diameter	6.5 mm	8.1 mm	8.1 mm	8.1 mm	8.1 mm	8.1 mm
Weight	105 mg	210 mg	210 mg	210 mg	210 mg	210 mg
Debossment	Debossed	Debossed	Debossed	Debossed	Debossed	Debossed
Color	Orange	Red	Pink	Purple	Green	Blue
Formulation	C	C	D	D	D	D

The sponsor proposed that Fycompa should be taken once daily before bedtime. Treatment should be initiated with a dose of 2 mg/day. The dose may be increased based on clinical response and tolerability by 2 mg/day increments on a weekly basis to a target dose of 4 mg to 12 mg/day. The maximum recommended daily dose is 12 mg. Dose increases should occur no more frequently than at weekly intervals.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The perampanel clinical development program for the proposed indication included 27 Phase 1 studies in healthy subjects or specific populations, 4 completed Phase 2 studies (Study 203, 206, 208 and 231), 3 completed Phase 3 trials (Study 304, 305 and 306), one ongoing study in adolescents (Study 235), and 3 ongoing open-label extension studies (Study 207, 233 and 307). Design features of these studies are briefly presented in Table 2 (please refer to Appendix 4.3 Filing Review for details). In addition, there were 4 population PK analysis reports: CPMS-E2007-2011-002 based on 19 Phase 1 studies, EMFFR2008/06/00 based on 2 Phase 2 studies, CPMS-E2007-2011-003 based on 3 pivotal Phase 3 studies (all patients), and CPMS-E2007-2011-004 based on 3 pivotal Phase 3 studies (adolescent patients).

Table 2. Perampanel Clinical Pharmacology Studies

Study Category Study No.	Perampanel Doses Evaluated	Study Type/Population
Single-dose PK and PD studies in healthy subjects		
E2007-E044-001	0.2, 0.5, 1, 2, 4, 6, and 8 mg	Ascending dose study/adult males
E2007-E044-003	1 mg	Food effect/adults
E2007-E044-007	2 mg	Mass balance/elderly
E2007-A001-008	2 mg	Bioequivalence/adults
E2007-J081-010	0.25, 0.5, 1, 2, 4, 6, and 8 mg	Dose evaluation/Japanese males
E2007-E044-016	4 mg	Bioequivalence/adults
E2007-E044-017	8 mg	Bioavailability and mass balance/adult males
E2007-E044-028	4 mg	Bioavailability/adults
E2007-E044-037	12 mg	Bioequivalence/adults
E2007-A001-039	6 mg	Bioequivalence/adults
E2007-A001-040	12 mg	Bioequivalence/adults
Multiple-dose PK and PD studies in healthy subjects		
E2007-E044-002	1, 2, 4, and 6 mg QD	Ascending-dose study/adult males
E2007-E044-009	6 mg single dose	Food effect/adults
	6, 8, and 10 mg QD	Morning vs. evening dosing/adults
E2007-J081-026	2 and 4 mg QD	Ascending-dose study/Japanese males
Studies of PK and PD in epileptic patients		
E2007-E049-203	1 and 2 mg QD	Epileptic adults with partial-onset seizures
E2007-J081-231	2, 4, 6, 8, 10, and 12 mg QD	Epileptic adults with partial-onset seizures
Evaluation of intrinsic factors on PK and PD: studies in special populations		
E2007-E044-004	1 and 2 mg single dose	PK and PD in healthy elderly subjects
E2007-E044-015	1 mg single dose	PK in adults with hepatic impairment vs. healthy adults

Effect of extrinsic factor on PK: drug-drug interaction (DDI) studies		
E2007-E044-005	1 mg	Ketoconazole comparator/healthy adult males
E2007-E044-006	2 mg	Carbamazepine comparator/healthy adult males
E2007-A001-014	6 mg QD	Midazolam comparator/healthy adults
E2007-E044-019	2 and 4 mg QD	Microgynon® 30 ED comparator/healthy premenopausal females
E2007-E044-029	6 mg single dose; 4, 8, and 12 mg QD	Microgynon 30 ED comparator/healthy premenopausal females
E2007-E044-025	4 mg QD	Levodopa comparator/healthy adults
E2007-E044-030	4, 8, and 12 mg single dose and QD	Alcohol study/healthy adults
Special studies in healthy subjects		
E2007-A001-013	6, 8, 10, and 12 mg QD	QT interval study/healthy adults
E2007-E044-020	2 and 6 mg QD	Phototoxic potential study/healthy adults
E2007-A001-023	8, 12, 16, 20, 24, 28, 32, and 36 mg single dose	MTD and abuse liability/recreational polydrug users
E2007-A001-024	8, 24, and 36 mg single dose	Abuse liability/recreational polydrug users

Source: Appendix 2
MTD = maximum tolerated dose, QD = once daily, PD = pharmacodynamics, PK = pharmacokinetics

Pivotal Clinical Studies:
Studies 304, 305, and 306 were multi-center, randomized, double-blind, placebo-controlled, parallel-group studies to evaluate the efficacy, safety, and tolerability of fixed doses of perampanel given as adjunctive therapy (i.e., added onto one to three concomitant anti-epilepsy drugs (AEDs)) in epileptic patients aged 12 years and older (18 years and older for sites in some countries). The three studies had similar design but differed in the doses of perampanel evaluated, as illustrated in Figures 1 and 2.

Figure 1. Study Diagram for E2007-G000-304 and E2007-G000-305

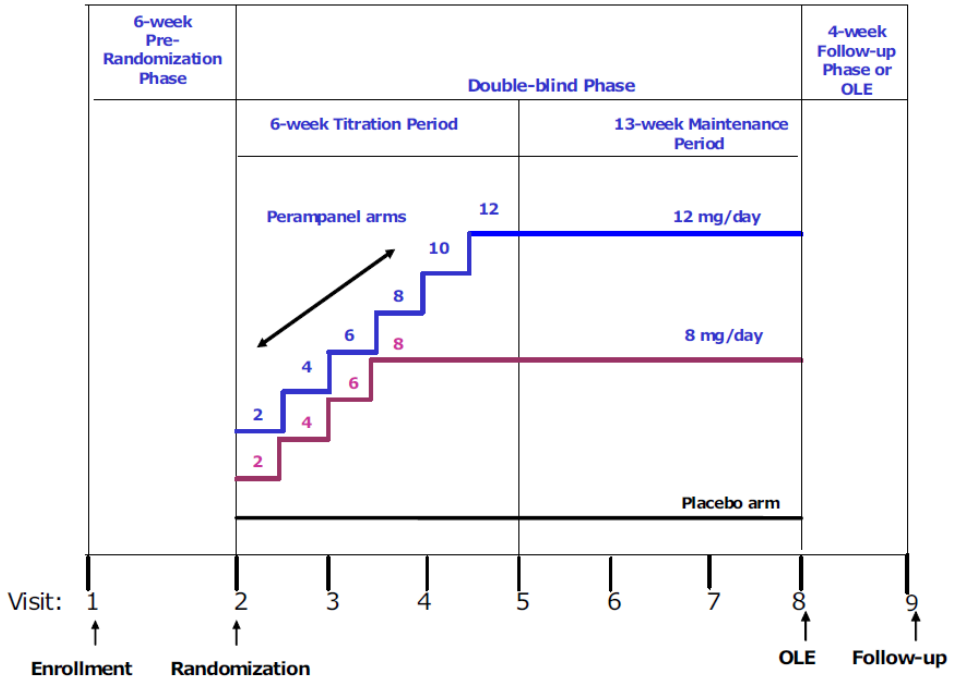
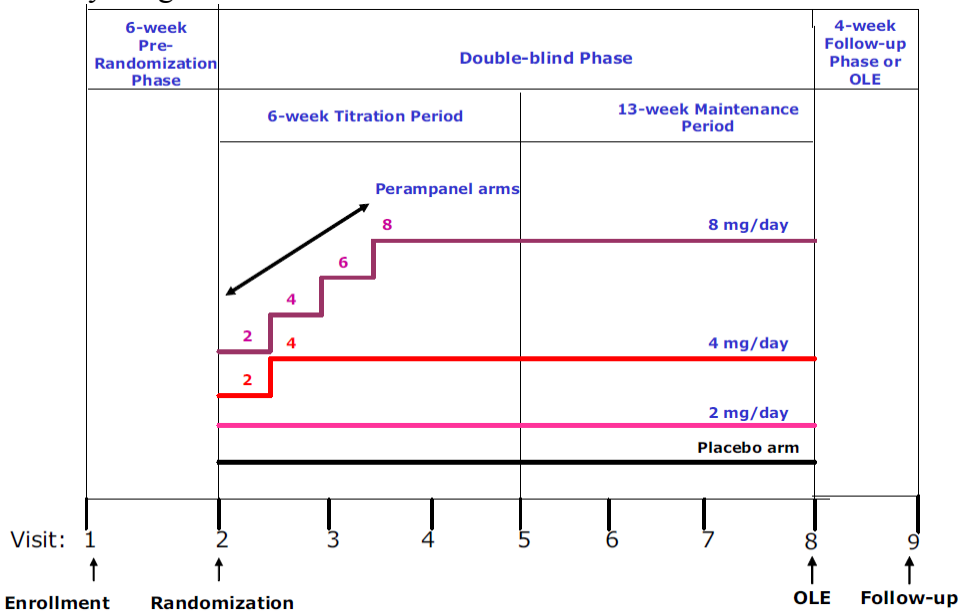


Figure 2. Study Diagram for E2007-G000-306



Subjects who met seizure frequency and type criteria during the Pre-randomization Phase were randomly assigned with equal probability to receive study medication (placebo or 2, 4, or 8 mg perampanel in Study 306; placebo or 8 or 12 mg perampanel in Studies 305 and 304) administered once daily before bedtime with food. During the Titration Period, dosage was increased in 2-mg increments on a weekly basis until the target dose was achieved. Subjects continued to take their baseline AED medication regimen throughout the double-blind Phase and no changes to the concomitant AEDs were permitted. Only one inducer AED (defined in the protocol as carbamazepine, phenytoin, phenobarbital, or primidone) out of the maximum of three AEDs was allowed. Down-titration of study medication was permitted during the Double-blind Phase for subjects experiencing intolerable adverse events; more than one down-titration was discouraged and the dose was to be increased again as soon as tolerability improved. Subjects who completed the Double-blind Phase could enter the OLE study (307) and receive treatment with open-label perampanel. Subjects who did not elect to enroll in the OLE study or who withdrew prematurely during the Double-blind Phase entered the 4-week Follow-up Phase. Study medication was discontinued at the start of this phase (i.e., no downward titration of study drug was required).

2.2.2. What is the basis for selecting the clinical endpoints or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint in the three Phase 3 studies was the percent change in seizure frequency per 28 days during the Double-blind Phase relative to the Pre-randomization Phase. Information about the number and type of seizures experienced was recorded in a daily diary. The primary analysis was an analysis of covariance (ANCOVA) in the Intent-to-Treat (ITT) dataset and later on was amended to Full ITT dataset (please refer to Statistical review by Dr. Ququan Liu for details). Both the

baseline seizure frequency per 28 days and the percent change per 28 days during treatment were rank-transformed separately. ANCOVA was then conducted on these rank-transformed percent change data, with treatment and pooled countries as factors, and the ranked baseline seizure frequency per 28 days as a covariate.

The key secondary endpoint was responder rate. A responder was defined as a subject who experienced a 50% or greater reduction in seizure frequency per 28 days during the maintenance period of the double-blind treatment phase relative to baseline.

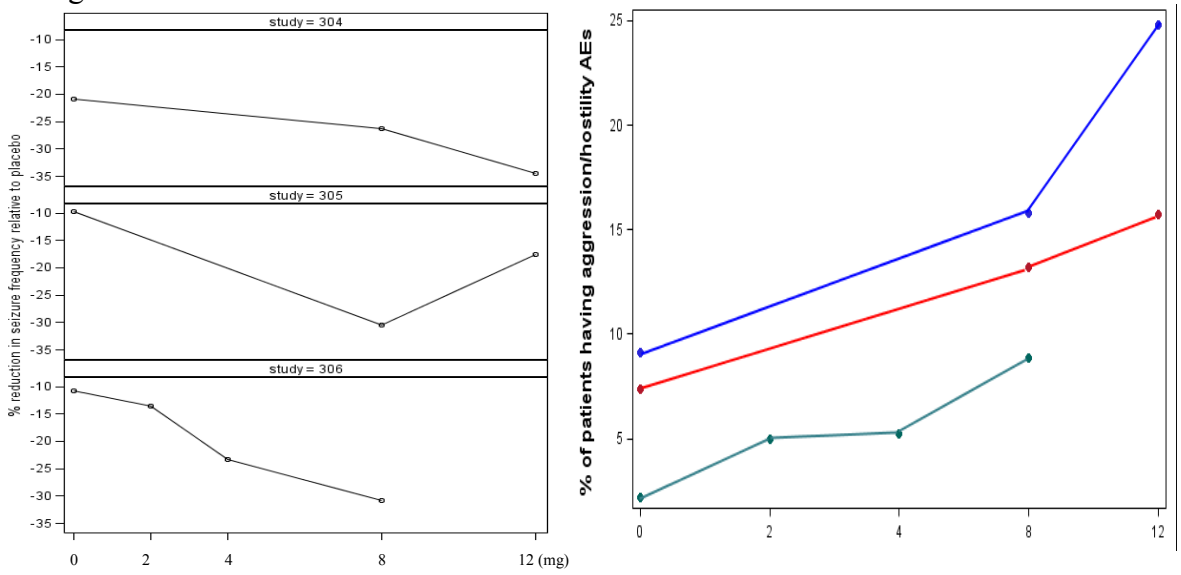
2.2.3 Exposure-Response

2.2.3.1. Is there any significant exposure-response relationship? And does the relationship support the proposed dosing regimen?

Yes, according to the pharmacometric reviewer's assessments, there were clear dose- and exposure-response relationships for both efficacy and safety data from three Phase 3 trials. The primary endpoint (reduction in seizure frequency) was used for efficacy assessment. For safety analysis the adverse events related to hostility/aggression based on Standardized MedDRA Queries (SMQs) were extracted from the adverse event dataset.

Dose-Response Relationships
As illustrated in Figure 3, the seizure frequency decreased in a dose-dependent manner with little difference between 8 mg and 12 mg, while the proportion of patients with hostility/aggression related adverse events increased in the dose range of 8 mg and 12 mg.

Figure 3. Efficacy and Safety of Perampanel in Patients with Partial-Onset Seizures on Different Maintenance Doses of Perampanel. Left Panel: Efficacy - Percentage of Reduction in Seizure Frequency during Double-Blind Phase from the Baseline; Right Panel: Percentage of Patients Having Hostility/Aggression Related Adverse Events during Double-Blind Phase



The dose of 2 mg did not meet the statistically significant criteria (p-value=0.4197). However, the doses of 4 mg, 8 mg and 12 mg showed effectiveness in all studies, although 12 mg failed to show greater efficacy compared to 8 mg in Study E2007-G000-305.

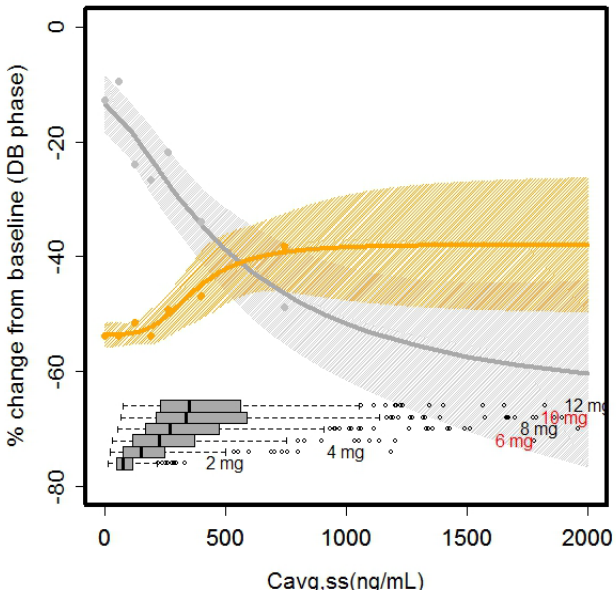
Table 3. Summary of Results of Primary Efficacy Analyses (based on Full ITT analysis set) The numbers are the median percent reduction of seizure frequency during double-blind phase from the baseline relative to placebo with p-values in parentheses.

Study / Dose	2mg	4mg	8mg	12mg
306	-4.36 (0.4197)	-13.7 (0.0026)	-20.1 (<0.0001)	
305			-19.1 (0.0008)	-13.69 (0.0105)
304			-13.53 (0.0261)	-14.2 (0.0158)

Exposure-Response Relationships

The pharmacometric reviewer also analyzed the efficacy and safety data with corresponding perampanel average concentrations at steady state (Css,avg) which were predicted from the Phase 3 population PK model. The analysis shows that the seizure frequency decreased in concentration-dependent manner with little difference between exposures after 8 mg and 12 mg, while the proportion of patients with hostility/aggression related adverse events increased in the concentration range corresponding to doses of 8 mg and 12 mg.

Figure 4. The Benefit and Risk Profiles of Perampanel. The grey and orange shaded areas represent the efficacy (% reduction in seizure frequency) and safety (% patients of having hostility/aggression related AEs), respectively. The solid lines are model-predicted relationship and the dots are observed data at the ranked six bins of perampanel steady state concentrations. The boxplots indicate the distribution of concentration at each dose group (6 mg and 10 mg were *simulated* assuming the same variability as 4 mg).



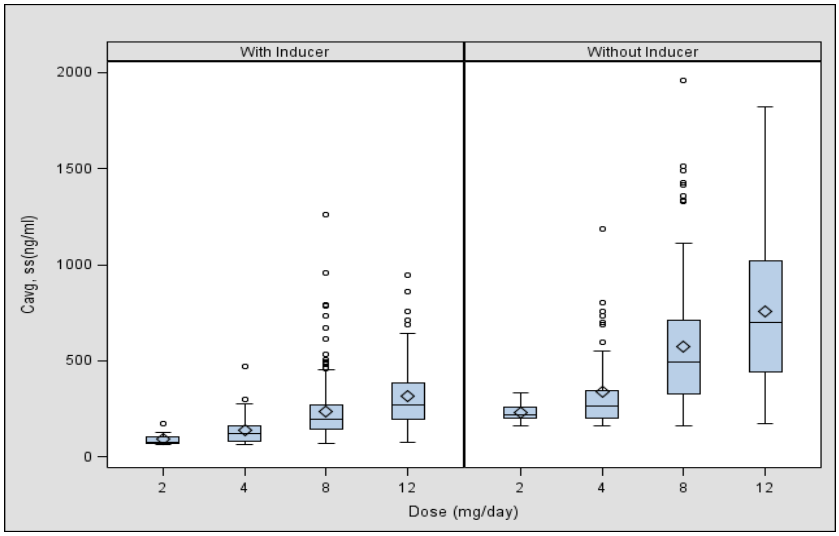
Sub-group Analysis by Inducer and Non-inducer AEDs

The Sponsor conducted dose-response analysis in patients taking enzyme-inducing AEDs at baseline (any of carbamazepine, oxcarbazepine, and phenytoin, defined as inducer group) and patients not taking these AEDs at baseline (defined as non-inducer group). The analysis indicated smaller effect sizes of perampanel in inducer group compared to non-inducer group for the same maintenance doses (see Table 8 and Table 9 in Appendix 4.2 Pharmacometric Review for details).

It is concerned that the sub-group analysis conducted by the sponsor can be confounded by co-medications as approximately 80-90% of patients in all three efficacy trials took 2 or 3 AEDs as background therapies. Consequently, an exploratory concentration-efficacy analysis was performed for each group in order to examine the potential confounding effect by unbalanced baseline characteristics including other AEDs use in inducer and non-inducer groups.

Examining the distribution of perampanel Css,avg in the two groups shows that the Css,avg of perampanel in inducer group were about 1/3-1/2 of that in non-inducer group. This is consistent with the findings from the dedicated DDI study with carbamazepine and also the Phase 3 population PK analysis which showed that carbamazepine, oxcarbazepine and phenytoin increased perampanel apparent clearance to 2-3 folds of that in control groups (see Section 2.4 Extrinsic Factors for details).

Figure 5. The Distribution of Perampanel Average Concentration at Steady State by Dose in Inducer and Non-inducer Groups



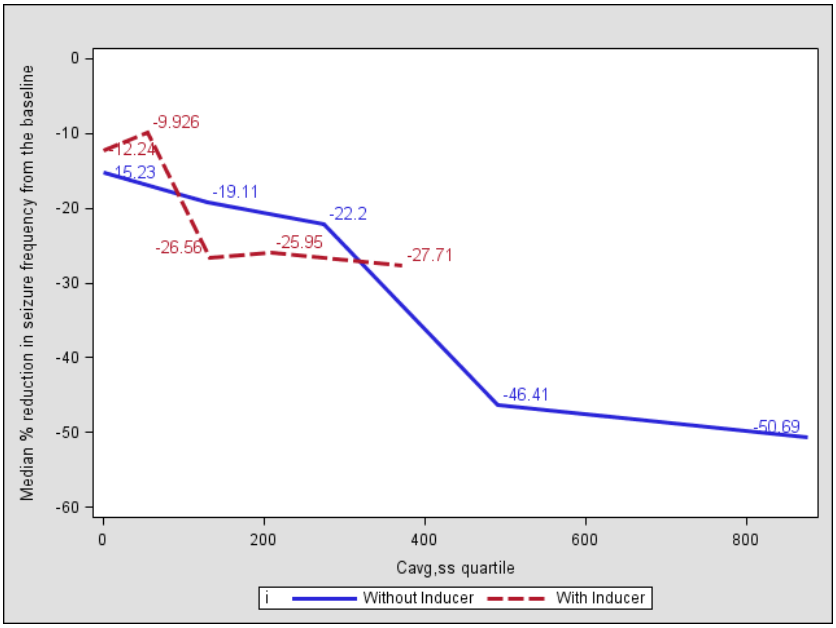
The Css,avg was binned by quartiles for inducer and non-inducer groups. The median concentration with range in each bin is displayed by groups in the following table.

Table 4. The Median and Range of Average Concentrations of Perampanel (ng/mL) at Steady State in Each Quartile by Inducer and Non-inducer Groups.

Quartile	Inducer Group: median (range)	Non-Inducer Group: median (range)
1st	55 ng/ml (10-88)	129 ng/ml (21-203)
2nd	132 ng/ml (92-167)	275 ng/ml (204-365)
3rd	209 ng/ml (168-267)	491 ng/ml (367-650)
4th	371 ng/ml (268-1260)	876 ng/ml (672-1958)

The median percent of reduction in seizure frequency was calculated for each bin of concentration and shown in Figure 6 by groups of inducer and non-inducer. The plots suggest that, at similar concentration ranges of perampanel, the reduction in seizure frequency is similar between inducer and non-inducer groups. If an assumption of similar distribution of baseline characteristics including other background treatments can be made for patients across concentration quartile bins, then the data suggests that there is no additional pharmacodynamic interaction. The lack of pharmacodynamic interaction implies that dose of perampanel can be increased in patients taking enzyme-inducing AEDs to reach perampanel concentrations closer to those observed in patients not taking enzyme-inducing AEDs.

Figure 6. Median Change in Seizure Frequency versus Steady State Average Perampanel Concentrations in Studies of 304/305/306. The effect size is displayed at the median concentrations at each bin.



Recommendation: Due to the significant increase of perampanel clearance by enzyme-inducing AEDs and resulted lower perampanel exposure, dosing recommendation is proposed separately for patients on treatment with enzyme-inducing AEDs or non-inducers. Herein, enzyme-inducing AEDs include carbamazepine, oxcarbazepine, phenytoin, phenobarbital and primidone. Phenobarbital and primidone are generally considered as broad-spectrum enzyme inducers as carbamazepine and phenytoin and are

expected to have inducing effect on perampanel clearance. The population PK analysis with limited data did not detect such effect and the results were inconclusive. (see Section 2.4 Extrinsic Factors for details)

Given that efficacy and safety profiles of perampanel show little difference in efficacy between 8 mg and 12 mg but higher risk with increasing dose/concentration, the target maintenance dose is recommended to be 8 mg once daily for patients not on treatment with any enzyme-inducing AEDs. Perampanel treatment should be initiated at 2 mg/day, and increased by an increment of 2 mg/day every week to a target dose of 8 mg/day. The labeling of FYCOMPA will describe the risk of hostility/aggression and recommend close monitoring of patients during titration period and at higher doses of perampanel. Given that, dose of perampanel may be further increased to 12 mg/day in some patients, based on individual clinical response and tolerability.

For patients already on any of the enzyme-inducing AEDs, perampanel treatment should be initiated at 4 mg/day and increased by an increment of 2 mg/day every week to a maximum dose of 12 mg. If sufficient seizure control is not achieved at 12 mg dose, patients should be switched to alternate treatment. Further increase of dose beyond 12 mg is not recommend since doses higher than 12 mg have not been studied in patients. Furthermore, when these enzyme-inducing AEDs are introduced into or withdrawn from patients on perampanel treatment, the patients should be closely monitored for their clinical response and tolerability, and dose adjustment (increase or decrease) for perampanel may be necessary.

2.2.3.2 Does this drug prolong the QT or QTc interval?

No significant QTc prolongation effect of perampanel was detected in the TQT study (E2007-A001-013) where healthy subjects received 6 mg once daily from Day 1- Day 7, 8 mg on Day 8, and 10 mg on Day 9 followed by 12 mg once daily for another 7 days (Day 10 – 16). The largest upper bounds of the 2-sided 90% CI for the mean differences between perampanel (6 mg and 12 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. In this study 12 mg dose produced a mean perampanel C_{max} value of 800 ± 222 ng/ml. As described later (Table 6), a steady-state C_{max} of 661 ng/ml (1.89 μM) was predicted for perampanel administered under fasted condition following the dosing regimen proposed for clinical use (i.e, 2 mg × 7 days → 4 mg × 7 days → 6 mg × 7 days → 8 mg maintenance dose). Drug-drug interaction study E2007-E044-005 showed that strong CYP3A inhibitor ketoconazole (400 mg once daily) increased AUC of perampanel by 20% and decreased its C_{max} by 10%. Thus, the C_{max} observed in the TQT study following the 12-mg dose covered these scenarios. Details are available in the review for the thorough QT study documented by Dr. Joanne Zhang, and the review memo documented by Dr. Mónica L. Fiszman of the QT-IRT review team.

2.2.4 What are the PK characteristics of the drug and its major metabolite?

2.2.4.1 What are the single and multiple dose PK parameters?

Single- and multiple-dose PK characteristics of perampanel were evaluated in a number of Phase 1 studies including a single-dose escalation Study E2007-E044-001 and a multiple-dose escalation Study E2007-E044-002 in Western populations. The PK profiles of perampanel obtained from these two studies are shown below.

PK Profiles

Figure 7. Mean (+SD) Plasma Concentration Profiles of E2007 after Single Doses in Healthy Male Volunteers (Left panel: 0-48 hrs; Right Panel: 0-168 hrs) (Study E2007-E044-001)

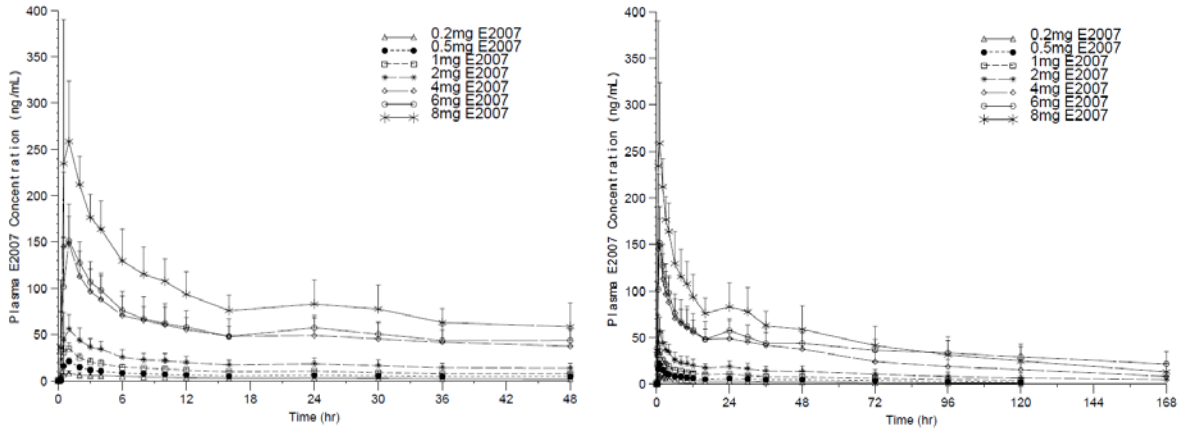
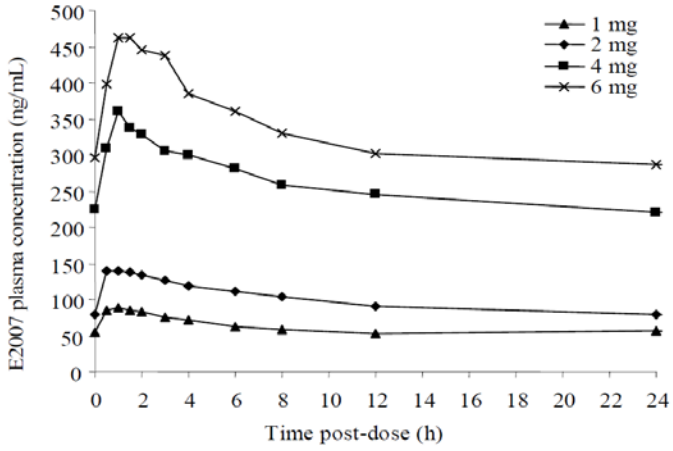


Figure 8. Mean Perampanel Plasma Concentration-Time Profiles after 14 Days Repeated Dosing (once daily) in Healthy Male Volunteers (Study E2007-E044-002)



[Note: Dosing regimen for 6 mg was different from those for 1 – 4 mg. Doses of 1, 2 and 4 mg were administered once daily for 14 days. For 6 mg cohort, 4 mg was given q.d. for the first 7 days, followed by 6 mg for another 7 days.]

PK Parameters

The terminal $t_{1/2}$ of perampanel varied among studies ranging from 53–157 hrs. On average perampanel has a long terminal $t_{1/2}$ around 100 hrs. A population PK analysis (CPMS-E2007-2011-002) was performed based on 19 Phase 1 studies using a two-compartment model with first-order absorption. The PK parameters presented in the table

below were calculated for each subject using the population PK model, perampanel doses, and covariates for each subject.

Table 5. Mean (SD) Perampanel Pharmacokinetic Parameters Calculated from the Population Pharmacokinetic Modeling of Phase 1 Data (Study CPMS-2007-2011-002)

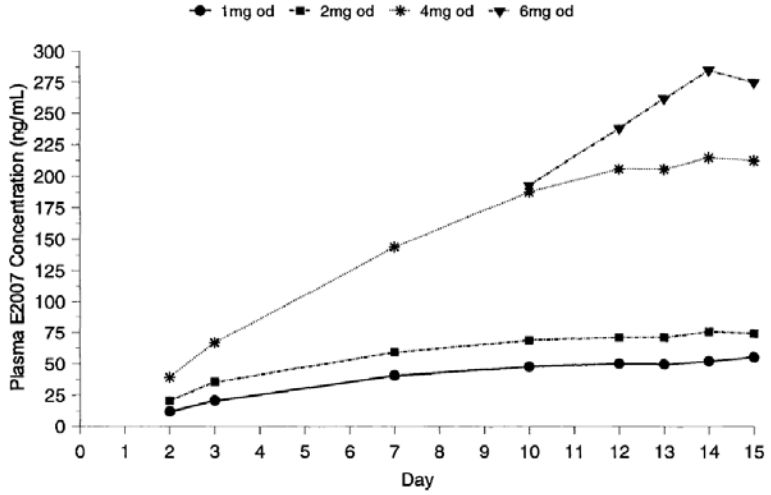
Perampanel dose	t_{max}[a] (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)	$AUC_{(0\text{-inf})}$ (ng·h/mL)	CL/F (mL/min)
			Single Dose		
1 mg (N=24)	1.00 (0.50-3.00)	36.8 (12.2)	111 (59.6)	2251 (1189)	9.77 (5.75)
2 mg (N=106)	1.00 (0.50-8.00)	60.7 (20.7)	85.2 (44.2)	3379 (156)	12.0 (5.73)
4 mg (N=68)	1.00 (0.50-6.00)	123 (46.5)	117 (133)	8092 (5142)	10.0 (3.83)
8 mg (N=64)	1.00 (0.50-10.0)	222 (79.2)	99.1 (42.7)	14113 (7373)	11.2 (4.50)
12 mg (N=45)	1.00 (0.50-4.00)	336 (120)	104 (51.6)	21033 (10034)	11.7 (6.18)
			Repeated Dosing (QD)		
4 mg (N=39)	1.00 (0.50-8.00)	372 (161)	98.1 (51.4)	7352 (3377)	11.0 (5.17)
8 mg (N=26)	1.00 (0.50-8.00)	702 (251)	122 (89.1)	15577 (7656)	10.5 (4.62)
12 mg (N=93)	1.00 (0.50-6.00)	1139 (487)	73.4 (41.5)	15999 (8438)	15.4 (6.53)

a. Presented as Median (Minimum – Maximum)

Steady-State

Time to reach steady state: Following once-daily dosing of perampanel, attainment of steady-state was approached by Day 14 and was achieved within 21 days, based on the results from Studies E2007-E044-002, E2007-E044-014, E2007-E044-025, E2007-J081-026 and E2007-E044-029.

Figure 9. Geometric Mean Pre-dose Plasma Perampanel Concentrations (Study E2007-E044-002)



[Note: For 6 mg group, concentrations on Days 10, 11, 12, 13 and 14 are those following 6 mg perampanel q.d. for 3, 4, 5, 6 and 7 days, respectively.]

In addition, as illustrated in Table 6, steady state of perampanel could be reached earlier for a high maintenance dose when perampanel dose is titrated up by a step of 2 mg every week. For example, 94% of the $C_{max,ss}$ values, 90% of the $C_{av,ss}$ values and 92% of the $C_{min,ss}$ values are projected to be achieved after 1-week daily administration of 8 mg.

Accumulation: Following once-daily dosing of 1, 2 or 4 mg perampanel, AUC_{0-24hr} on Day 14 was on average 4.3-fold of that on Day 1 (E2007-E044-002 and E2007-J081-026). The extent of accumulation is less than that (6.83-fold) predicted based on the terminal $t_{1/2}$ (~105 hrs) which assumes that administered drug is entirely eliminated during the terminal phase (i.e., one-compartment model with oral absorption). The observed lower accumulation ratio is in consistent with the nature of multi-phasic PK profile of perampanel and results in an estimated effective $t_{1/2}$ around 65 hrs. The accumulation ratio (on average 2.5-fold) for C_{max} at steady state was less than that observed for AUC_{0-24hr} (E2007-E044-002 and E2007-J081-026).

Fluctuation: After 14-day once-daily dosing the fluctuation index (FI%, calculated as $(C_{max,ss} - C_{min,ss})/C_{avg,ss}$ x 100%) for perampanel ranged from 57 to 82% with an average of 68% (E2007-E044-002 and E2007-J081-026). In Study 002, perampanel was administered under fasted state everyday. In Study 026 perampanel was administered once daily at 30 minutes after the start of breakfast, except on Days 1, 7, and 14 of Step 1 and Days 1, 14, 21, and 28 of Step 2 when perampanel was administered after overnight fast and the fasting was maintained for 4 hrs after administration. The PK parameters were derived from the intensive PK sampling on these days, which reflect more of the PK profile under fasted state. A lower FI% (28%) was observed for 10-mg dose of perampanel in Study E2007-E044-009 where once-daily doses of perampanel were administered to morning dosing group of subjects immediately before low-fat breakfasts.

Phase 1 population PK model was utilized to simulate the concentration-time profiles of perampanel administered under fasted conditions following such a dosing regimen: initiating perampanel dose from 2 mg q.d. for one week and increasing daily dose every week by 2 mg until reaching the maintenance doses. Based on the simulated concentration-time profiles, exposure parameters C_{max}, C_{min}, and C_{avg} were calculated for various days as presented in the following Table. A fluctuation index around 42% was predicted based on these simulated data.

Table 6. Time Course of Perampanel Exposure with Repeated Administration: Estimated Exposure Parameters during Titration/Maintenance Periods for Three Dosing Regimens

Dose (mg/day)	Study Day	Total Days	C_{max} (ng/mL)	% Day 28 $C_{max,ss}$	C_{min} (ng/mL)	% Day 28 $C_{min,ss}$	C_{av} (ng/mL)	% Day 28 $C_{av,ss}$
4 mg QD Titration/Maintenance Dose Regimen								
2	7	7	133	40	79.1	35	98.0	38
4	7	14	290	88	183	82	219	86
4	8	15	Start of Maintenance Phase					
4	10	17	309	93	202	90	236	92
4	14	21	321	97	215	96	247	97
4	28	35	330	100	224	100	256	100
8 mg QD Titration/Maintenance Dose Regimen								
2	7	7	133	20	79.1	18	98.0	19
4	7	14	290	44	183	41	219	43
6	7	21	454	69	294	65	345	67
8	7	28	618	94	405	90	473	92
8	8	29	Start of Maintenance Phase					
8	14	35	651	99	439	98	503	98
8	28	49	661	100	448	100	512	100
12 mg QD Titration/Maintenance Dose Regimen								
2	7	7	133	13	79	12	98	13
4	7	14	290	29	183	27	219	29
6	7	21	454	46	294	44	345	45
8	7	28	618	62	405	60	473	62
10	7	35	784	79	518	77	601	78
12	7	42	949	96	630	94	729	95
12	8	43	Start of Maintenance Phase					
12	14	49	982	99	663	99	759	99
12	28	63	992	100	673	100	768	100

C_{av} = average plasma concentrations, $_{Cav,ss}$ = C_{av} at steady state, C_{max} = maximum plasma concentrations, $C_{max,ss}$ = C_{max} at steady state, C_{min} = minimum plasma concentrations, $C_{min,ss}$ = C_{min} at steady state, QT = once daily.

[Note: QT should be QD. The Pharmacometric reviewer performed the simulation independently using the Phase 1 population PK model and confirmed the above results provided by the Sponsor.]

Time-independent PK

In healthy subjects, CL/F of perampanel after multiple dosing was 11.9 mL/min on average (range: 9.9 – 15.3 mL/min), which is similar to that after single-dose administration (11.7 mL/min on average, range: 7.1 – 18.7 mL/min), suggesting that there is no auto-induction or auto-inhibition of perampanel metabolism by itself. This is also supported by the findings from the Phase 3 population PK analysis (CPMS-E2007-2011-003) that perampanel CL/F in patients not receiving enzyme-inducing AEDs remained the same between Visit 6 (week 10) and Visit 8 (week 19), as shown in Table 7.

Table 7. Model-Predicted Apparent Clearance Values: Effect of Time (Study CPMS-E2007-2011-003)

Time effect on CL/F	Dose 8 mg, without significant AED[a], FBM 17.1 kg			
	Males		Females, FBM	
	Estimated	Ratio[c]	Estimated	Ratio[c]
Visit 6 (start of Maintenance Phase)	0.765 L/h	NA	0.641 L/h	NA
Visit 7 (Visit 6 + 28 days)	0.748 L/h	0.98	0.623 L/h	0.97
Visit 8 (Visit 7 + 28 days)	0.730 L/h	0.95	0.605 L/h	0.94

a. Significant AEDs were those identified by the population pharmacokinetic model as having statistically significant effect on the clearance of perampanel (i.e., carbamazepine, oxcarbazepine, phenytoin, and topiramate).

c. Ratio to estimated value on Visit 6

2.2.4.2 What are the characteristics of drug absorption?

Perampanel is rapidly absorbed with median T_{max} values ranging from 0.5 to 2.5 hrs after single- or multiple-dose administration. Absolute bioavailability of perampanel was estimated to be 116% (N=5; range: 105-129%) from Study E2007-E044-017 where 10 healthy male volunteers received a single oral 8-mg dose of perampanel under fasted state followed by a single 10-μg (200 nCi) i.v. microdose of ^{14}C-perampanel. ^{14}C-perampanel was intravenously administered as a 15-min infusion starting 45 minutes after administration of the oral dose. The AUC after oral dose was calculated based on perampanel concentrations determined by LC-MS/MS, while the AUC for intravenous dose was estimated based on unchanged ^{14}C-perampanel concentrations determined by accelerated mass-spectrometry (AMS).

The reason for the absolute oral bioavailability being over 100% is unclear. It should be noted that the absolute bioavailability can only be estimated for 5 out of 10 subjects in this study. For the remaining 5 subjects, quality controls (QC) for the AMS assay failed to pass the acceptance criteria (i.e., at least 6 out of 9 QC samples need to fall within 80-120% of the actual concentrations) and thus reliable plasma concentrations of ^{14}C-perampanel could not be obtained. It is also noted that there was a small secondary peak around 24 hrs post-dosing in the concentration vs. time profile of non-radiolabeled perampanel as also observed in some other studies. The reason for such phenomenon (secondary peak or 'shoulder') remains unknown. One of the possible explanations is entero-hepatic recycling, which could lead to an absolute bioavailability beyond 100%. Nevertheless, the estimated absolute bioavailability from this study, along with mass-balance study results (Section 2.2.4.4), indicates that absorption of perampanel is essentially complete.

High-fat meal reduced perampanel C_{max} by 28-40% but did not affect the extent of perampanel absorption (AUC).

2.2.4.3 What are the characteristics of drug distribution?

Following the achievement of C_{max}, there was an initial, relatively rapid decline in perampanel plasma concentrations before 12 hrs post drug administration, followed by a slow decline. The plasma concentration-time profiles have been described using a two- or three-compartment model with first-order absorption. The apparent volume of distribution (Vd/F) ranged 51–105 L across single-dose PK studies, with an average of 77 L, which is consistent with the value (75 L) estimated from Phase 1 population PK analysis.

Plasma protein binding of perampanel (95-96%) was constant over a concentration range from 20 to 2000 ng/mL. Perampanel mainly bound to albumin and α1-acid glycoprotein and to a lesser extent to γ-globulin in human serum. Saturable binding was observed with α1-acid glycoprotein between the perampanel concentrations of 20 and 2000 ng/mL. Consistent with these *in vitro* results (Studies B00033 and AE-4737-G), Study E2007-E044-017 showed that the fraction of perampanel bound to plasma protein *in vivo* was

95.9±1.36% at 1 hr post-dose. The ex vivo protein binding results also showed that the extent of protein binding of perampanel was decreased by mild hepatic impairment and more obviously by moderate hepatic impairment, as summarized in Table 8.

Table 8. Mean (SD) Unbound Fraction of Perampanel (N=6 in each group, measured at 2-hrs post drug administration)

Parameter	Normal A	Child-Pugh A	Normal B	Child-Pugh B
f_u	0.033 (0.016)	0.042 (0.015)	0.034 (0.012)	0.059 (0.024)

Note: Normal A and B were healthy subject groups as demographic-matched controls for Child-Pugh A and B groups, respectively.

The blood-to-plasma ratio of perampanel ranged from 0.55 to 0.59.

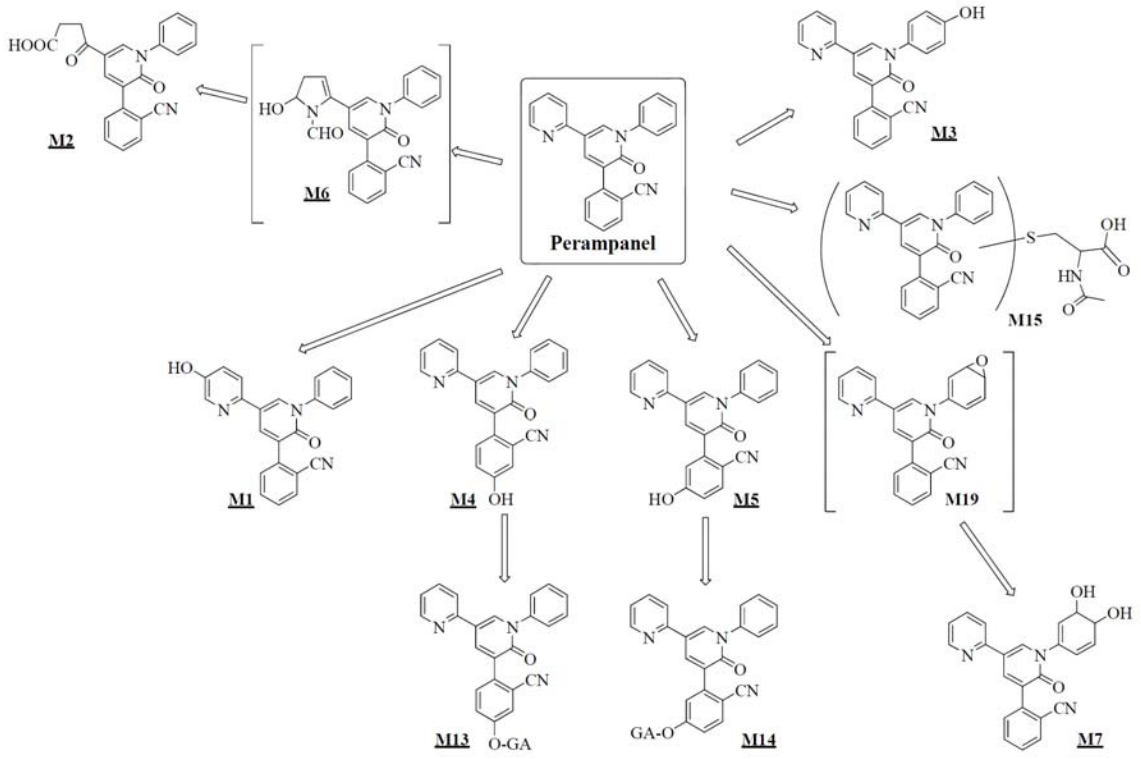
2.2.4.4 What are the characteristics of drug metabolism?

Mass-Balance: Perampanel appears to be extensively metabolized in humans. In a mass-balance study (E2007-E044-007) where 2 mg perampanel tablet with 200 nCi ^{14}C-perampanel was orally administered to 8 healthy elderly subjects, 70% of radiolabeled dose was recovered over a period of 42 days, with 22% of dose found in urine and 48% in feces. The 3% of total radioactivity recovered in feces within the first 48 hrs post drug administration suggested that most of the dose administered had been absorbed from the gastrointestinal tract. Metabolic profiling was further performed for urine and feces samples. However, the information obtained was very limited since only urine samples collected between 4- 8 hrs and feces samples collected between 144-168 hrs were analyzed for metabolite profiles.

Metabolic Profiling of Urine and Feces: More informative results of metabolic profiling were obtained from the absolute bioavailability study (E2007-E044-017) which also used radiolabeled perampanel as described in the previous section (Section 2.2.4.2). AMS analysis of urine samples collected at 0-24, 132-156, and 300-324 hrs post drug administration revealed the presence of a number of metabolites. Unchanged perampanel was also detected, but only accounted for 1-5% of the total radioactivity in each time-interval, which is consistent with less than 0.2% of perampanel dose eliminated as parent drug into urine within 48 hrs after single-dose administration or 24 hrs following multiple-dose administration (Studies E2007-044-001 and E2007-E044-002). Collectively, these findings suggest that renal clearance of perampanel is negligible. AMS analysis of 0-24, 48-72, and 120-168 hrs feces samples revealed numerous peaks on HPLC-radiochromatogram, which suggests the presence of a number of metabolites besides parent drug. The peak of unchanged perampanel on the chromatogram was comparable or smaller relative to metabolites. However, quantitative interpretation of these results was hampered by the low extraction efficiencies of feces samples (around 20%).

Metabolic Pathways: Metabolic pathways of perampanel in humans are proposed as following,

Figure 10. Proposed Metabolic Pathways of Perampanel in Humans



GA: glucuronic acid

Perampanel is primarily eliminated by oxidative metabolism followed by glucudonide conjugation for some metabolites. However, the relative contributions of these metabolic pathways in humans remain unknown, as majority of administered dose was excreted into feces and metabolic profiling results of feces samples were not quantitative.

Gap between In Vitro Findings and In Vivo Results: *In vitro* studies suggested that oxidative metabolism of perampanel is mainly mediated by CYP3A4/5. A study using recombinant human CYP isozymes showed that 25% of perampanel was metabolized after incubation with CYP3A4 microsomal preparation, while less than 5% of perampanel were metabolized in other CYP isozyme microsomes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1) (Study B04006). Another study showed that CYP3A5 metabolized perampanel to a similar extent as CYP3A4 (Study B06012). The other study using human liver microsomes revealed that 0.3 μM ketoconazole and anti-CYP3A4 antibody inhibited 60-65% of the metabolite formation for M1, M3, M4 and M19 (Study B07001). Ketoconazole and anti-CYP3A4 antibody also inhibited the formation of M6, M7 and M8, but quantitative results were not available. Though these *in vitro* studies suggested that CYP3A4/5 may be the major enzyme responsible for perampanel metabolism, the dedicated DDI study (E2007-E044-005) showed that strong CYP3A4/5 inhibitor, ketoconazole, increased exposure of perampanel by 20% only, pointing to a possible limited role of CYP3A4/5 in perampanel metabolism in humans. On the other hand, carbamazepine, a broad-spectrum enzyme inducer, which can induce CYP3A4/5 and also CYP2C8, CYP2C9, CYP2C19, CYP2B6

and non-CYP enzymes, was shown to increase CL/F of perampanel to 3-fold of control group (E2007-E044-006), indicating the involvement of non-CYP3A enzymes in perampanel metabolism.

Caveats for In Vitro Studies: The contributions of non-CYP3A metabolic enzymes to perampanel metabolism have not been fully characterized due to several limitations of the *in vitro* studies: first, perampanel was incubated with microsomes of each CYP isozyme for only 30 minutes in Study B04006, which may not be long enough to detect the full effect of an enzyme for the metabolism of a drug with low clearance; secondly, there were no positive controls in that study, as probe substrates for CYP isozymes were not included. Thus, enzyme activity and validity of experimental conditions were not warranted. Either insufficient enzyme activity or deficient experimental condition can results in under-estimation of the contribution from an enzyme; thirdly, Study B07001 using human liver microsomes did not assess the contribution of CYP3A4/5 to the formation of all identified metabolites (e.g., M5 and M15). Both M5 and M15 were detected in urine and feces (Study E2007-E044-017); lastly, Study B07001 did not evaluate the contribution of any other enzyme beyond CYP3A4/5 for the formation of any metabolite.

Uncertainty about Metabolism: Due to the aforementioned limitations of both mass-balance study and absolute bioavailability study, relative contribution of each metabolic pathway in overall metabolism of perampanel is unknown (Figure 10). If a metabolic enzyme is primarily responsible for the formation of one or multiple metabolites as the major metabolic pathway(s) of perampanel, concomitant use of a potent inhibitor of this enzyme will be expected to significantly increase the exposure of perampanel in humans.

Absence of Major Circulating Metabolites: Studies E2007-044-007 and E2007-044-017 reported that unchanged perampanel accounted for 75-80% of total radioactivity in plasma. Metabolic profiling by AMS analysis of plasma samples collected at 1-, 132-, 216-, 312- and 480-hrs post-dose did not reveal any major peak on HPLC-radiochromatogram except that of parent drug, suggesting the absence of major metabolite with exposure >10% of total drug-related material in systemic circulation. In accordance, LC/MS/MS assay validated for measurements of M1, M2, M3, M4, M5 and M7 were used to analyze plasma samples with or without the addition of β-glucuronidase. The plasma concentrations of these metabolites were below the lower limit of quantification (1 ng/ml) for the majority of subjects at the majority of time points (from pre-dose to 480 hrs post-dose, except 50 and 55 min post-dose).

In vitro pharmacology Study M09014 showed that metabolites M1, M3, M4, M5 and M7 had antagonistic effects on AMPA receptor. Based on the IC_{50} values, their effects were weaker than perampanel by 44-, 3.0-, 3.8-, 7.7- and 27-fold, respectively. No activity was observed with M2 up to 10 μM (refer to Pharmacology and Toxicology review documented by Dr. Christopher D. Toscano for details).

<u>*Recommendation*</u>: Further *in vitro* study(ies) are requested as a PMR to elucidate the contribution of metabolic enzymes other than CYP3A to perampanel metabolism, e.g.,

characterizing the enzymes involved in the formation of all identified metabolites (including M5).

2.2.4.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Hepatic metabolism represented the major route of elimination, with 48% of total dose administered recovered in feces over a period of 41 days post drug administration. 22% of dose was recovered in urine, with little amount of parent drug (See Section 2.2.4.4 for additional details).

2.2.4.6 What are the characteristics of drug elimination?

Perampanel is cleared primarily by oxidative metabolism followed by glucuronide conjugation for some metabolites. The metabolites were excreted into both feces and urine (See Section 2.2.4.4 for additional details).

Across the single- and multiple-dose studies in healthy volunteers perampanel CL/F was 11.7 mL/min (0.7 L/hr) on average. In the Phase 1 population PK analysis the estimated CL/F for perampanel was 10.9 mL/min (0.652 L/hr). The mean terminal $t_{1/2}$ of perampanel was approximately 100 hrs following single- and multiple-doses.

2.2.4.7 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?

AUC of perampanel increased dose-proportionally over the range of 0.2-12 mg after single-dose administration and 1-12 mg after multiple-dose administration. C_{max} of perampanel increased in a dose-proportional manner after single-dose administration of 0.2-8 mg and increased less than dose-proportionally beyond dose of 8 mg.

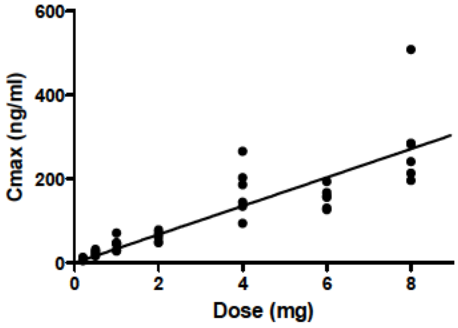
In studies for single-dose escalation (E2007-E044-001 in Western population and E2007-J081-010 in Japanese), multiple-dose escalation (E2007-E044-002 in Western population), and for elderly population (E2007-E044-004), linear PK was examined using regression analysis with a power function to determine if the value of the exponential term differed from 1.0. The results of these evaluations are summarized in the table below. In general, the exponential term was close to the value of 1.0, suggesting that AUC and C_{max} of perampanel increased in a dose-proportional manner (Figure 11). Linear PK of perampanel after multiple dosing is also supported by Study E2007-J081-026 conducted in Japanese population, where C_{max}, C_{min} and $AUC_{0\text{-}tau}$ for 4 mg dose group were double of corresponding parameters for 2 mg dose.

Table 9. Evaluations of Potential Nonlinearity in Perampanel PK

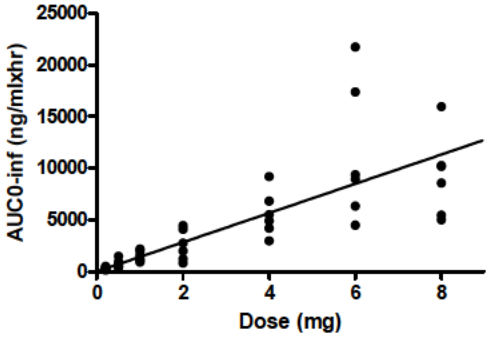
Source	Day	Perampanel Dose (mg)	Test	Parameter	Point Estimate (95% CI)
001, Table 11	1	0.2, 0.5, 1, 2, 4, 6, 8	Power Function	C_{max}	0.88 (0.80, 0.96)
				$AUC_{(0-t)}$	0.98 (0.89, 1.07)
				$AUC_{(0-inf)}$	0.96 (0.84, 1.08)
002, Table 13	14	1, 2, 4, 6	Power Function	C_{max}	0.99 (0.79, 1.20)
				$AUC_{(0-24h)}$	1.03 (0.77, 1.29)
004, Table 11	1	1, 2	Dose-Adjusted Ratio	C_{max}	1.00 (0.80, 1.25)[a]
				$AUC_{(0-t)}$	0.99 (0.83, 1.19)[a]
				$AUC_{(0-inf)}$	1.00 (0.73, 1.36)[a]
010, Table 11.4.4-2	1	0.25, 0.5, 1, 2, 4, 6, 8	Power Function	C_{max}	0.95 (0.88, 1.03)
				$AUC_{(0-inf)}$	1.01 (0.92, 1.10)

Figure 11. Dose-Exposure Relationship of Perampanel after Single Doses from 0.2-8 mg

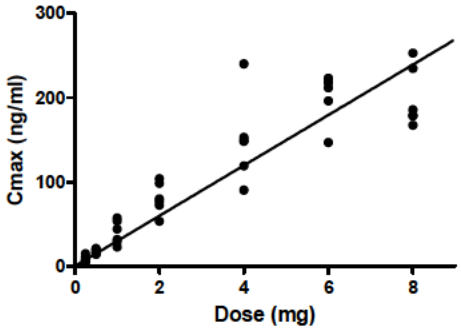
C_{max} (Study E2007-E04-001)



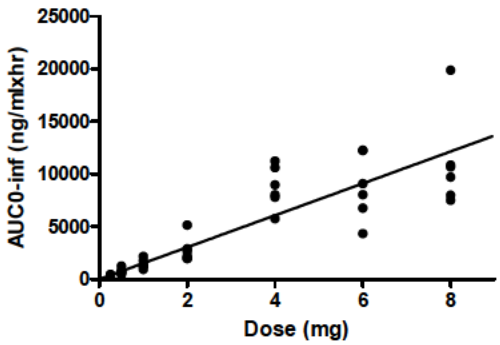
AUC (Study E2007-E044-001)



C_{max} (Study E2007-J081-010)



AUC (Study E2007-J081-010)



Single-dose PK of higher doses of perampanel was also evaluated in two abuse potential studies (E2007-A001-023 and E2007-A001-024). As shown in Figure 12 (left panel), dose-normalized C_{max} gradually decreased when dose increased from 8 mg to 36 mg,

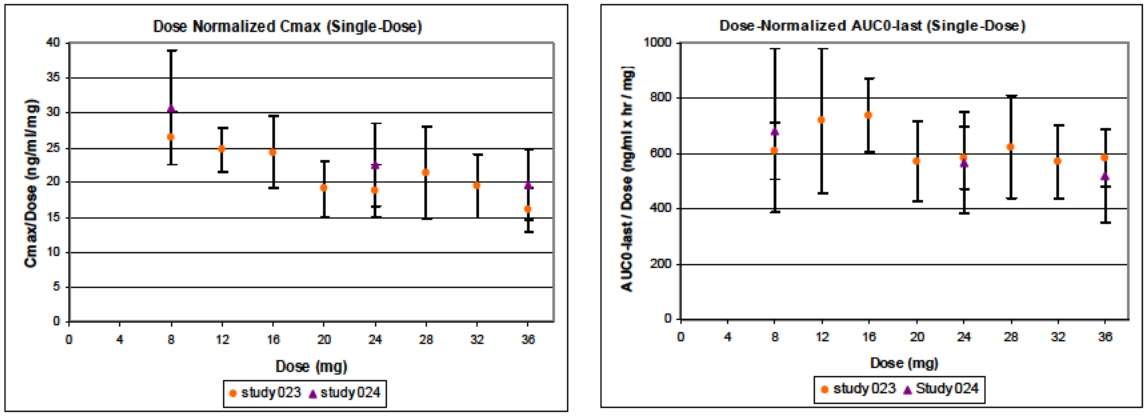
indicating that C_{max} increased less than dose proportionally. Of note, in Study E2007-A001-024, median T_{max} was prolonged from 1.5 hrs after 8 mg dose to 3.5 hrs after 24 mg or 36 mg. The less than dose-proportional increases in C_{max} at higher doses of perampanel may be attributed to the delayed absorption due to limited solubility of the drug. Solubility of perampanel (pKa=3.24) is pH-dependent and is higher in acidic condition, as shown in Table 10. Complete dissolution was not observed at pH 4.5 or above because of insufficient solubility of perampanel.

Table 10. Solubility of Perampanel in Various Dissolution Test Media at 37 °C

Media	Value (mg/mL)
0.1 mol/L HCl	0.47
pH 4.5 USP acetate buffer	0.0022
pH 7.5 USP phosphate buffer	0.0018

In contrast, AUC of perampanel increased in an approximately dose-proportional manner at doses greater than 8 mg (Figure 12, right panel). Dose-normalized AUC in Study E2007-A001-024 seemed to decrease slightly when dose increased. Since blood samples were collected only up to 48.5 hrs post drug administration, thus the AUC values from this study was more subject to the influence of changes in C_{max}.

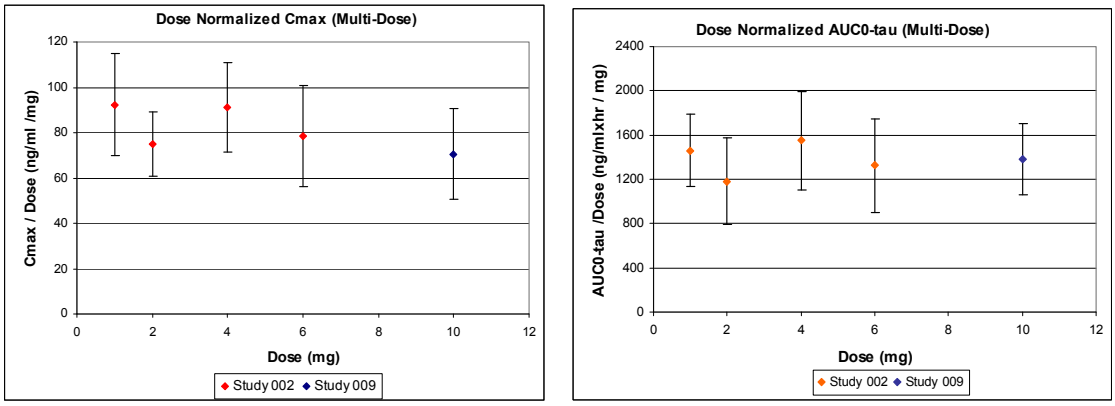
Figure 12. Dose-Exposure Relationship of Perampanel after Single Dose from 8 mg to 36 mg. Left panel: Dose-normalized C_{max}; Right panel: Dose-normalized AUC_{0-t}



[AUC_{0-last}: AUC_{0-72hr} for Study E2007-A001-023, N= 6-8; $AUC_{0-48\ 5hr}$ for Study E2007-A001-024, N = 37 or 38]

Multiple-dose PK of higher dose of perampanel has been evaluated in Study E2007-E044-009 where healthy subjects received 6 mg perampanel for the first week and 8 mg for the second week followed by 10 mg for the last week. As shown in Figure 13, dose-normalized AUC_{0-tau} at 10 mg dose level was comparable to those of 1 to 6 mg. Dose-normalized C_{max} for 10 mg dose was slightly lower than those of 1 to 6 mg. It should be noted that perampanel was administered immediately before breakfast everyday for the morning dose group in Study 009. It is unknown whether the breakfast served (a selection of cereals, two pieces of toast with flora + jam, marmalade or marmite) could reduce C_{max} of perampanel.

Figure 13. Dose-Exposure Relationship of Perampanel after Multiple Doses from 1 to 10 mg. Left panel: Dose-normalized C_{max}; Right panel: Dose-normalized AUC_{0-t}



The Phase 3 population PK analysis showed that CL/F of perampanel was comparable between 4 mg and 12 mg doses in patients, suggesting approximately dose-proportional increase of perampanel AUC in a dose range up to 12 mg after multiple-dose administration.

Table 11. Model-Predicted Apparent Clearance Values: Effect of Perampanel Dose (Study CPMS-E2007-2011-003)

Dose effect on CL/F	Visit 8 without significant AED[a], FBM 17.1 kg			
	Males		Females	
	Estimated	Ratio[b]	Estimated	Ratio[b]
Dose 4 mg	0.662 L/h	0.91	0.537 L/h	0.89
Dose 8 mg	0.730 L/h	NA	0.605 L/h	NA
Dose 12 mg	0.798 L/h	1.09	0.673 L/h	1.11

a. Significant AEDs were those identified by the population PK model as having statistically significant effect on the clearance of perampanel (i.e., carbamazepine, oxcarbazepine, phenytoin, and topiramate).
b. Ratio to estimated value at dose 8 mg

2.2.4.8 How does the PK of the drug and its major metabolites in healthy subjects compare to that in patients?

Pharmacokinetics of perampanel in epilepsy patients was similar to that in healthy subjects. From the Phase 3 population PK analysis CL/F of perampanel in patients not on enzyme-inducing AEDs (defined as carbamazepine, oxcarbazapine, phenytoin and topiramate in the analysis) was estimated as 0.73 L/hr or 0.605 L/hr for males and females, respectively. These estimates were similar to the CL/F (0.652 L/hr) estimated for healthy subjects based on the Phase 1 population PK analysis (CPMS-E2007-2011-002).

2.2.4.9 What is the inter- and intra-subject variability of PK parameters in healthy subjects and patients?

In healthy subjects the variability (expressed as CV%) of perampanel C_{max} ranged from 15% to 40% across single-dose and multiple-dose studies. After single-dose

administration CV% of $AUC_{0\text{-}inf}$ for majority of the studies fell within 30-60%. The CV% of $AUC_{0\text{-}tau}$ after multiple-dose administration was approximately 30%.

Based on population PK analyses between-subject variability (IIV) for CL/F of perampanel in healthy subjects and patients was estimated to be 49.5% and 46.4%, respectively. The within-subject variability (IOV) for CL/F of perampanel in patients was approximately 21.3%.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

Intrinsic factors, such as age, gender, race, weight, renal impairment and hepatic impairment, were studied in Phase 1 studies and/or Phase 3 trials, as described in the following Sections.

2.3.1.1 Elderly

Pharmacokinetics of perampanel in healthy elderly subjects were evaluated in Study E2007-044-004 where 8 subjects (4 males and 4 females) received 1 mg single dose and another 8 subjects (4 males and 4 females) received 2 mg dose. Mean CL/F of perampanel was 10.2 or 11.1 mL/min in elderly males, and 10.6 or 9.8 mL/min in elderly females. These values were similar to that for younger adults (10.9 mL/min) derived from Phase 1 population PK analysis, indicating that perampanel clearance is not affected by aging.

2.3.1.2 Gender

The Phase 1 population PK analysis suggested that CL/F of perampanel in females was 24% lower than that in males, which translated into 32% higher AUC in females compared to males. Similarly, the Phase 3 population PK model indicated that CL/F of perampanel in female patients was 16-20% lower than that in male patients. These differences are not considered clinically important.

2.3.1.3 Race

A single-dose escalation study (E2007-J081-010) was conducted in Japanese healthy male subjects. CL/F of perampanel was on average 11.8 mL/min (mean CL/F ranging 8.0–13.3 mL/min across doses from 0.25–8 mg). A multiple-dose study (E2007-J081-026) was performed in Japanese healthy males with mean CL/F of perampanel estimated to be 9.9 or 10.6 mL/min (for 2 mg and 4 mg doses, respectively). These values were similar to 10.9 mL/min derived for overall healthy population (479 Caucasians, 28 Black/African Americans, 20 Asians, 60 Japanese, and 19 subjects of other races) based on the Phase 1 population PK model. Similarly, the Phase 3 population PK analysis

indicated that perampanel CL/F in patients was not significantly affected by race (837 Whites, 24 Blacks, 133 non-Chinese Asians, 85 Chinese, and 30 patients of other racial groups.).

2.3.1.4. Weight

Simulation based on the Phase 1 population PK model showed that for subjects with body weight of 100 kg perampanel concentrations were totally contained within the 90% prediction interval for perampanel concentrations in subjects with 50 kg body weight, suggesting that body weight is not a significant covariate.
As summarized in the table below, the Phase 3 population PK analysis showed that CL/F of perampanel decreased slightly with increasing fat body mass. Such difference is not considered clinically relevant.

Table 12. Model-Predicted Apparent Clearance Values: Effect of Fat Body Mass (Study CPMS-E2007-2011-003)

FBM effect on CL/F	Dose 8mg, Visit 8, without significant AED[a]			
	Males		Females	
	Estimated	Ratio[d]	Estimated	Ratio[d]
FBM 17.1 kg	0.730 L/h	NA	0.605 L/h	NA
FBM 40.72 kg (95 percentile)	0.583 L/h	0.80	0.458 L/h	0.76
FBM 7.93 kg (5 percentile)	0.787 L/h	1.08	0.662 L/h	1.09

a: Significant AEDs were those identified by the population PK model as having statistically significant effect on the clearance of perampanel (i.e., carbamazepine, oxcarbazepine, phenytoin, and topiramate).
d: Ratio to estimated value of subject whose FBM 17.1 kg

2.3.1.5. Pediatric

All three pivotal trials included adolescent patients (12–17 yr). The CL/F of perampanel in adolescents, regardless of gender, was estimated to be 0.787 L/hr from the population PK model CPMS-E2007-2011-004 based on pooled adolescents data. Although this CL/F value is slightly higher than that in adults (0.605-0.73 L/hr), the differences are not considered clinically meaningful.

2.3.1.6 Renal impairment

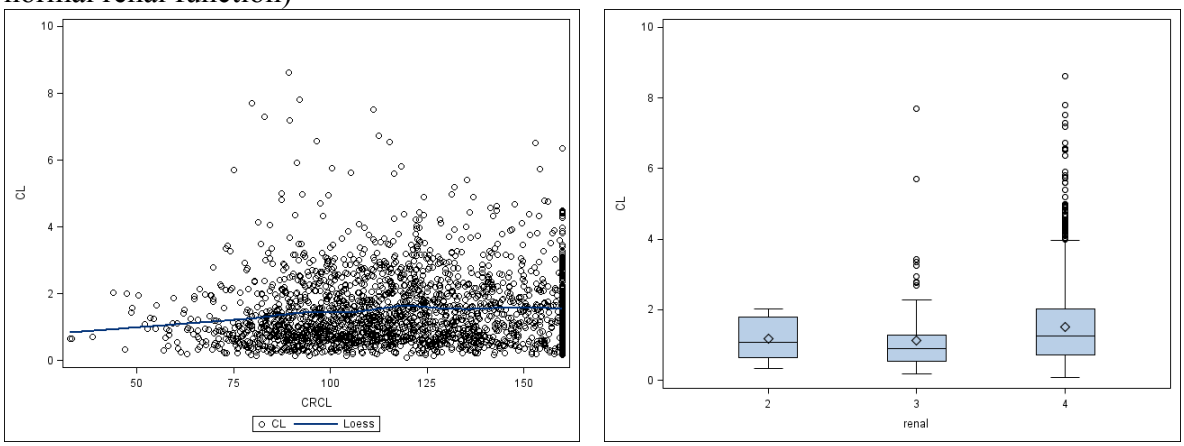
No dedicated study has been conducted in subjects with renal impairment. Effect of renal impairment on perampanel clearance was evaluated via population PK approach using Phase 3 data. As shown in the Table 13, median CL/F of perampanel was 27% lower in patients with mild renal impairment compared to patients with normal renal function, which corresponded to a 37% higher AUC in patients with mild renal impairment. However, there was substantial overlap in exposure between the two groups of patients (Figure 14, right panel). In addition, the plot of CL/F of perampanel versus estimated creatinine clearance (CLcr, mostly larger than 50 mL/min) did not reveal significant correlation between perampanel clearance and renal function (Figure 14, left panel). Therefore, no dose adjustment is needed for patients with mild renal impairment. It is noted that there were only 3 subjects with moderate renal impairment in the dataset. Considering that little parent drug was excreted into urine (see Section 2.2.4.4) and renal

clearance of perampanel is negligible, perampanel can be used in patients with moderate renal impairment with close monitoring. A slower titration may be considered. On the other hand, effects of severe renal impairment and end stage of renal diseases on perampanel PK can not be readily predicted, and thus use of perampanel in these patients is not recommended.

Table 13. Oral Clearance of Perampanel in Patients with Different Renal Function

Renal function category (CLcr, mL/min)	Normal (> 80)	Mild (50-80)	Moderate (30-50)
Number of Patients	711	52	3
Perampanel CL/F (L/hr, median)	1.25	0.91	1.07

Figure 14. Left Panel: Relationship between Perampanel Oral clearance and Creatinine Clearance (CLcr). Right Panel: Oral clearance of Perampanel in Patients with Different Categories of Renal Function (2: moderate renal impairment; 3: mild renal impairment; 4: normal renal function)



Recommendation: No dose adjustment is needed for patients with mild renal impairment. For patients with moderate renal impairment, it is recommended that perampanel be used with caution and close monitoring. A slower titration may be considered based on clinical response and tolerability. Perampanel is not recommended for patients with severe renal impairment or patients on hemodialysis.

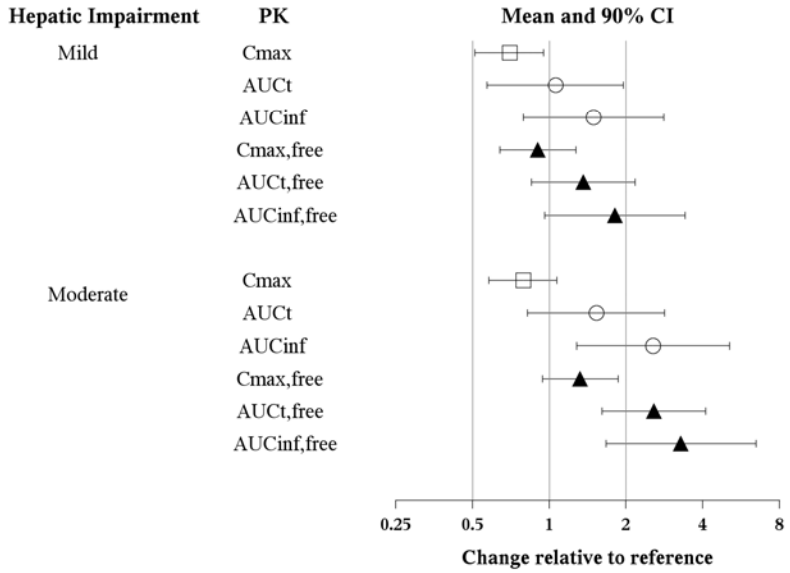
2.3.1.7 Hepatic impairment

In a dedicated hepatic impairment study (E2007-044-015), single-dose PK of 1 mg perampanel administered after food was evaluated in patients with reduced hepatic function (Child-Pugh A and Child-Pugh B) and their demographic-matched healthy controls (6 subjects in each group).

As shown in Figure 15, total $AUC_{0\text{-}inf}$ (free drug and drug bound with plasma protein) of perampanel was increased by 49% in patients with mild hepatic impairment compared to healthy controls, with $t_{1/2}$ prolonged from 125 ± 56 hrs to 306 ± 275 hrs. In patients with moderate hepatic impairment total $AUC_{0\text{-}inf}$ of perampanel was more than doubled (2.55-

fold) compared to controls, with $t_{1/2}$ prolonged from 139 ± 145.5 hrs to 295 ± 116.3 hrs. Due to decreased plasma protein binding of perampanel in hepatically impaired patients (see Section 2.2.4.3), the $AUC_{0\text{-}inf}$ values of free perampanel in patients with mild and moderate hepatic impairment were 1.81- and 3.28-fold, respectively, of those in healthy matched controls.

Figure 15. Effect of Mild and Moderate Hepatic Impairment on PK of Perampanel



Recommendation: Dose of perampanel should not exceed 4 mg in patients with moderate hepatic impairment and 6 mg is recommended as the maximum dose of perampanel for patients with mild hepatic impairment. Due to the prolonged $t_{1/2}$ (2-3 times), patients with mild or moderate hepatic impairment should be dose-titrated more slowly with close monitoring. Dose increases of perampanel should occur every two weeks, rather than weekly, in these patients.

2.4 Extrinsic Factors

2.4.1 Is the drug and/or the major metabolite a substrate, inhibitor or inducer of CYP enzymes on an in vitro basis?

Metabolism by CYP: Results from *in vitro* studies (B04006, B06012 and B07001) suggested that CYP3A4/5 is the major enzyme responsible for perampanel metabolism, while other CYP enzymes (e.g., CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1) may also be involved.

Inhibition potential: Perampanel did not inhibit CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, UGT1A1, UGT1A4 and UGT1A6 (Studies B00030, AE-4739-G, and XT095036). It is a weak inhibitor of CYP2C8, UGT1A9 and UGT2B7 (IC_{50} > 30

μM), and is not expected to result in clinically significant inhibition on these enzymes. Perampanel is a time-dependent inhibitor of CYP3A4, with k_{inact} and K_I estimated as 0.036 min^{-1} and 40.6 μM. Perampanel increased CYP2B6 activity to 2.2 – 3.6 fold of control group at a concentration of 30 μM. It is noted that steady state C_{max} of perampanel at a dose of 12 mg is predicted to be 992 ng/ml or 2.83 μM (Table 6), and it is unknown whether perampanel exerts the similar stimulating effect for CYP2B6 activity at its therapeutic concentrations. If such CYP2B6 stimulating effect exists at therapeutic concentrations, perampanel would potentially decrease the plasma concentrations of CYP2B6 substrates (e.g., buproprion) in humans and thus reduce the efficacy of these drugs.

Recommendation: A PMC is proposed to request the Sponsor to conduct an *in vitro* study to investigate the effect of perampanel at clinically relevant concentrations on CYP2B6 activity to provide clarity for the drug-drug potential between perampanel and CYP2B6 substrates. It is recommended that a higher concentration of perampanel (e.g., 30 μM) be included in the study to serve as a comparator. In addition, the PMC study is recommended to be performed with probe substrate of CYP2B6 (e.g., buproprion) per the Agency's Guidance for studying the drug-drug interaction.

Induction potential: Perampanel did not induce CYP1A2 at concentrations up to 30 μM in human hepatocytes. It is a weak inducer of CYP2B6 and is not expected to result in clinically significant CYP2B6 induction. Perampanel at concentrations of 3 μM and above induced CYP3A4/5, but the induction effect was weak compared to the positive control - rifampicin (Study GE-0045). Perampanel may induce UGT1A1 (≥ 3 μM) and to a lesser extent induce UGT1A4 (30 μM) (Study XT093050). It remains unknown whether perampanel has induction effect on UGT1A6, UGT1A9, and UGT2B7, as the positive controls used did not exhibit inducing effect, either.

2.4.2 Is the drug and/or the major metabolite a substrate and/or an inhibitor of P-glycoprotein transport processes or any other transporter system?

Perampanel is not a substrate for P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT2, OAT3, OAT4, OCT1, OCT2 or OCT3 (Studies GE-0258-G, DMPKT2011-002, GE-0404-G and B06015). Perampanel is a weak inhibitor of P-gp, BCRP, OAT1, OAT3, OCT1 and OCT3, and is not expected to result in clinically significant inhibition on these transporters. Perampanel increased OAT2 activity at concentrations of 1 μM and above, which is not expected to occur in humans considering the much lower concentrations of unbound perampanel at its therapeutic dose level.

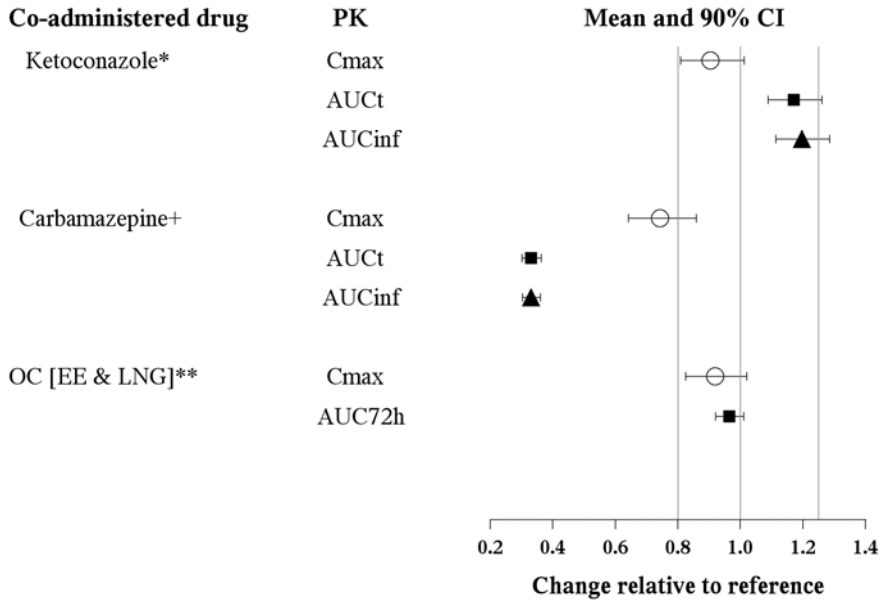
2.4.3 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered? If yes, is there a need for dosage adjustment?

2.4.3.1 Effect of co-administered drugs on perampanel

(1) Ketoconazole

Study E2007-044-005 (N=26) was conducted to examine the effect of ketoconazole (a strong CYP3A4 inhibitor) on PK of single 1-mg dose of perampanel in healthy males. As illustrated in Figure 16, co-administration of ketoconazole 400 mg QD for 8 days (Day 3-10) increased perampanel AUC by 20% and slightly prolonged its $t_{1/2}$ from 58.4 hrs to 67.8 hrs, suggesting that CYP3A4/5 may play a limited role in perampanel metabolism in humans.

Figure 16. Effects of Co-administered Drugs on PK of Perampanel



* Perampanel 1 mg; Ketoconazole, 400 mg QD [Days 1-10]
\+ Perampanel 2 mg; Carbamazepine 100 mg BID [Days 11-17], 200 mg BID [Days 18-24], 300 mg BID [DAYS 25-41]
** Ethinylestradiol (EE) 30 mcg and Levonorgestrel (LNG) 150 mcg [Days 1-21]

(2) Antiepileptic Drugs (AEDs):
Study E2007-044-006 (N=14) was conducted to examine the effect of carbamazepine (a strong CYP3A inducer, also known as a broad-spectrum inducer for CYP2C8, CYP2C9, CYP2C19, CYP2B6 and non-CYP enzymes) on PK of single 2-mg dose of perampanel in healthy males. Co-administration of carbamazepine 300 mg BID for 10 days (Day 32-41) increased CL/F of perampanel to 3-fold, decreased perampanel C_{max} and AUC to 74% and 33% of controls, respectively, and significantly reduced perampanel $t_{1/2}$ from 56.8 hrs to 25.3 hrs. Given the potential inducing effect by carbamazepine on several CYPs and non-CYP enzymes as well as the magnitudes of inhibition and induction observed in these studies (Studies 005 and 006), it is likely that other CYP and/or non-CYP enzymes may also be involved in perampanel metabolism in humans besides CYP3A4/5. However, the contributions of these enzymes to perampanel metabolism have not been fully characterized. Due to the limitations of *in vitro* and *in vivo* studies (see Section 2.2.4.4) it remains unknown whether any of these non-CYP metabolic enzymes could be a major enzyme responsible for perampanel metabolism. Consequence of adverse drug-drug interaction between perampanel and concomitant medication that is potent inhibitor of a major enzyme (if there is such an enzyme) can be significant. Given that

consideration, we recommend a PMR which requests the sponsor to further characterize the contributions of CYP enzymes (other than CYP3A4/5) and non-CYP enzymes to the metabolism of perampanel with *in vitro* study(ies). Pending *in vitro* results, *in vivo* study may also need to be considered (see Section 1.2).

Consistent with the dedicated DDI study conducted in healthy subjects, as shown in the table below, the Phase 3 population PK analysis suggested that carbamazepine also induced perampanel CL/F to about 3-fold of that in patients not receiving enzyme-inducing AEDs. In addition, population PK analysis suggested that phenytoin and oxcarbazepine induced perampanel CL/F to about 2-fold of that in patients not on enzyme-inducing AEDs. These increases in CL/F of perampanel will lead to reduction of perampanel exposure to 1/3 – 1/2 of that in patients not receiving enzyme-inducing AEDs. Similar inducing effects of carbamazepine and oxcarbazepine were also observed in adolescent patients. Topiramate was found to induce perampanel CL/F as well, but to a lesser extent (23-29%) which is not considered clinically significant.

Table 14. Model-Predicted Apparent Clearance Values for Adult Patients: Effects of Antiepileptic Drug Inducers (Study CPMS-E2007-2011-003)

AEDs' effect on CL/F	Dose 8 mg, Visit 8, FBM 17.1 kg			
	Males		Females	
	Estimated	Ratio[a]	Estimated	Ratio[a]
Without significant AED[b]	0.730 L/h	NA	0.605 L/h	NA
With carbamazepine	2.016 L/h	2.76	1.891 L/h	3.13
With oxcarbazepine	1.377 L/h	1.89	1.253 L/h	2.07
With phenytoin at concentration=16204 ng/mL	1.455 L/h	1.99	1.330 L/h	2.20
With topiramate	0.905 L/h	1.24	0.781 L/h	1.29

AED = antiepileptic drug, CL/F = apparent clearance, FBM = fat body mass
a. Ratio to estimated value without significant AED
b. Significant AEDs were those identified by the population pharmacokinetic model as having a statistically significant effect on the clearance of perampanel (i.e., carbamazepine, oxcarbazepine, phenytoin, and topiramate).

Table 15. Model-Predicted Apparent Clearance Values for Typical Adolescent Patients (Study CPMS-E2007-2011-004)

	Estimated CL/F	Ratio[b]
Without significant AED[a]	0.787 L/h	NA
With carbamazepine	2.322L/h	2.95
With oxcarbazepine	1.629 L/h	1.629

a. Significant AEDs include those identified as having a statistically significant effect on perampanel CL/F in the adolescent subgroup (carbamazepine and oxcarbazepine).
b. Ratio to estimated value without significant AED.

The Phase 3 population PK analysis included data from patients receiving carbamazepine (N=379), lamotrigine (N=357), valproate (N=350), levetiracetam (N=330), topiramate (N=226), oxcarbazepine (N=201), clobazam (N=115), zonisamide (N=94), phenytoin (N=91), clonazepam (N=82), phenobarbital (N=54), and primidone (N=18). The analysis

reported that clobazam, clonazepam, lamotrigine, levetiracetam, phenobarbital, primidone, valproate, and zonisamide did not have an effect on perampanel CL/F. It should be noted that this claim of negative effect by phenobarbital and primidone (prodrug of phenobarbital) is questionable. Phenobarbital is a broad-spectrum enzyme inducer like carbamazepine and phenytoin. As described in Topomax® label, topiramate is a mild inducer of CYP3A4. Though there is no direct comparison between phenobarbital and topiramate with respect to their enzyme-inducing effects, phenobarbital is generally thought to be a more potent inducer of CYP3A4, and is expected to exert its inducing effect on perampanel clearance in between that of phenytoin and topiramate. The reason that the population PK analysis did not detect such an effect may be due to small size of patients receiving phenobarbital or primidone, since the number of patients on phenobarbital or primidone represented only about 6% of the total PK population.

Recommendation: Since these AEDs (carbamazepine, oxcarbazepine, phenobarbital, phenytoin, and primidone) can greatly increase the perampanel CL/F through enzyme induction, perampanel plasma exposure will be significantly reduced in patients concomitantly taking these AEDs. Thus, the dosing recommendation of perampanel should be differentiated for patients taking these enzyme-inducing AEDs versus patients not taking these AEDs (see Section 2.2.3.1 for detailed dosing recommendations).

Concomitant use of other strong CYP3A inducers (e.g., rifampicin and St. John's wort) with perampanel should be avoided, as these drugs or herb medications are expected to greatly reduce perampanel plasma concentrations but not provide therapeutic benefit in seizure control.

(3) Oral Contraceptive:
Part B of Study E2007-044-029 evaluated the effect of multiple doses of oral contraceptive (OC: Microgynon-30®, containing ethinylestradiol (EE) 30 μg and levonorgestrel (LNG) 150 μg) on PK of single 6-mg dose of perampanel. Twenty-four subjects received 6 mg perampanel on Day 1 (Treatment period 1). After a washout of at least 7 days, subjects received the OC on Day 1–Day 21 (Treatment period 2). On Day 21 subjects also received 6 mg perampanel. As shown in Figure 16, combination of EE and LNG does not affect PK of perampanel.

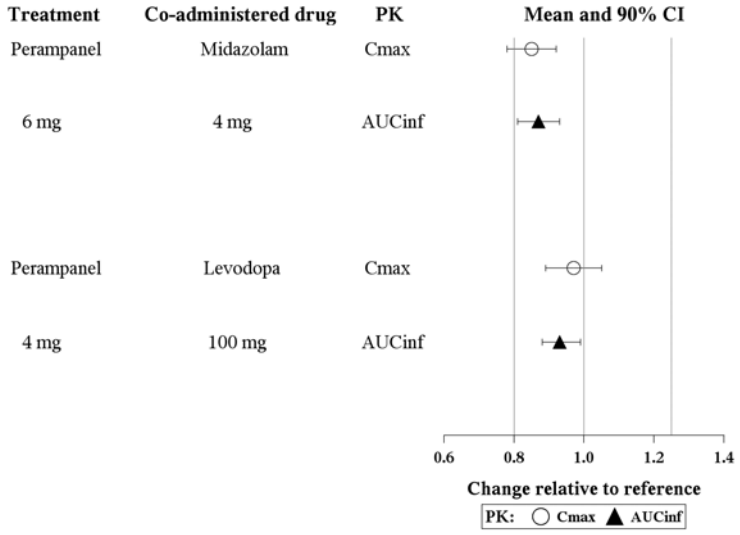
2.4.3.2 Effect of Perampanel on co-administered drugs

(1) AEDs:
The Phase 3 population PK analysis (CPMS-E2007-2011-003) reported no significant effects of perampanel on the clearance of clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate, or zonisamide. On the other hand, perampanel increased the clearance of carbamazepine, clobazam, lamotrigine, and valproic acid; however, the magnitudes of these effects were <10% at the highest perampanel dose (12 mg QD) and were not considered clinically relevant.

The analysis of oxcarbazepine concentrations showed a 26% decrease in its clearance in the presence of perampanel. The clinical impact is unknown, since oxcarbazepine clearance is rarely estimated and its pharmacological action results from exposure to its major metabolite, 10-monohydroxy metabolite (MHD), which was not measured by the Sponsor.

(2) Probe substrate for CYP3A4:
Study E2007-A001-014 (N=35) was conducted to examine the effect of 6-mg QD doses of perampanel for 20 days (Day 2 to 21) on single-dose PK of 4-mg midazolam (probe CYP3A4 substrate) given on Day 1 and Day 22. As shown in Figure 17, 6-mg perampanel decreased C_{max} of midazolam by 15% and AUC by 13%, suggesting that perampanel is a weak inducer of CYP3A4/5 *in vivo* and is expected to have minimal effect on PK of CYP3A4 substrates.

Figure 17. Effect of Perampanel on PK of Midazolam and Levodopa



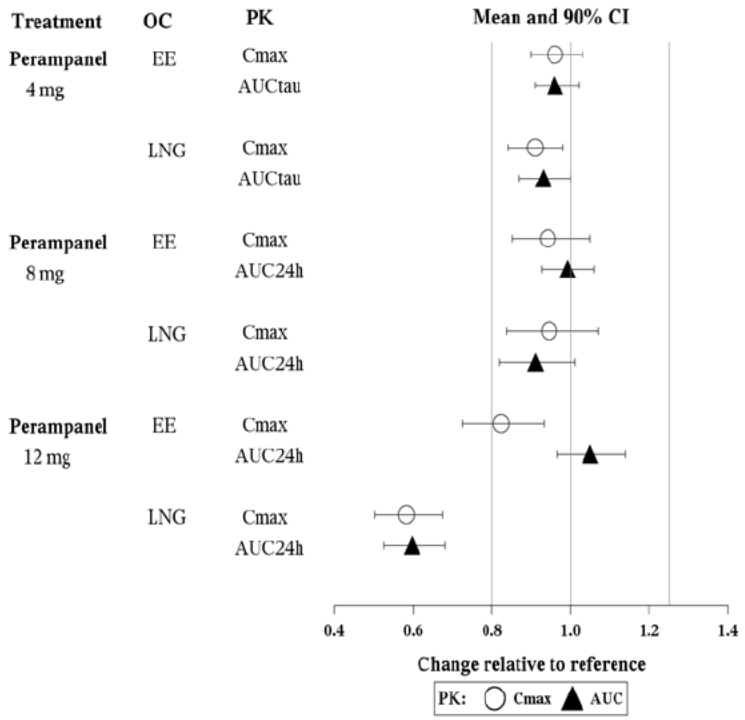
(3) Levodopa:
Study E2007-044-025 (N=59) was conducted to examine the effect of 4-mg QD doses of perampanel for 19 days (Day 2 to 20) on single-dose PK of 100 mg levodopa (Sinemet® 110 tablet) given on Day 1 and Day 21. As shown in Figure 17, perampanel did not affect PK of levodopa.

(4) Oral contraceptives:
Studies E2007-044-019 (N=22) and E2007-044-029 (N=28) were conducted to examine the effect of repeated doses of perampanel on multiple-dose or single-dose PK of OC (Microgynon-30®, EE 30 µg and LNG 150 µg).

In Study E2007-E044-019, OC was given once daily for 21 days (Day 1–21). Perampanel was then administered as 2 mg QD for 7 days (Day 22–28, no OC). Both OC and 4 mg

perampanel were administered for 21 days QD from Day 29 to 49. As shown in Figure 18, 4 mg perampanel did not have impact on C_{max} and $AUC_{0\text{-}tau}$ of EE or LNG.

Figure 18. Effect of Perampanel on PK of Oral Contraceptive



In Study E2007-E044-029, OC was initially given on Day 1 as a single dose, followed by a 7-day wash-out period. Perampanel was then given once daily for 35 days (4 mg x 7 days → 8 mg x 7 days → 12 mg x 21 days, with downward adjustment to 8 mg/day allowed concerning the tolerability). Another single-dose of OC was administered on the last day of perampanel treatment. Blood samples for PK analysis were collected after respective OC doses until 24 hrs post drug administration. As shown in Figure 18, perampanel at 12-mg dose significantly reduced C_{max} and $AUC_{0\text{-}24hr}$ of LNG by 42% and 40%, respectively, and decreased C_{max} of EE by 18% without affecting $AUC_{0\text{-}24hr}$ of EE. The exact mechanism for the decreased AUC and C_{max} of LNG with concomitant 12-mg doses of perampanel is still unknown. It is noted, however, that LNG is metabolized by both sulfate and glucuronide conjugation, whereas the *in vitro* induction potential of perampanel on UGT1A1 and UGT1A4 has been reported (see Section 2.4.1). A lack of effect of 12-mg doses of perampanel on AUC of EE (metabolized via sulfate conjugation and CYP3A4-mediated hydroxylation) suggested that perampanel at this dose level does not exert significant inducing effect on CYP3A.

Perampanel at a lower 8-mg dose did not significantly alter the PK of EE or LNG, though decreases in $AUC_{0\text{-}24\ hr}$ and $AUC_{0\text{-}inf}$ of LNG (by 8.9% and 12.4%, respectively) were observed.

Recommendation: Administration of perampanel at 12 mg/day may decrease the effectiveness of levonorgestrel-containing hormonal contraceptives. If 12 mg/day dose of perampanel is used, additional non-hormonal forms of contraception should be used.

2.5 General Biopharmaceutics

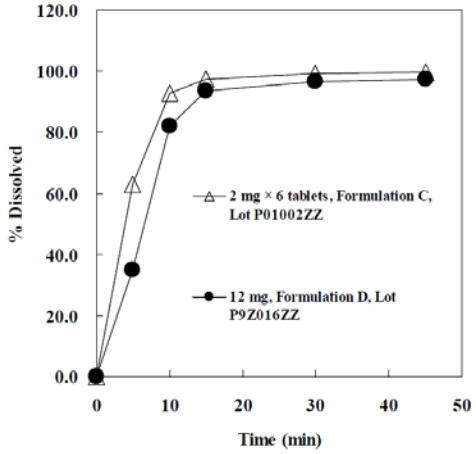
2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation?

A formal BCS classification for perampanel has not been determined.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

Formulation C of perampanel (2 mg strength) was used in all the three pivotal trials. Both Formulation C (2 and 4 mg strengths) and Formulation D (6, 8, 10 and 12 mg strengths) are the proposed commercial formulations. Dose strength bioequivalence between 2 and 4 mg strengths of Formulation C has been demonstrated in Study E2007-E044-016 (N=24). Formulation D has never been tested in clinical trials except in three BE studies. A BE (Study E2007-044-037, N=25) was initially conducted but failed to pass BE criteria for C_{max} (the lower bound of geometric mean ratio of Formulation D vs. Formulation C was 78%). Two additional BE studies (E2007-A001-039, N=52 and E2007-A001-040, N=51) were conducted and successfully demonstrated the bioequivalence between Formulation D (6 mg strength in Study 039 and 12 mg strength in Study 040) and Formulation C. The sponsor requested a biowaiver for the intermediate 8 mg and 10 mg strengths of Formulation D and was granted the biowaiver based on comparisons of *in vitro* dissolution data (Figure 19, also refer to the Biopharmaceutical review by Dr. Tien-Mien Chen of ONDQA for additional details).

Figure 19. Similarity of Dissolution Profiles for Formulations C and D

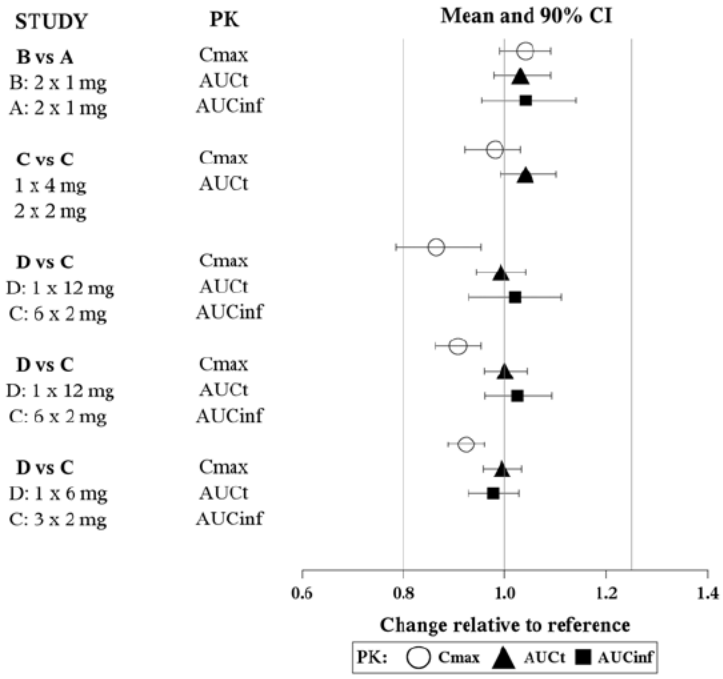


Formulation A (0.1, 1, and 5 mg tablets) was developed to initiate clinical study and used in the early stage of clinical trials (mainly in Phase 1 studies). Formulation A was then re-formulated to Formulation B (b) (4)

(b) (4). Formulation B (0.25, 0.5, 1, and 2 mg tablets) was used in the middle stage of clinical trials (mainly in Phase 1 and 2 studies). A BE study (E2007-A001-008, N=32) was conducted demonstrating bioequivalence between the two formulations.

The results of statistical analyses for formulation comparisons are presented in Figure 20 with point estimate and the 90% CI for the geometric mean ratios of exposure parameters of perampanel.

Figure 20. BE Studies Comparing Different Formulations or Strengths of Perampanel



As presented in the table below, Formulation C (1, 2, and 4 mg strengths, debossed on both sides) and Formulation B (b) (4). The *in vitro* testing showed more than (b) (4) drug released in 15 min with superimposing dissolution profiles from different strengths of Formulations B and C. Thus, no *in vivo* study for formulation bridging is necessary.


(b) (4)

2.5.3. What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Food effect has been evaluated for Formulation A and Formulation B of perampanel. Study E2007-044-003, a cross-over, two-period, two-sequence study conducted in 24 healthy subjects, showed that high-fat meal decreased C_{max} of perampanel (Formulation A) by 40%, delayed T_{max} (median) by 2 hrs, but had no effect on perampanel AUC ($AUC_{0\text{-}168hr}$ and $AUC_{0\text{-}inf}$). Part 1 of Study E2007-044-009, with a parallel design (8 subjects in fasted group, 8 subjects in fed group), evaluated the food effect on Formulation B. Results showed that high-fat meal decreased perampanel C_{max} by 28%, delayed its T_{max} (median) by 3 hrs, but did not alter perampanel $AUC_{0\text{-}24hr}$.

Concentration-time profiles of perampanel and graphical presentation of statistical analysis results of point estimate and 90% CI for the geometric mean ratios of perampanel exposure for food effect are shown below.

Figure 21. Food Effect on Perampanel PK

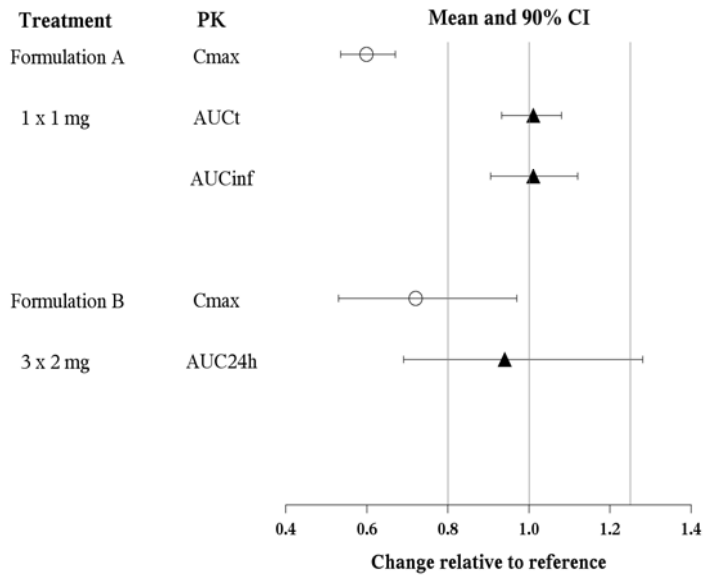
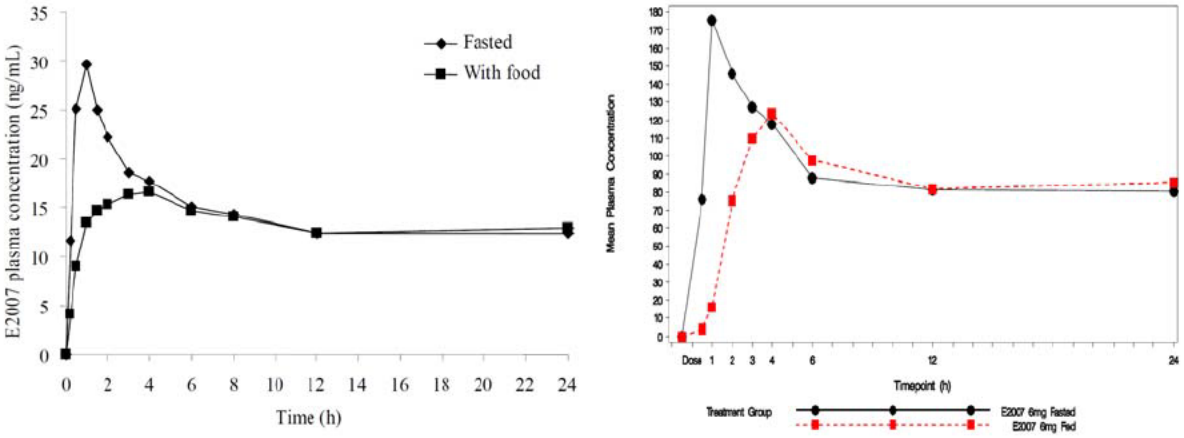
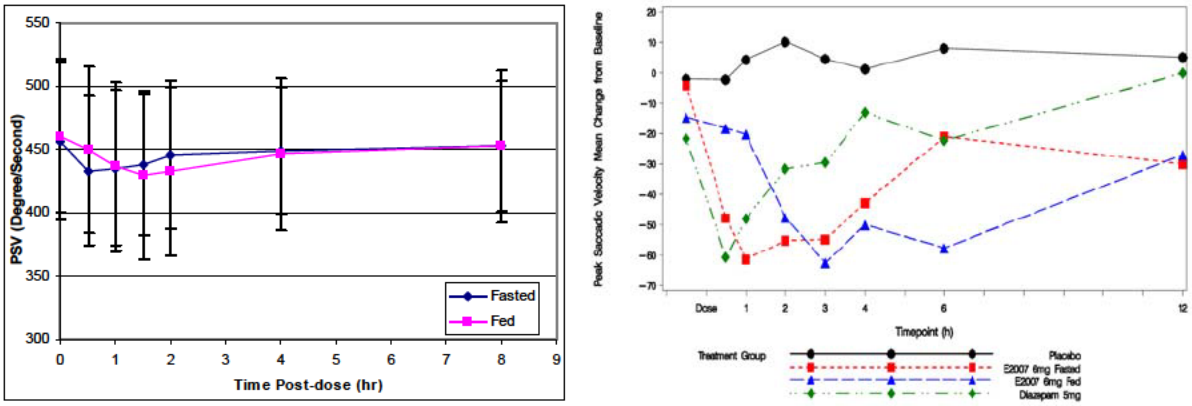


Figure 22. Concentration versus Time Profiles of Perampanel under Fasted and Fed Conditions (Left panel: Study E2007-044-003 (Formulation A); Right panel: Study E2007-044-009 (Formulation B))



As shown in Figure 22, compared to administration under fed state (high-fat meal), C_{max} of perampanel was 67% higher when taken under fasted condition for Formulation A (Left panel), and 39% higher for Formulation B taken under fasted condition (Right panel). It should be noted that administration under fasted state shortened the median T_{max} of perampanel by 2~3 hrs (from 3-4 hrs to 1 hr), in addition to increasing C_{max} of perampanel. Such difference in pharmacokinetics translated into difference in pharmacodynamic effects as measured by peak saccadic velocity (PSV). PSV is an objective assessment of sedation effect and has been shown to correlate with perampanel plasma concentrations in several studies (E2007-E044-001, E2007-E044-002, E2007-J081-010, E2007-J081-026). The lower PSV values indicate stronger sedation effects. As shown in Figure 23, PSV decreased after administration of perampanel under both fasted and fed conditions. Although the extent of decrease in PSV was similar, the time to reach maximal decrease of PSV occurred earlier under fasted state compared to fed condition (0.5 hr vs. 1.5 hrs in Study 003; 1 hr vs. 3 hrs in Study 009), suggesting an earlier onset of sedation effect when perampanel administered under fasted state.

Figure 23. Time Profiles of Peak Saccadic Velocity after Administration of Perampanel under Fasted or Fed Conditions (Left panel: Study E2007-E044-003, 1 mg single dose; Right panel: Study E2007-E044-009, 6 mg single dose)



All the three pivotal trials were conducted with the instruction of taking perampanel before bedtime with food. The sponsor's proposed labeling suggests taking perampanel before bedtime but does not specify the timing relative to bedtime. Considering how

patients were dosed in efficacy trials and the correlation between $T_{max,PK}$ of perampanel plasma concentrations and $T_{max,PD}$ of sedation effect as measured by PSV, perampanel would be taken preferably with food before bedtime. If taken without food, perampanel would be administered immediately before bedtime.

Recommendation: To simplify the dosing recommendation, we recommend perampanel be taken ***at*** bedtime regardless of food intake.

2.5.4. What is the effect of timing of drug administration on the bioavailability (BA) of the drug from the dosage form?

Study E2007-044-009 compared PK of perampanel after once daily morning dosing versus evening dosing. Evening dosing resulted in a 40% higher C_{min} than morning dosing after the first dose (76.9 ± 28.7 ng/ml vs. 51.5 ± 4.1 ng/ml). However, the difference in C_{min} diminished as doing duration prolonged, i.e., 27% higher after Day 7, 23% higher after Day 14, and eventually the same as morning dosing after Day 21. Both the maximal decrease in PSV (E_{max}) and the area under the time curve for PSV ($AUEC_{0-12hr}$) were larger after morning dosing than evening dosing, suggesting that evening dosing may produce less daytime sedation than morning dosing.

2.5.5. What is the relative bioavailability of [redacted] (b) (4) ?

[redacted] (b) (4)

2.6 Analytical Section

2.6.1 Were the active moieties identified and measured in the plasma in the clinical pharmacology study?

Yes.

2.6.2 What analytical method was used to determine drug concentrations and was the analytical assay method adequately validated?

Ten bioanalytical methods including liquid chromatography-fluorescence (LC-FI) and liquid chromatography-tandem mass spectrometry (LC/MS/MS) were developed to quantify perampanel in human plasma samples from clinical studies. These methods were validated; cross validation were performed between LC-FI (105-001) and LC-MS/MS methods (238/001), and also between two LC-MS/MS methods (EIS-R791R2/BTM-

1076-R0) and SH09-E01-TR352) developed by different contract laboratories. Another LC-MS/MS method [redacted]/QBR101589-2) was developed and validated to quantify perampanel and its metabolites (M1, M2, M3, M4, M5 and M7) in human plasma. These assay validations are deemed acceptable per the Agency's Bioanalytical Guidance.

The bioanalytical methods for determination of perampanel in human plasma were examined for possible interferences caused by concomitant drugs (e.g., AEDs, ketoconazole, levodopa, and oral contraceptive). It was determined that these concomitant drugs did not interfere with the quantitation of perampanel.

In addition, assay methods using accelerator mass spectrometry (AMS) were developed to quantify the ^{14}C-radioactivity for ^{14}C-perampanel in human plasma, whole blood, urine and feces samples. Both methods are not considered validated but can serve the qualitative or quantitative purpose of the studies. This method consisted of HPLC separation and fraction collection, followed by AMS analysis, and was also used for metabolite profiling.

Listed below were details for the 4 analytical methods [redacted]-US/BTM-1076-R0, QPS/45-0603, [redacted]/105-001 and [redacted]/QBR101589-2) which were used to analyze the plasma samples for most of the clinical studies.

Table 17. Bioanalytical Methods for the Determination of Perampanel in Plasma Samples Obtained in Clinical Studies

Report Title	Determination of E2007 in human plasma by LC-MS/MS	Determination of E2007 in human plasma by LC-MS/MS	Determination of E2207 in human plasma by HPLC with fluorescence detection	Validation of an LC-MS/MS method for the measurement of free and total E2007 and Metabolites M1, M2, M3, M4, M5 and M7 in human plasma
Used in Clinical Study	039, 040, 304, 305, 306	013, 014, 023, 024, 210, 214, 218, 226, 227	002, 003, 004, 005, 006, 007, 009, 015, 016, 019, 201, 202, 203, 204, 205	017, 028, 029, 030, 037
Lab/Project Code	(b) (4)-US/BTM-1076-R0	(b) (4)/45-0603	(b) (4)-(b) (4)105-001	(b) (4)/QBR101589-2
Analyte Names	perampanel	perampanel	perampanel	Perampanel, Metabolite M1, M2, M3, M4, M5 and M7
Internal Standard (IS)	(b) (4)			
Analytical Method Type	LC/MS/MS	LC/MS/MS	LC-FI	LC/MS/MS
Stock solution solvent	methanol	methanol	Not mentioned	ethanol
Extraction Method	Protein precipitation by methanol	Liquid/liquid	Liquid/liquid	Liquid/liquid
Linear range	1 to 500 ng/mL	2.5 to 1000 ng/mL	1.01 to 504 ng/mL	1 to 250 ng/mL
Range of Recovery (%)	90.6 to 96.3% (average 93.7%)	72.4 to 87.2% (average 81.9%)	60 to 73%	76.3 to 83.1% (average 80.5% for perampanel); 65.9 to 84.3% (average 68.5 to 80.3% for M1, M2, M3, M4, M5 and M7)
Average Recovery of IS (%)	100.8%	84.6%	70%	
QC concentrations	3.0, 50, 380 ng/ml	2.5 (intra only), 7.5, 150, 750 ng/mL	1.03, 2.92, 247.02, 397.38 ng/ml	3, 80, 200 ng/ml
QC Intra-assay Precision	1.9 to 6.5%	3.3 to 9.1%	1.05 to 1.74%	≤ 7.8% (perampanel), ≤ 12.3% (M1, M2, M3, M4, M5 and M7)
QC Intra-assay Accuracy	91.8 to 100.4%	84.9 to 107.2%	100 to 114%	≤ ± 7.5% (perampanel), ≤ ±14.6% (M1, M2, M3, M4, M5 and M7)
QC Inter-assay Precision	2.5 to 5.6%	3.0 to 7.3 %	0.63 to 6.45%	≤ 10.0 % (perampanel), ≤ 12.2% (M1, M2, M3, M4, M5 and M7)
QC Inter-assay Accuracy	94.6 to 98.0%	97.3 to 103.5%	106 to 108%	≤ ±7.5% (perampanel), ≤ ±12.2% (M1, M2, M3, M4, M5 and M7)
Stock solution storage stability	At least 283 days at 4°C, 7 hr at RT	At least 383 days at -20°C, 9 hr at RT	At least 485 days at 5°C, 17 hr at RT	At least 28 days at 4°C (88.4 to 99.6%)
QC sample long term storage stability	at least 276 days at -20°C,	239 days at -70°C	at least 295 day at -20°C	at least 90 days at -20°C,
QC sample bench-top stability	at least 6 hr at RT	24 hr at RT	4 hr at RT	24 hr at RT
Processed sample stability	at least 45 hr at RT	109 hr at RT	23 hr at RT	28 hr at RT
Freeze/thaw stability in plasma	3 cycles at -20 C	3 cycles at -20 C, 7 cycles at -70 C	3 cycles at -20 C	3 cycles at -20 C

Dilution integrity	5000 ng/mL diluted 20-fold	2500 ng/mL diluted 10-fold	503.98 ng/mL diluted 10-fold, 964.78 ng/mL diluted 50-fold,	2000 ng/mL diluted 10-fold
Specificity	No significant interfering peaks	No significant interfering peaks	No significant interfering peaks	No significant interfering peaks

In addition, two LC-MS/MS methods were developed and validated for quantitation of perampanel in human urine samples.

Table 18. Bioanalytical Methods for the Determination of Perampanel in Urine Samples Obtained in Clinical Studies

Report Title	Assay validation for the quantitative analysis of unchanged drug (E2007) in human urine	Assay validation for the quantitative analysis of unchanged drug (E2007) in human urine
Used in Clinical Study	001	002
Lab/Project Code	(b) (4)	
Analyte Names	Perampanel (E2007)	Perampanel (E2007)
Internal Standard (IS)	(b) (4)	
Analytical Method Type	LC-FI	LC-MS/MS
Stock solution solvent	ethanol	ethanol
Extraction Method	Liquid/liquid	Liquid/liquid
Linear range	0.2555 to102.2 ng/mL	49.68 to 1006.02 pg/ml
Range of Recovery (%)	95%	90-94%
Average Recovery of IS (%)	95%	NA
QC concentrations	0.714, 40.8, 81.6 ng/ml	49.97, 185.92, 399.73, 752.98 pg/ml
QC Intra-assay Precision	0.6 to 4.7%	5.63 to 7.32%
QC Intra-assay Accuracy	98.3 to 111.8%	97 to 116%
QC Inter-assay Precision	0.9 to 2.5%	1.27 to 7.17%
QC Inter-assay Accuracy	96.7 to103%	101 to 107%
Stock solution storage stability	At least 283 days at 4 C, 7 hr at RT	at least 174 days when stored at 4 C, 17 hr at RT
QC sample long term storage stability	at least 3 months at -20 C	NA
QC samples at 5 C	At least 2 days at 5 C	NA
QC sample bench-top stability	at least 2 days at RT	at least 4 hr at RT
Processed sample stability	at least 2 days at RT	at least 1 day at RT
Freeze/thaw stability in human urine	4 cycles at -20 C	3 cycles
Dilution integrity	2040 ng/mL diluted 100-fold or 204 ng/mL diluted 10-fold	Diluted 2- and 5-fold
Specificity	No significant interfering peaks	NA

3. Detailed Labeling Recommendations

The Office of Clinical Pharmacology has reviewed the proposed labeling for Fycompa (perampanel) immediate release oral tablets and found it acceptable provided that the recommended revisions are made to the labeling language.

Labeling recommendation to be sent to the Sponsor:
The following describes the proposed changes: the underlined text is the proposed change to the label language; the ~~Strikethrough text~~ is recommendation for deletion from the perspective of OCP.

4. Appendices

4.1. Proposed Labeling

Highlights of Prescribing Information

(b) (4)

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2. Consult Review

Office of Clinical Pharmacology: Pharmacometric Review

1. SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is there any covariate which affects perampanel PK?

Yes, the sponsor's analysis showed that clearance (CL/F) of perampanel was related to gender, fatty body mass (FBM, kg) as well as co-administration of carbamazepine, oxcarbazepine, phenytoin and topiramate.

A population PK analysis had been conducted in a dataset composed of 770 patients enrolled into three phase III studies (304/305/306).

The sponsor's final model showed that perampanel apparent clearance (CL/F) was slightly lower in a typical female subject (0.605 L/h) than in a male subject (0.730 L/h), assuming FBM=17.1 kg and without co-administration of the AEDs found to induce perampanel clearance. Visit (as time effect), dose, and FBM were also significant covariates on CL/F of perampanel; CL/F slightly increased with increasing dose, slightly decreased at later visits and with higher FBM (Appendix 1). However, these effects were small and not considered clinically meaningful. Perampanel CL/F was not significantly affected by baseline seizure frequency, age, or renal or liver function (Appendix 2).

Regarding to co-administered AEDs, CL/F of perampanel increased approximately 3 fold, 2 fold and 2 fold with carbamazepine, oxcarbazepine and phenytoin co-administration, respectively (Appendix 1). Also the use of topiramate appeared to increase CL/F of perampanel slightly (0.73L/h (no use) vs. 0.91 L/h (use)).

The sponsor also evaluated the effect of perampanel on the CL of AEDs. All the statistically significant effects of perampanel on the CL of the AEDs were minimal in magnitude and thus of no clinical relevance (Table 5).

1.1.2 Is there any significant exposure-response relationship? And does the relationship support the proposed dose?

Yes, there was a clear exposure-response relationship for both efficacy and safety. However, the dose of 8 mg / day rather than 12 mg / day seems to be reasonable target dose based on the reviewer's assessment.

Sponsor conducted three Phase III studies; E2007-G000-304, E2007-G000-305 and E2007-G000-3006. The primary endpoint was the percent reduction in seizure frequency during double-

blind phase (DB) from the baseline. The doses of 8 mg and 12 mg with placebo were evaluated in E2007-G000-304, E2007-G000-305 whereas the doses of 2mg, 4mg and 8mg were compared to placebo in E2007-G000-306. The dose of 2 mg did not meet the statistically significant criteria (p-value=0.4197). However, the doses of 4mg, 8mg and 12 mg showed effectiveness in all studies, although 12 mg failed to show superiority compared to 8mg in E2007-G000-305 (Table 1).

Table 1. The summary of primary efficacy analyses results. The numbers are the median percent reduction during DB phase from the baseline relative to placebo with p-values in parentheses.

	2mg	4mg	8mg	12mg
306	-4.36 (0.4197)	-13.7 (0.0026)	-20.1 (<0.0001)	
305			-19.1 (0.0008)	-13.69 (0.0105)
304			-13.53 (0.0261)	-14.2 (0.0158)

Regarding to the safety, the probability of gait disturbance, dysarthria (speech disorder), nausea, weight increase, fatigue, irritability, somnolence and dizziness was shown to increase significantly with an increase in plasma concentrations of perampanel (Figure 6).

The reviewer re-analyzed the data from three phase III studies linked to perampanel average concentration at steady state to assess whether the sponsor's proposed dosing regimen is appropriate or not. For efficacy the same primary endpoint was used, and for safety analysis the adverse events related to hostility/aggression were extracted based on Standardized MedDRA Queries (SMQs) from the adverse event dataset.

The benefit-risk assessment shows that the seizure frequency decreased in concentration-dependent manner with little difference between 8mg and 12mg while the proportion of patients with hostility/aggression related adverse events increased in the concentration range of 8mg and 12 mg (Figure 1).

Figure 1. The benefit and risk profile of perampanel. The grey and orange parts represent the efficacy (% reduction in seizure frequency) and safety (% patients of having hostility/aggression related AEs), respectively. The solid lines are model-predicted relationship, and the dots are observed data at the ranked six bins of perampanel steady state concentrations. The boxplots indicate the distribution of concentration at each dose group (6 mg and 10 mg were simulated assuming the same variability as 4 mg).

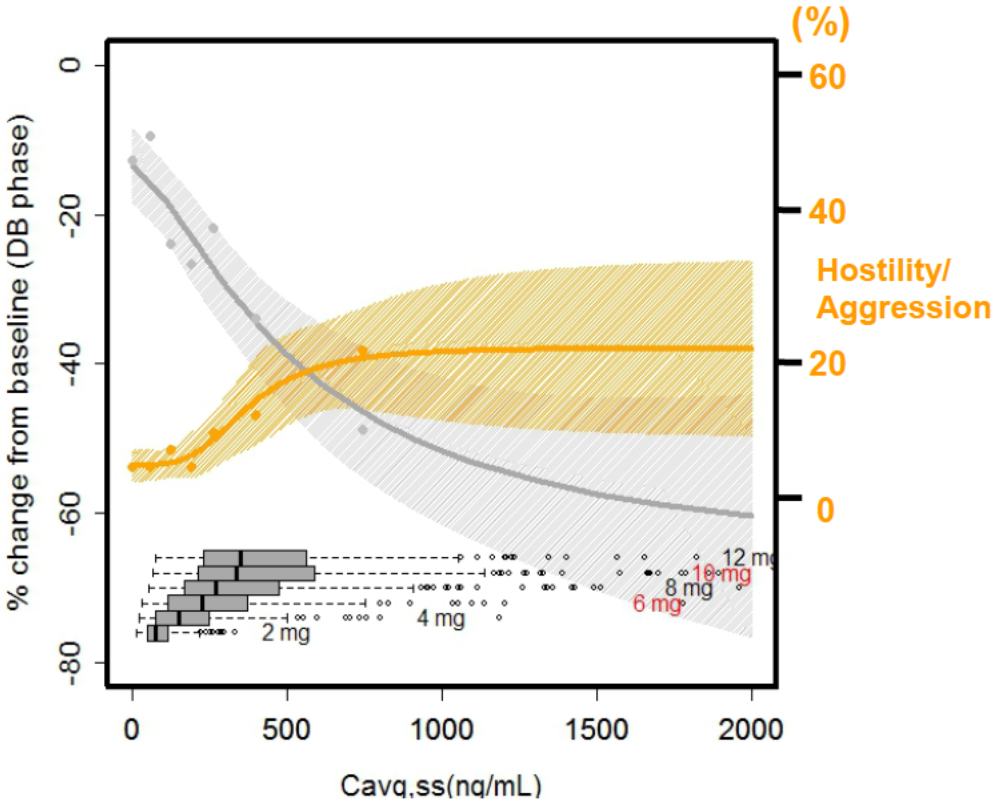


Table 2. Predicted % reduction in seizure frequency and % hostility/aggression-related adverse event based on the modeling results shown in Figure 1. The prediction was made at the median concentration at each dose. (6 mg and 10 mg were predicted based on the simulated exposure range).

Dose	Efficacy (% reduction in seizure)	Safety (% patients of having hostility/aggression)
Placebo	-13.5	6.4
2mg	-16.4	6.5
4mg	-20.7	7.1
6mg	-25.2	8.7
8mg	-27.7	10.2
10mg	-31.2	12.8
12mg	-32.1	13.4

Given the efficacy and safety profiles of perampanel which show little difference in efficacy between 8 mg and 12 mg and higher risk with increasing concentration, the targeted maintenance dose should be 8 mg/day.

1.2 Recommendations

The Division of Pharmacometrics has reviewed the submission (NDA 202834), and there is one recommendation on the dosing regimen as follows;
Given the efficacy and safety profiles of perampanel, the targeted maintenance dose should be 8 mg/day.

2. Pertinent Regulatory Background

The sponsor is seeking the approval for perampanel for the treatment of patients with partial-onset seizures, with or without secondary generalization. Perampanel is an orally active, noncompetitive, and highly selective α -amino-3-hydroxy-5- methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist. The half-life of perampanel is about 105 hours which was the basis for once-daily dosing. The sponsor's proposed dosing regimen is as follows:

- Perampanel should be initiated with a dose of 2 mg/day.
- The dose may be increased based on clinical response and tolerability by 2 mg/day increments to a dose of 4 mg to 12 mg/day.
- The maximum recommended daily dose is 12 mg.
- Dose increases should occur no more frequently than at weekly intervals.

3. Results of Sponsor's Analysis

Population PK analyses
A population PK analysis had been conducted in a dataset composed of 770 patients enrolled into three phase III studies (304/305/306).

Blood samples for the determination of perampanel concentrations were collected at two time points 1 to 2 hr apart at visit 6, visit 7 and visit 8 (during the maintenance period).
A single blood sample for the determination of plasma concomitant AED(s) was to be collected at visit 1, visit 2, and visit 9 or early discontinuation visit if applicable. In addition, blood samples were to be collected at two time points, 1 to 2 hr apart at visit 6, visit 7 and visit 8. The AEDs and AED metabolites to be determined included the following: carbamazepine, carbamazepine epoxide, phenytoin, phenobarbital, primidone,
valproic acid, topiramate, lamotrigine, gabapentin, tiagabine, zonisamide, levetiracetam
and the 10-monohydroxy metabolite of oxcarbazepine.

The prior analyses in healthy subjects and in subjects with partial seizures or with Parkinson's disease have shown that a two-compartment disposition model with zero or first order absorption, and absorption time lag, first-order elimination described perampanel PK well. However, since the dose was administered at bedtime, and the first sample was to be taken at the

clinic during a daytime visit, absorption and distribution were complete when the plasma concentrations were collected, preventing fitting a PK model with an absorption phase. Therefore, only one compartment PK model with bolus input and first-order elimination could be fitted to the data.

The covariates tested in the population PK analysis are gender (0 for males, 1 for females),age, dose, race (coded 1 for Caucasians, 2 for Blacks, 3 for Orientals, 4 for "Other races"), body weight(kg), body mass index (BMI), fatty body mass (FBM), Creatinine Clearance (CLCR , ml/min), alanine amino transferase (IU/L). The covariate selection was repeated using different strategies, trying to estimate the most parsimonious model. Because of the AED comedications were not distributed evenly between demographic groups, the full model was built in two stages:

- Only demographic and baseline characteristic covariates excluding AEDs were selected for univariate analysis.
- Then all significant covariates and all selected AEDs (dichotomous Yes/No) were included concurrently, using multiplicative models, on the parameter clearance.
- The full model was submitted to univariate backward deletion, to rank the effects of AEDs, i.e., the effect of each AED (Y/N) was estimated in the presence of all others. Non-significant effects were removed from the model.
- Finally, the effect of significant AEDs was evaluated as a function of their concentration or of their daily dose and the most significant function was selected leading to the final PK model.

Table 3 summarizes the baseline characteristics for the patients included in population PK model.

Table 3. Summary of demographic and baseline characteristics

		Treatment					
		2 mg	4 mg	8 mg	12 mg	Placebo	All
Sex							
Male	N	58	68	163	82	170	541
	%	5.2	6.1	14.7	7.4	15.3	48.8
Female	N	76	68	161	94	169	568
	%	6.9	6.1	14.5	8.5	15.2	51.2
Race							
White	N	86	86	256	148	261	837
	%	7.8	7.8	23.1	13.3	23.5	75.5
Black	N	.	.	7	7	10	24
	%	.	.	0.6	0.6	0.9	2.2
Asian	N	27	28	30	12	36	133
	%	2.4	2.5	2.7	1.1	3.2	12.0
Chinese	N	20	21	21	.	23	85
	%	1.8	1.9	1.9	.	2.1	7.7
American Indian/Alaska native	N	.	.	3	1	.	4
	%	.	.	0.3	0.1	.	0.4
Other	N	1	1	7	8	9	26
	%	0.1	0.1	0.6	0.7	0.8	2.3
Age	Mean	33.2	33.4	35.6	35.0	34.3	34.5
	SD	12.9	12.0	13.4	14.1	13.7	13.4
	Median	31.5	32.0	34.5	34.0	33.0	33.0
	Minimum	13.0	12.0	12.0	12.0	12.0	12.0
	Maximum	65.0	68.0	70.0	74.0	76.0	76.0
Weight (kg)	Mean	65.3	70.1	72.4	73.9	71.1	71.1
	SD	16.0	17.8	18.1	19.4	18.2	18.2
	Median	63.7	68.8	71.5	69.0	69.0	69.0
	Minimum	37.2	25.0	33.8	36.2	31.9	25.0
	Maximum	113.0	133.0	139.5	142.2	142.9	142.9
Height (cm)	Mean	165.3	167.8	167.3	166.3	167.0	166.9
	SD	9.1	11.2	9.5	9.8	10.4	10.0
	Median	165.0	167.3	167.0	167.0	167.0	167.0
	Minimum	146.0	126.0	142.0	140.5	136.0	126.0
	Maximum	188.0	198.0	193.0	193.5	193.0	198.0
BMI (kg.m-2)	Mean	23.7	24.7	25.8	26.6	25.4	25.4
	SD	4.5	4.9	5.7	6.1	5.6	5.6
	Median	23.5	23.8	25.2	25.2	24.0	24.5
	Minimum	16.1	12.9	15.1	15.8	14.6	12.9
	Maximum	44.2	39.7	45.6	45.7	51.1	51.1
FBM (kg)	Mean	16.7	18.6	20.6	22.3	19.9	20.0
	SD	8.1	9.5	11.5	13.4	11.4	11.3
	Median	15.6	16.2	18.2	18.1	16.8	17.1
	Minimum	3.9	1.6	3.4	4.8	2.8	1.6
	Maximum	61.4	58.3	76.2	72.2	98.1	98.1
LBM (kg)	Mean	48.6	51.4	51.8	51.5	51.3	51.2
	SD	10.2	11.0	10.1	9.9	10.4	10.3
	Median	46.5	50.3	50.3	50.8	49.3	49.7
	Minimum	32.4	23.4	29.4	29.5	26.0	23.4
	Maximum	76.3	81.6	82.9	86.9	81.9	86.9
CLCR (mL/min)	Mean	115.0	117.0	118.8	124.1	120.5	119.5
	SD	27.1	27.7	26.6	27.8	29.4	27.9
	Median	112.6	114.8	116.9	125.3	122.3	118.8
	Minimum	47.1	57.3	47.3	38.6	51.7	38.6
	Maximum	160.0	160.0	160.0	160.0	160.0	160.0
ALT (IU)	Mean	20.0	22.8	21.3	20.0	20.8	21.0
	SD	10.6	20.1	12.2	10.7	11.7	12.9
	Median	17.0	18.0	18.0	17.0	18.0	18.0
	Minimum	8.0	6.0	5.0	6.0	4.0	4.0
	Maximum	66.0	184.0	84.0	88.0	86.0	184.0
AST (IU)	Mean	20.7	23.2	21.1	20.1	21.3	21.2
	SD	7.1	16.1	7.1	6.8	8.5	9.1
	Median	19.0	19.0	20.0	19.0	20.0	19.0
	Minimum	10.0	9.0	10.0	9.0	10.0	9.0
	Maximum	54.0	141.0	61.0	54.0	85.0	141.0
Baseline seizure frequency	Mean	33.1	73.0	34.9	41.2	29.0	38.5
	SD	62.2	398.2	83.9	91.0	50.7	155.3
	Median	9.8	10.0	12.0	13.3	11.6	11.3
	Minimum	3.3	3.3	3.2	2.9	3.2	2.9
	Maximum	438.0	4504.0	1022.6	591.8	572.1	4504.0

Source: the sponsor's pop pk report, page169.

The sponsor's final model of perampanel apparent clearance is described as follows:

CL/F(L/h)=0.770*(1+COV1+COV2)
where
COV1 = -0.138 x (FBM/17.1)+0.0220 x (DOS-2)-0.162 x (SEX-1)-0.0231*(VIS-6)
COV2 =1.67*CAR+0.841*OXC+0.942*FENC/16204+0.228*TOP
where FBM = fatty body mass; DOS = perampanel dose, SEX = 1 for male, 2 for female; VIS = effect of visit relative to Visit 6; CAR = 1 (with) or 0 (without) carbamazepine; OXC = 1 (with) or 0 (without) oxcarbazepine; FENC = phenytoin concentration.
The apparent volume of distribution (V) was fixed to 129 L.

The sponsor's final model showed that perampanel apparent clearance (CL/F) was slightly lower in a typical female subject (0.605 L/h) than in a male subject (0.730 L/h), assuming FBM=17.1 kg and without co-administration of the AEDs found to induce perampanel clearance. Visit (as time effect), dose, and FBM were also covariates. CL/F slightly increased with increasing dose, slightly decreased at later visits and with higher FBM; however, these effects were small and not considered clinically relevant.

Specifically, CL/F decreases when fat body mass increases (0.73 L/h for FBM=17.1kg, 0.787 L/H for FBM=7.93kg, and 0.583 L/H for FBM=40.72kg). CL/F decreases slightly by 2.31% at each visit after Visit 6. CL/F increases slightly by 2.20% for an increase of dose of 1 mg per day, above the minimum dose of 2 mg. However, these effects were small and not considered clinically meaningful.

Regarding to co-administered drugs, CL/F of perampanel increased approximately 3 fold, 2 fold and 2 fold with carbamazepine, oxcarbazepine and phenytoin co-administration, respectively. Also the use of topiramte appeared to increase CL/F of perampanel slightly (0.73L/h (no use) vs. 0.91 L/h (use)).

Perampanel CL/F was not significantly affected by baseline seizure frequency, age, or renal or liver function (estimated with creatinine clearance or circulating liver enzymes respectively).

Table 4 presents the parameter estimates from the sponsor's final population PK model.

Table 4. The parameter estimates from the sponsor's final PK model

Residual error model	Symbol	Final estimate	SEE	SEE %	95% CI	IIV
proportional	θ_1	0.0800	0.00436	5	[0.0715; 0.0885]	8.0
additive	θ_2	4.02	0.841	21	[2.37; 5.67]	4.0
Fixed effects						
CL basal (L/h)	θ_3	0.770	0.0452	6	[0.681; 0.859]	
Effect of FBM (centred to 17.1 kg)	θ_4	-0.138	0.0314	23	[-0.2; -0.076]	
Effedt of perampanel dose	θ_5	0.0220	0.00696	32	[0.008; 0.036]	
Effect of sex	θ_6	-0.162	0.0438	27	[-0.248; -0.076]	
Effect of visit relative to Visit 6	θ_7	-0.0231	0.00771	33	[-0.038; -0.008]	
Effect of carbamazepine co-administration	θ_8	1.67	0.137	8	[1.401; 1.939]	
Effect of oxcarbazepine co-administration	θ_9	0.841	0.0942	11	[0.656; 1.026]	
Effect of phenytoin co-administration by concentration (centrelized to 16204)	θ_{10}	0.942	0.137	15	[0.673; 1.211]	
Effect of topimarate co-administration	θ_{11}	0.228	0.0565	25	[0.117; 0.339]	
Between subject variability						
on CL	ω^2_1	0.215	0.0143	7	[0.187; 0.243]	46.4
	IOV	0.0455	0.00485	11	[0.036; 0.055]	21.3

Source: the sponsor's pop pk report, page 184.

The sponsor also evaluated the effect of perampanel on the pharmacokinetics of other AEDs.

Plasma AED concentrations, treated as Cavss, were used to determine the apparent clearance from the ratio between the dosing rate (daily dose/24) and Cavss. AED clearance was affected by between-subject and inter-occasion variability. Table 5 summarizes the results from the analyses for the AEDs. All the statistically significant effects of perampanel on the CL of the AEDs were minimal in magnitude and thus of no clinical relevance.

Table 5. The results from population PK model for co-administered drugs.

AED	Statistically significant covariates	Statistically significant effects of perampanel
Carbamazepine	CL increases with carbamazepine dose and with valproic acid (YN)	CL increases with dose: <5% at 12 mg
Clobazam	CL is lower in females, decreases when body weight increases, increases with phenytoin (YN).	CL increases with concentrations: <5% in males at dose 12 mg <8% in females at dose 12 mg
Clonazepam	CL increases with phenytoin (YN), valproic acid (YN) and clobazam(YN)	No effect
Lamotrigine	CL increases with carbamazepine dose and phenobarbital(YN), decreases with valproic acid(YN)	CL increases with Log(dose): <10% at dose 12 mg
Levetiracetam	CL is lower in females, increases with body weight, decreases with phenytoin (YN) and valproic acid (YN)	No effect
Oxcarbazepine	CL is lower in females, increases with phenytoin	CL decreases: by 26% at any dose
Phenobarbital	CL greater with greater AST/ALT, decreases with lamotrigine or oxcarbazepine	No effect
Phenytoin	CL increases with its dose, increases with oxcarbazepine (YN) or zonisamide (YN)	No effect
Topiramate	CL increases with body weight and with phenytoin (YN) and zonisamide (YN)	No effect
Valproic acid	CL increases with body weight	CL increases with dose: <5% at dose 12 mg
Zonisamide	CL increases with phenytoin (YN) and phenobarbital (YN) and, decreases with clobazam (YN)	No effect

Source: the sponsor's report, page 11.

Exposure-Response Analyses

The sponsor conducted three Phase III studies: E2007-G000-304, 305 and 306. The primary endpoint was the percent reduction in seizure frequency during double-blind phase (DB) from the baseline. The doses of 8 mg and 12 mg with placebo were evaluated in the studies of E2007-G000-304, 305 whereas the doses of 2mg, 4mg and 8mg were compared to placebo in the study of E2007-G000-306. The dose of 2 mg did not meet the statistically significant criteria (p-value=0.4197). However, the doses of 4mg, 8mg and 12 mg showed effectiveness in all studies, although 12 mg failed to show superiority compared to 8mg in E2007-G000-305 (Tabe 6).

Table 6. The summary of primary efficacy analyses results. The numbers are the median percent reduction during DB phase from the baseline relative to placebo with p-values in parentheses.

	2mg	4mg	8mg	12mg
306	-4.36 (0.4197)	-13.7 (0.0026)	-20.1 (<0.0001)	
305			-19.1 (0.0008)	-13.69 (0.0105)
304			-13.53 (0.0261)	-14.2 (0.0158)

For the exposure-response analyses, data from three phase III studies (304/305/306) were pooled. The model-predicted perampanel concentration at steady state, Cavss, was derived at visits 6, 7 and 8 as follows:

Cavss= (DDOS/24)*1000/(CL/F)

For efficacy analysis, a log-transformed seizure frequency was used as a response variable. The final model was a drug effect proportional to predicted Cavss (in mg/L) with additive IIV (ETA2) on the slope (SLOP) as follows.

Log_e (seizures frequency/28days)

= Log (seizures frequency/28days of baseline) + 0.245*CLOB - 0.368 - 0.000595 x C_{avss}(ng/mL)

where CLOB = 1 (with) or 0 (without) clobazam; C_{avss} = average concentration of perampanel at steady state.

The model predicts that during maintenance, the seizure frequency in a typical subject (baseline of 11.33 seizures over a period of 28 days) is predicted to be: 7.5, 7.2, 6.7 and 6.4 seizures per 28 days when treated with perampanel and with a median concentration of 73.5, 146.3, 264.2 or 336.5 ng/mL respectively (median predicted Cavss in the 2 mg, 4 mg, 8 mg and 12 mg groups).

Regarding to the safety analyses, following 9 most frequent and clinically relevant adverse events (AEs) were analyzed related to perampanel concentration: euphoric mood, increased appetite, gait disturbances grouped with balance-disorder and fall, dysarthria grouped with aphasia and speech disorder, weight increases, fatigue grouped with asthenia and apathy, irritability grouped with aggression and anger, dizziness, and decreased appetite.

The probability of occurrence of a given AE was estimated using a logistic regression model. A linear predictor (logit) was estimated as a function of exposure (Cavss) to perampanel. The influence of demographic covariates and of concomitant AEDs (presence/absence) on this relationship was explored on the logit.

The sponsor's safety-exposure analyses showed that the probability of euphoric mood, gait disturbance, dysarthria, weight increase, fatigue, irritability, somnolence, dysarthria and dizziness was shown to increase significantly with an increase in plasma concentrations of perampanel whereas the probability of headache, increased or decreased appetite was not shown to be affected by an increase in plasma concentrations of perampanel.

Reviewer's comments:

- *The dose and visit (time effect) were found to be statistically significant covariates in the sponsor's population PK model.*
    - *Perampanel PK showed linearity in the dedicated study, and there was little difference in observed concentration by visit so the sponsor' finding seems to be counter-intuitive.*
    - *However, the magnitude of estimated CL/F is minimal so it is not expected to influence overall conclusions from the population PK analyses.*
- *The sponsor's exposure-response analyses are acceptable. However, there are a couple of minor comments as follows;*
    - *The sponsor's analyses did not account for the difference in efficacy profile between studies.*
    - *The sponsor's analyses did not account for correlation between visits.*
    - *The reviewer re-analyzed the data using the primary efficacy endpoint rather than log(seizure frequency) to be consistent with the primary efficacy analysis.*

4. REVIEWER'S ANALYSES

4.1 Introduction

The reviewer conducted independent analyses to assess whether the sponsor's proposed dose is reasonable or not. The relationship between primary endpoint, percent reduction in seizure frequency from baseline during double blind phase, and steady state average concentration was analyzed. In addition to exposure-efficacy relationship, the reviewer looked further into safety event focused on incidences related to hostility or aggression as it appeared to be dose-dependent increase, especially at doses of 8 mg/day and 12 mg/day.

4.2 Objectives

- To assess whether the sponsor's proposed dose is reasonable or not given efficacy and safety profile of perampanel.

4.3 Methods

The data from three phase III studies were included. Being consistent with the primary efficacy analyses, the percent reduction in seizure frequency during the double blind phase from the baseline phase was evaluated. The percent change was log-transformed, and t-distribution was assumed for log-transformed response variable as it seemed to provide better fit compared to a normal distribution according to Akaike Information Criteria (2527 vs. 2854).

For safety analyses, the adverse events including euphoric mood, gait disturbance, dysarthria (speech disorder), weight increase, fatigue, nausea, irritability, somnolence and dizziness were re-analyzed by the reviewer. Each adverse event was defined as 1 if a patient had occurred at least once during double blind phase, and logistic regression was applied for the relationship. In addition to that, the adverse events related to hostility/aggression were extracted based on Standardized MedDRA Queries (SMQs) from the adverse event dataset from three phase III studies. The exact adverse event used for the analyses are listed below;

Injury, Laceration, Skin Laceration, Aggression, Anger, Belligerence, Physical Assault, Abnormal Behaviour, Affect Lability, Agitation, Disinhibition, Human Bite, Hypomania, Impulse-Control Disorder, Impulsive behaviour, Irritability, Mania, Paranoia, Personality Change, Personality Disorder, Psychomotor Hyperactivity, Psychotic behaviour, Psychotic Disorder.

A logistic regression was applied with Emax function for structural relationship between the probability of adverse event and the steady state average concentration.

4.3.1 Data Sets

Data sets used are summarized in Table 7.

Table 7. Analysis Data Sets

Study Number	Name	Link to EDR

E2007-G000-304 E2007-G000-305 E2007-G000-306	Seizure_304.sas7bdat, AE_304.sas7bdat Seizure_305.sas7bdat, AE_305.sas7bdat Seizure_306.sas7bdat, AE_306.sas7bdat	

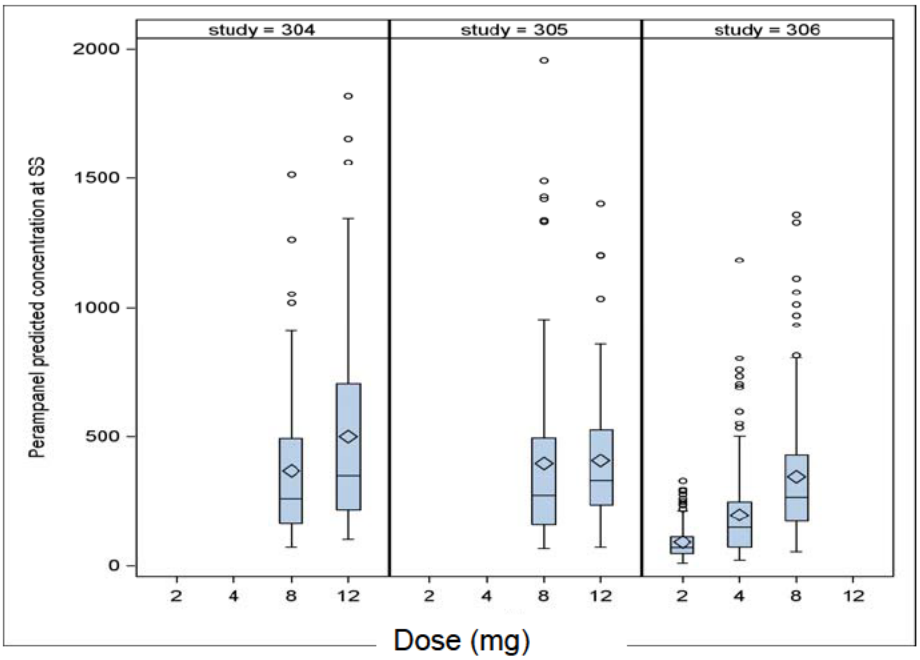
4.3.2 Software

SAS 9.2 and R 2.5 were used for the analysis.

4.3.3 Model Results

Figure 2 presented the distribution of perampanel average concentration at steady state by study and dose. It showed dose-proportionality but there appears to be large variability also.

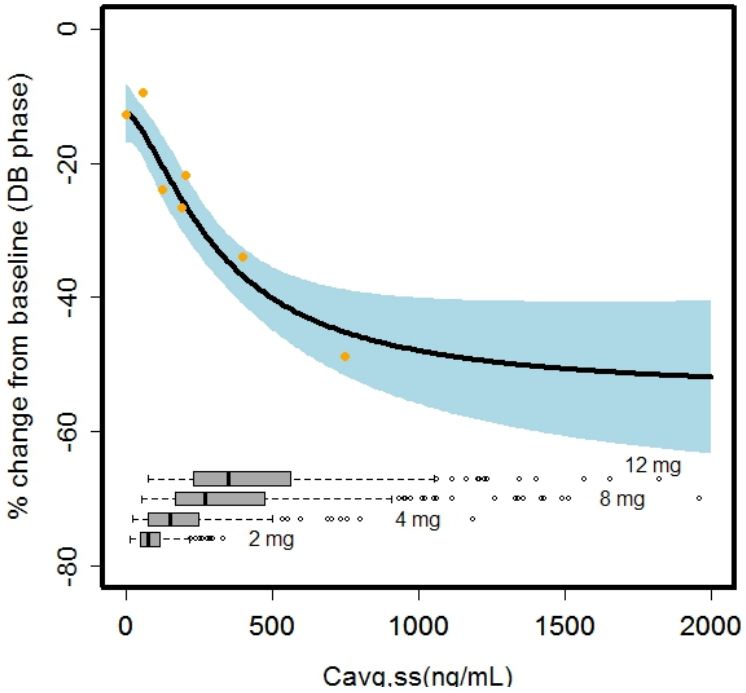
Figure 2. The distribution of Cavss (ng/ml) by study and dose.



Efficacy

Figure 3 presents the model-predicted relationship from the reviewer's independent assessment. The seizure frequency measured by the percent reduction clearly decreases in concentration-dependent manner but the predicted reduction at 12 mg does not seem to be much different from the one at 8 mg based on the model (28% reduction at 8 mg vs. 32% reduction at 12 mg).

Figure 3. The model predicted relationship for the percent reduction in seizure frequency and perampanel average concentration at steady state with 95% prediction interval (blue shaded area). The dots indicate the observed values at ranked six bins of perampanel concentration. Also four boxplots are the distribution of perampanel concentration at each dose.



Sub-group analysis by inducer and non-inducer group

The sponsor conducted dose response analysis in patients taking enzyme inducing AEDs (any of oxcarbazepine, carbamazepine, and phenytoin) and not taking enzyme inducing AEDs. Non-inducer group was defined as a patient not taking one of the above three AEDs. The results are shown in Table 8 and Table 9 which indicates smaller effect size in patients who took inducers than those who did not take any of inducers.

Table 8. Median Percent Change in Seizure Frequency and Responder Rate During Maintenance Period by Last (Actual) Dose and Baseline Co-administered AED, Completer Analysis Set for Studies E2007-G000-305 and E2007-G000-304, Excluding Central and South American Sites

Parameter/ Statistics	Concomitant CBZ, OXC, PHY			Concomitant CBZ or OXC			No Concomitant CBZ, OXC, or PHY		
		Perampanel Last Dose			Perampanel Last Dose			Perampanel Last Dose	
	Placebo	8 mg	12 mg	Placebo	8 mg	12 mg	Placebo	8 mg	12 mg
All partial seizure frequency per 28 days									
Total N	102	94	79	91	77	67	80	64	35
Median frequency – Prerandomization	14.74	10.21	12.78	12.98	10.50	13.66	10.72	13.84	17.18
Median percent change in Maintenance Period	-8.68	-25.82	-22.62	-5.87	-32.37	-27.82	-19.96	-50.63	-54.17
Median difference to placebo (95% CI)[a]		-17.77 (-31.807, -3.872)	-19.21 (-34.269, -4.409)		-25.92 (-40.446, -11.170)	-26.92 (-42.396, -11.338)		-24.37 (-37.818, -10.163)	-33.22 (-47.253, -17.673)
Responder rate									
Total N	102	94	79	91	77	67	80	64	35
Responders, n (%)	21 (20	29 (30.9)	26 (32.9)	17 (18	27 (35.1)	24 (35.8)	12 (15	32 (50.0)	19 (54.3)

Source: the sponsor's summary of efficacy report, page 108.

Table 9. Median Percent Change in Seizure Frequency and Responder Rate During Maintenance Period by Last (Actual) Dose and Baseline Co-administered AED, Completer Analysis Set for Study E2007-G000-306

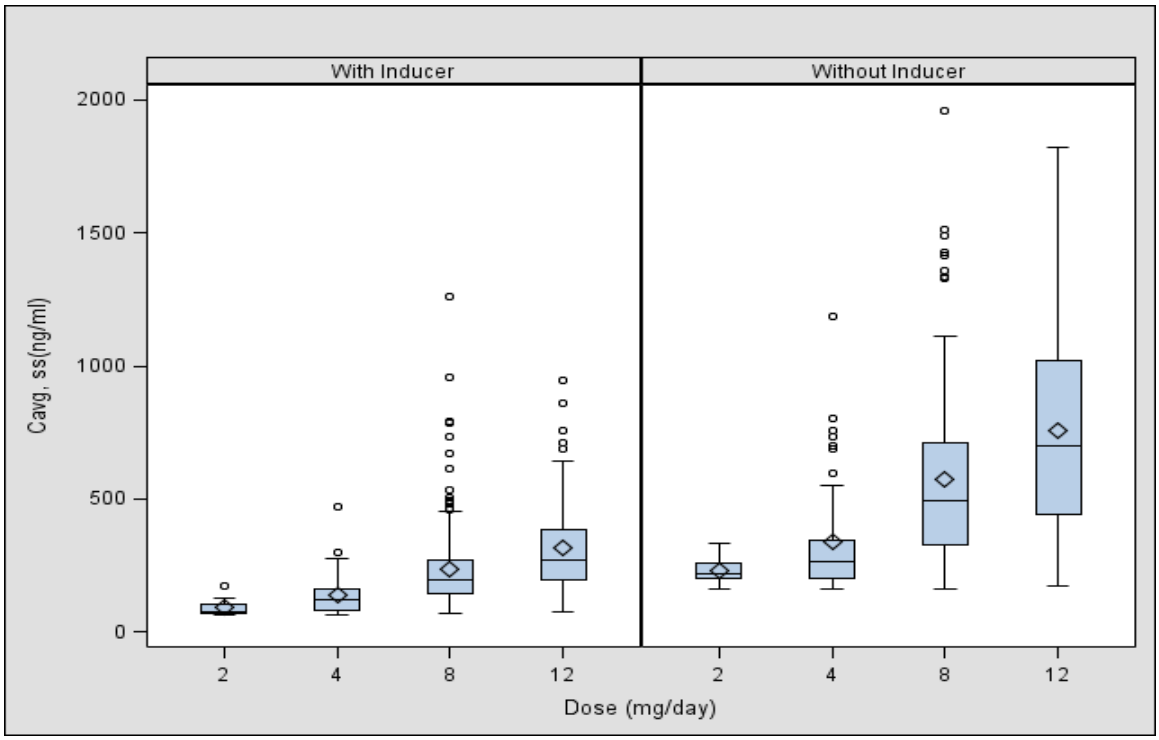
Statistics	All Partial Seizure Frequency per 28 days				Responder Rate	
	Total N	Median Prerandomization frequency	Median % change in Maintenance Period	Median difference to placebo (95% CI)[a]	Total N	Responder, n (%)
Concomitant CBZ, OXC, PHY						
Placebo	94	11.27	-14.39	--	94	17 (18.1)
Perampanel 2 mg	90	10.71	-16.40	-0.46 (-14.255, 12.712)	90	18 (20.0)
Perampanel 4 mg	84	11.33	-32.66	-11.86 (-24.469, 1.607)	84	22 (26.2)
Perampanel 8 mg	76	8.88	-22.92	-10.82 (-26.083, 4.654)	76	26 (34.2)
Concomitant CBZ or OXC						
Placebo	88	10.59	-13.93	--	88	15 (17.0)
Perampanel 2 mg	80	10.71	-14.44	-0.19 (-14.985, 13.534)	80	15 (18.8)
Perampanel 4 mg	72	11.19	-32.66	-13.46 (-26.396, 0.250)	72	19 (26.4)
Perampanel 8 mg	71	8.88	-24.34	-11.89 (-27.582, 3.806)	71	24 (33.8)
No concomitant CBZ, OXC, PHY						
Placebo	72	8.23	-16.04	--	72	14 (19.4)
Perampanel 2 mg	70	8.88	-22.81	-8.15 (-24.315, 7.057)	70	18 (25.7)
Perampanel 4 mg	69	9.56	-21.90	-15.31 (-31.125, 1.334)	69	24 (34.8)
Perampanel 8 mg	53	11.61	-40.27	-27.60 (-44.872, -11.385)	53	21 (39.6)

Source: the sponsor's summary of efficacy report, page 109.

The concern was raised by the pharmacometric reviewer that the sub-group analysis conducted by the sponsor can be confounded by other co-medication uses as patients were allowed to take up to three AEDs as background therapies in all three studies. In order to examine the potential confounding effect by unbalanced baseline characteristics including other AEDs use in the two groups, we conducted the exploratory concentration-efficacy analysis.

First, the reviewer examined the distribution of perampanel concentration by inducer groups, which shows that the concentration of those who took inducer is about 2-3 fold lower than that of those who did not (Figure 4)

Figure 4. The distribution of perampanel average concentration at SS by dose and inducer groups.



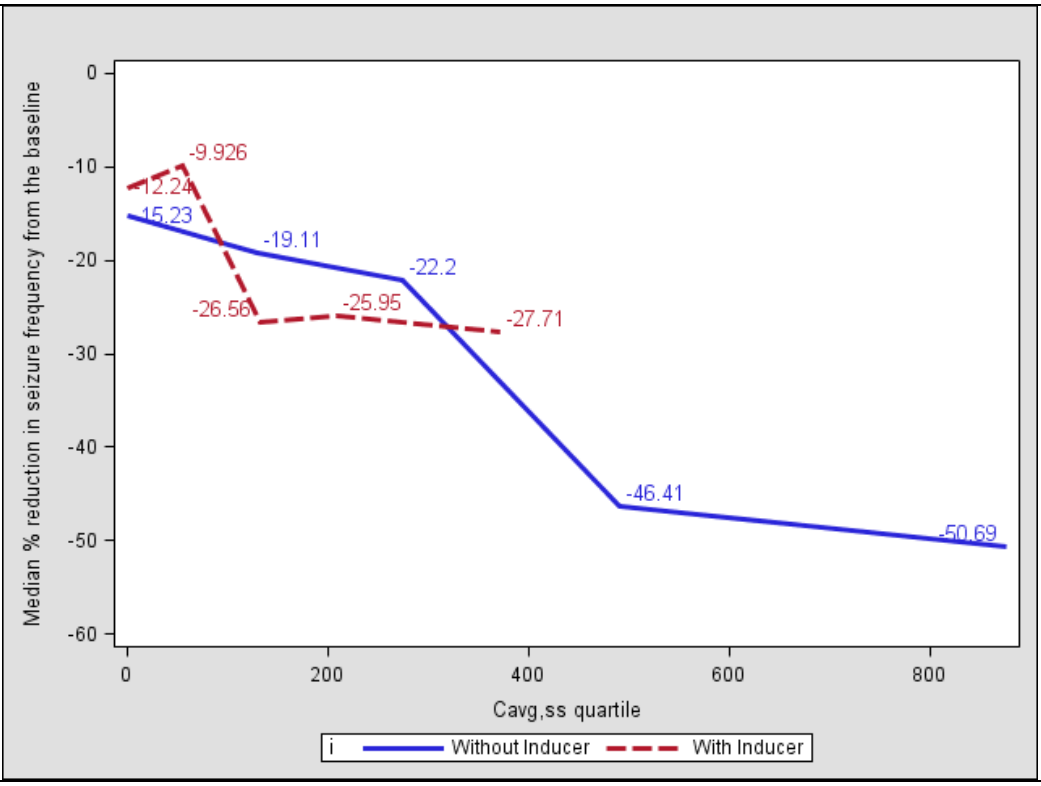
The steady-state average concentration was binned by quartiles by with-inducer and without-inducer groups. The median concentrations with range in each bin by groups are displayed in Table 10.

Table 10. The steady-state average concentration range (ng/ml) by with inducer and without inducer groups.

Quartile	With Inducer: median (range)	Without Inducer : median (range)
1st	55 ng/ml (10-88)	129 ng/ml (21-203)
2nd	132 ng/ml (92-167)	275 ng/ml (204-365)
3rd	209 ng/ml (168-267)	491 ng/ml (367-650)
4th	371 ng/ml (268-1260)	876 ng/ml (672-1958)

The median percent change in seizure frequency was calculated in each bin of concentration quartile by two groups of patients and the result is shown in Figure 5. One group was receiving enzyme-inducing AEDs while the other group was not receiving enzyme-inducing AEDs at baseline. The graph suggests that at similar concentration ranges of perampanel, the reduction in seizure frequency is similar between the two groups. If the assumption of similar distribution of baseline characteristics, other background treatments across concentration quartile bins can be made, then the data suggests that there is no additional pharmacodynamic interaction. The lack of pharmacodynamic interaction implies that dose of perampanel can be increased in patients taking enzyme inducing AEDs which would result in perampanel concentrations as observed in patients not taking enzyme inducing AEDs.

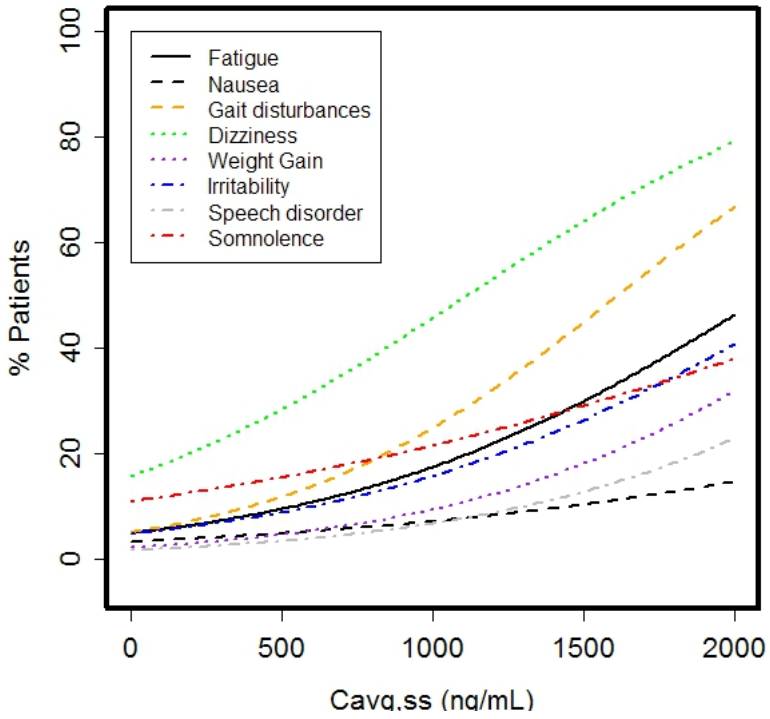
Figure 5. Median change in seizure frequency versus steady state average perampanel concentrations in studies of 304/305/306. The effect size is displayed at the median concentrations at each bin.



Safety

Perampanel blood levels were found to be statistically significant covariate in gait disturbance, dysarthria (speech disorder), weight increase, fatigue, nausea, irritability, somnolence and dizziness (Figure 6). The incidence of Fatigue, dizziness, irritability and gait disturbance shows relatively sharp increase with increasing perampanel concentration.

Figure 6. The safety profiles of perampanel linked to the concentration.



Based on the internal discussion with clinical team, the reviewer further analyzed data focused on the adverse event related to hostility and aggression. The reviewer looked into the adverse event of hostility and aggression based on Standardized MedDRA Queries. A total of 23 adverse events were extracted as stated in the method section.

Table 11 presents the percent of patients who had hostility/aggression related adverse events during DB phase. The result shows clear dose-dependent increase in the incidences, and the percentage appears to increase at about 215 ng/ml of perampanel blood level, which corresponds to majority of distribution at doses at 8 and 12 mg (Figure 7).

The adverse events were summarized by the severity (Table 12), and the severe adverse events were occurred only at 8 mg and 12 mg.

Table 11. The percent of patients who had hostility/aggression related adverse events during DB phase by dose and perampanel concentration. The perampanel concentration was ranked and grouped by 6 bins such that the equal number of patients was assigned to each bin.

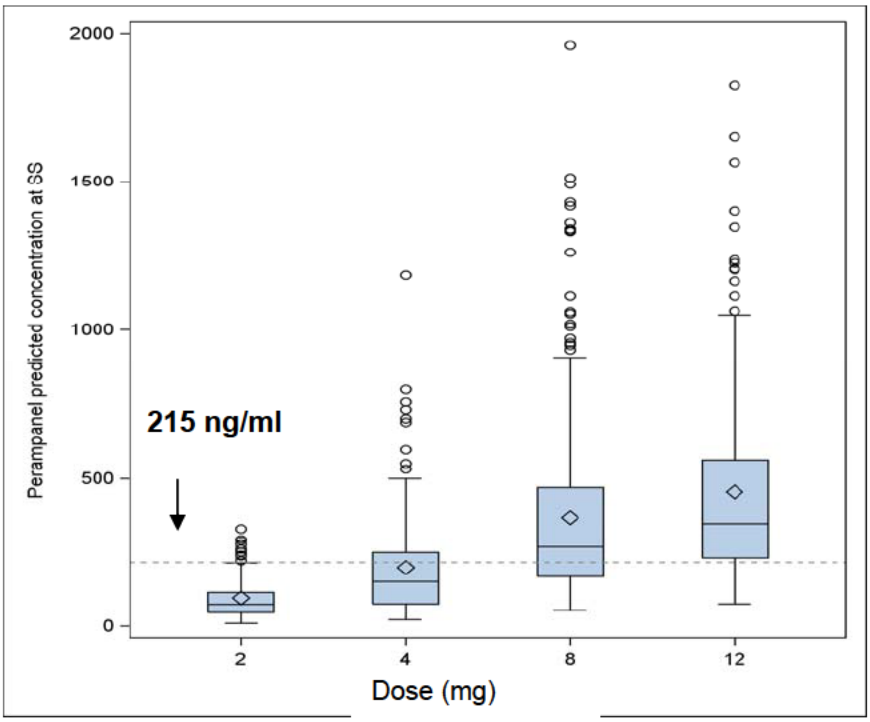
Study	Placebo	2 mg	4 mg	8 mg	12 mg	Total
304	9% (11/121)	—	—	16% (21/133)	25% (33/134)	17% (65/388)

305	7% (10/136)	—	—	13% (17/129)	16% (19/121)	12% (46/386)
306	2% (4/185)	5% (9/180)	5% (9/172)	9% (15/169)		5% (37/706)
Perampanel concentration, min-max, ng/ml (# patients)						
0	9.7-91.1 (n=128)	91.4-154.8 (n=128)	155.1-213.9 (n=129)	214.2-305.6 (n=128)	306.1-513.7 (n=129)	513.8-1958.1 (n=128)
6%	6%	8%	6%	11%	13%	22%

Table 12. The number of patients who had hostility/aggression related adverse events by severity. The multiple incidences per a patient were counted as an independent incidence.

study	Planned dose group	AE severity		
		Mild	Moderate	Severe
304	Placebo	11	5	0
	8mg	21	8	4
	12mg	22	22	6
305	Placebo	7	4	0
	8mg	13	4	2
	12mg	18	9	2
306	Placebo	3	1	0
	2mg	6	3	0
	4mg	8	1	0
	8mg	14	4	1

Figure 7. The distribution of perampanel concentration at steady state (ng/ml) from pooled data from three phase III studies (304/305/306).



The model-predicted relationship is shown in Figure 8. It is apparent that the probability of hostility and aggression increases in concentration-dependent manner. One thing we should notice here is that the probability seems to stay low (less than 10%) at the exposure range at 2 mg and 4 mg but it dramatically increases at 8 mg and 12 mg, which is consistent with the previous observation.

Figure 8. The model predicted relationship for the probability of hostility and aggression and perampanel average concentration at steady state with 95% prediction interval (blue shaded area). The dots indicate the observed proportion of patients at ranked six bins of perampanel concentration. Also four boxplots are the distribution of perampanel concentration at each dose.

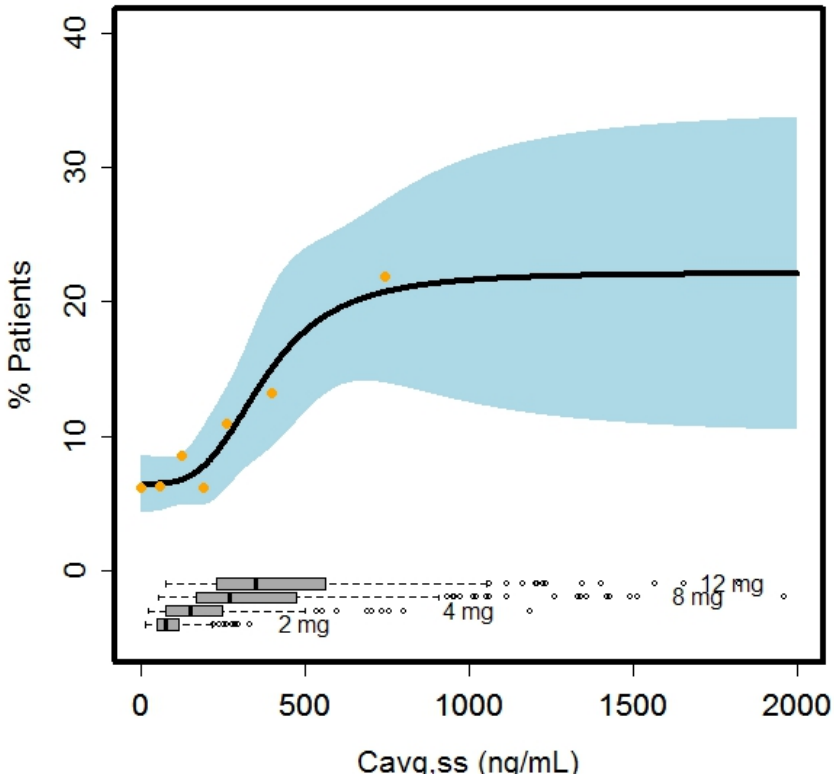


Figure 9 shows the benefit and risk profiles of perampanel, and based on the benefit and risk profile, the reviewer predicted the percent reduction in seizure frequency during DB phase and the probability of adverse events related to hostility and aggression (Table 13).

The distribution of concentration at 6 mg and 10 mg were simulated assuming the same variability as in 4 mg.

Figure 9. The benefit and risk profile of perampanel. The grey and orange parts represent the efficacy (% reduction in seizure frequency) and safety (% patients of having hostility/aggression related AEs), respectively. The solid lines are model-predicted relationship, and the dots are observed data at the ranked six bins of perampanel concentrations. The boxplots indicate the distribution of concentration at each dose group (6 mg and 10 mg were simulated assuming the same variability as 4 mg).

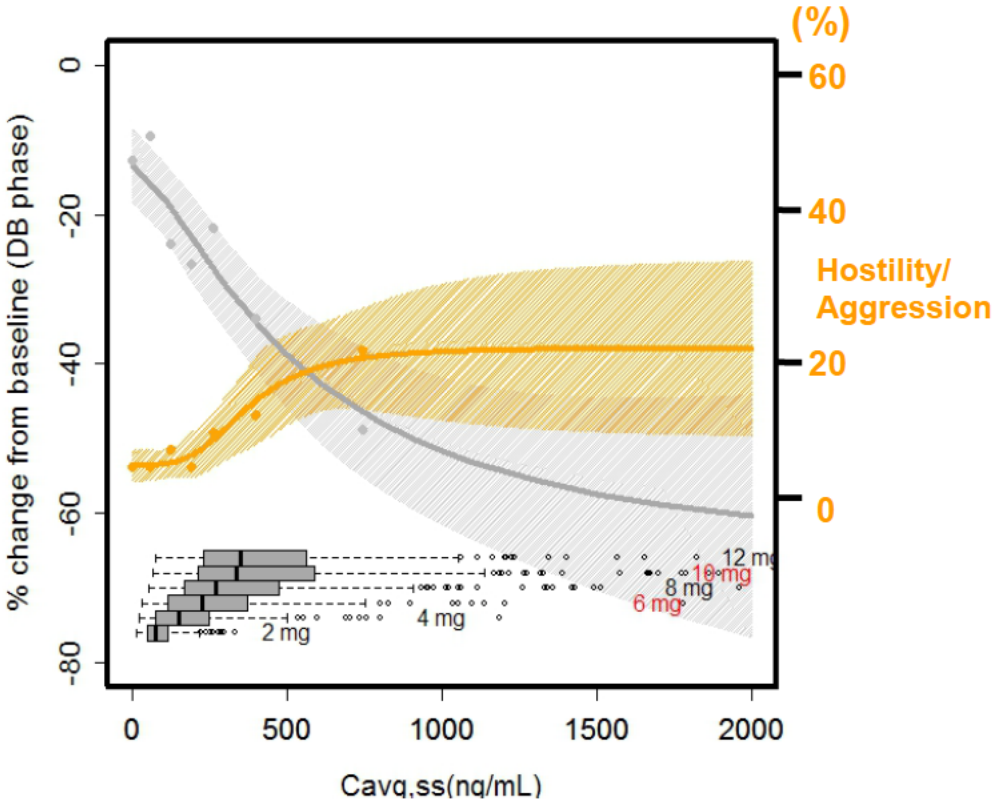


Table 13. Predicted % reduction in seizure frequency and %hostility/aggression-related adverse event based on the modeling results shown in Figure 9. The prediction was made at the median concentration at each dose. (6 mg and 10 mg were predicted based on the simulated exposure range).

Dose	Efficacy (% reduction in seizure)	Safety (% patients of having hostility/aggression)
Placebo	-13.5	6.4
2mg	-16.4	6.5
4mg	-20.7	7.1
6mg	-25.2	8.7
8mg	-27.7	10.2
10mg	-31.2	12.8
12mg	-32.1	13.4

Given the efficacy and safety profiles of perampanel which show little difference in efficacy between 8 mg and 12 mg, and higher risk with increasing concentration, the targeted maintenance dose should be 8 mg/day.

5. Listing of Analyses Codes and Output Files

File Name	**Description**	**Location in \\cdsnas\pharmacometrics**
Efficacy.sas Aggression.sas Safety.sas	The reviewer's exposure-efficacy analysis The reviewer's exposure-safety analysis	

6. Appendix

Appendix 1. The effect of significant covariates on perampanel CL/F.

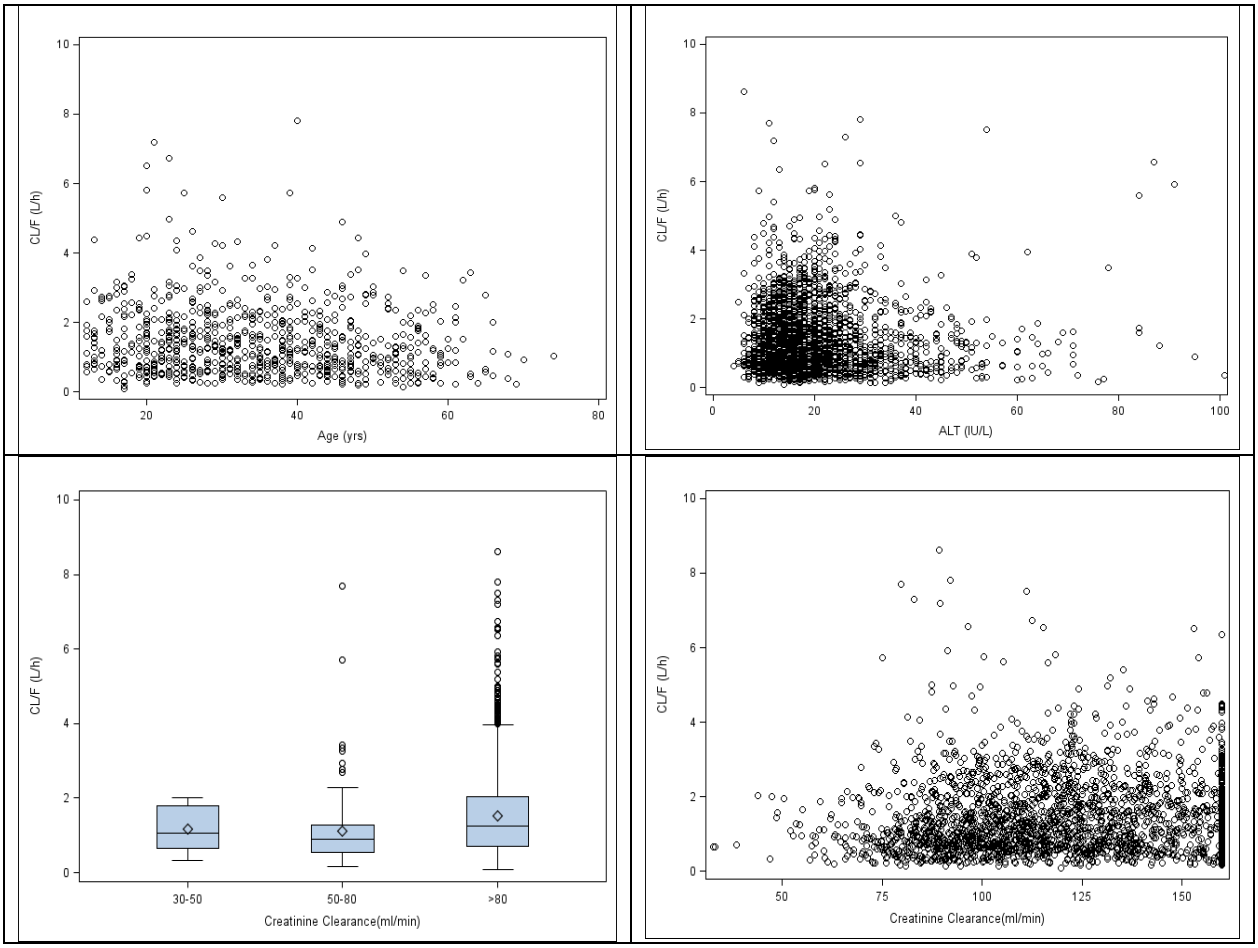
Dose effect on CL/F	Visit 8 without significant AED, FBM 17.1 kg			
	Males		Females	
	Estimated	Ratio[1)]	Estimated	Ratio[1)]
Dose 4 mg	0.662 L/h	0.91	0.537 L/h	0.89
Dose 8 mg	0.730 L/h	NA	0.605 L/h	NA
Dose 12 mg	0.798 L/h	1.09	0.673 L/h	1.11
Time effect on CL/F	**Dose 8 mg, without significant AED, FBM 17.1 kg**			
	Males		**Females, FBM**	
	Estimated	Ratio[2)]	Estimated	Ratio[2)]
Visit 6	0.765 L/h	NA	0.641 L/h	NA
Visit 7	0.748 L/h	0.98	0.623 L/h	0.97
Visit 8	0.730 L/h	0.95	0.605 L/h	0.94
FBM effect on CL/F	**Dose 8mg, Visit 8, without significant AED**			
	Males		**Females**	
	Estimated	Ratio[3)]	Estimated	Ratio[3)]
FBM 17.1 kg	0.730 L/h	NA	0.605 L/h	NA
FBM 40.72 kg (95 percentile)	0.583 L/h	0.80	0.458 L/h	0.76
FBM 7.93 kg (5 percentile)	0.787 L/h	1.08	0.662 L/h	1.09

[1)]: Ratio to estimated value at dose 8 mg
[2)]: Ratio to estimated value on Visit 6
[3)]: Ratio to estimated value of subject whose FBM 17.1 kg
NA: Not applicable

AEDs' effect on CL/F	Dose 8 mg, Visit 8, FBM 17.1 kg			
	Males		Females	
	Estimated	Ratio[1)]	Estimated	Ratio[1)]
Without significant AED	0.730 L/h	NA	0.605 L/h	NA
With carbamazepine	2.016 L/h	2.76	1.891 L/h	3.13
With oxcarbazepine	1.377 L/h	1.89	1.253 L/h	2.07
With phenytoin at concentration=16204 ng/mL	1.455 L/h	1.99	1.330 L/h	2.20
With topiramate	0.905 L/h	1.24	0.781 L/h	1.29

[1)]: Ratio to estimated value without significant AED
NA: Not applicable

Appendix 2. The relationship between perampanel CL/F and other covariates.



4.3. OCP Filing Review Form

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		**Information**
NDA/BLA Number	202,834	**Brand Name**	FYCOMPA™
OCP Division	DCP-I	**Generic Name**	Perampanel (E2007)
Medical Division	HFD-120	**Drug Class**	AMPA receptor antagonist
OCP Reviewer	Xinning Yang	**Indication(s)**	Partial-onset seizure with or without secondarily generalized seizure in patients aged 12 years and older (Adjunctive therapy)
OCP Team Leader	Angela Men	**Dosage Form**	Tablet (2, 4, 6, 8, 10 and 12 mg)
Pharmacometrics Reviewer	Joo-Yeon Lee	**Dosing Regimen**	4 - 12 mg once daily before bedtime
Date of Submission	12/22/2011	**Route of Administration**	Oral
Estimated Due Date of OCP Review	8/22/2012	**Sponsor**	Eisai Co.
Medical Division Due Date	8/30/2012	**Priority Classification**	Standard
PDUFA Due Date	10/22/2012		

Clin. Pharm. and Biopharm. Information

The sponsor submitted this original NDA 202834 (NME) on May 25th, 2011 seeking for approval of FYCOMPA® (Perampanel, E2007) for the adjunctive treatment of partial-onset seizures with or without secondarily generalized seizures in patients aged 12 year and older. This NDA is under regular review classification.

Perampanel is a noncompetitive and highly selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist. AMPA receptors play a key role in mediating cortical glutamatergic transmission. AMPA antagonists could potentially reduce excessive excitatory activity and excitotoxicity, and thus exhibit anticonvulsant and potentially antiepileptogenic effects.

The proposed products are film-coated tablets available as 2, 4, 6, 8, 10 and 12 mg. Treatment with FYCOMPA® should be initiated with a dose of 2 mg/day. The dose may be increased based on clinical response and tolerability by 2 mg/day increments to a dose of 4 mg to 12 mg/day. Dose increases should occur no more frequently than at weekly intervals.

There are 29 clinical pharmacology studies submitted, which include 2 BA studies, 5 BE studies, 2 food effect studies, 2 SAD studies, 2 MAD studies, 1 mass balance study, 1 elderly population, 1 hepatic impairment study, 6 drug-drug interaction studies, 1 QT study, 1 alcohol study, 2 abuse potential studies and 1 phototoxic study. There are 4 population PK/PD reports, 16 bioanalytical validation reports and 20 *in vitro* studies. In addition, there are 4 Phase 2 trials, 3 Phase 3 pivotal trials and 3 open-label extension studies.

All clinical studies were conducted with tablet formulations. The earliest clinical studies utilized formulation A which was demonstrated to be BE with formulation B. Formulation B was used in some Phase 1 and also Phase 2 studies, while Formulation C was used in Phase 2 studies and all the pivotal Phase 3 trials. According to the sponsor, (b) (4) from Formulation B to C. Therefore, a formal BE study was not conducted. Instead, *in vitro* dissolution test was used to support BE between formulation B and C. Formulation D was not tested in any clinical studies and is proposed for commercial use besides Formulation C. Three BE studies were performed showing BE between these two formulations.

This NDA consists of

- **Biopharmaceutics studies (9 studies):**
  1. BA: (2 studies)
     E2007-E044-017: Absolute Bioavailability, SD p.o. 8 mg and i.v. ^{14}C-labeled microdose, N=10 (F:116% ± 9.4%, data available from only 5 subjects due to analytical problems)
     E2007-E044-028: Relative Bioavailability, SD 4 mg Tablet vs. 4 mg oral suspension, N=16 (oral suspension has similar AUC, but lower Cmax and prolonged Tmax)
  2. BE: (5 studies)
     E2007-A001-008: SD 2x1 mg Formulation B vs. 2x1 mg Formulation A, n=34 (BE)
     E2007-E044-016: SD 1x4 Formulation C vs. 2x2 Formulation C, n=24 (BE)
     E2007-E044-037: SD 1x12 Formulation D vs. 6x2 Formulation C, n=28 (BE for AUC0-t and AUC0-inf, but not Cmax with GMR of 86.4% and 90% CI of [78.4, 95.3])
     E2007-A001-039: SD 1x6 Formulation D vs. 3x2 Formulation C, n=54 (BE)
     E2007-A001-040: SD 1x12 Formulation D vs. 6x2 Formulation C, n=54 (BE)

  3. Food effect: (2 studies)
     E2007-E044-003: SD 1 mg Formulation A, fasted vs. high fat, n=24 (No effect on AUC, reduced Cmax by 40% and prolonged Tmax by ~2hr)
     E2007-E044-009 (part 1): SD 6 mg Formulation B, fasted vs. high fat, n=8 in each group (parallel design) (No effect on AUC0-24hr, reduced Cmax by 28% and prolonged Tmax by ~3hr)

  4. Analytical methods: (12 methods, 16 validation studies)

- **Human Pharmacokinetic studies (16 studies):**
  1. Healthy subject PK and tolerability: (6 studies)
     (dose-proportional SD 0.2-8 mg, MD QD 1-10 mg)
     E2007-E044-001: SAD (0.2-8 mg), n=55 (renal CL is minimal)
     E2007-J081-010: SAD in Japanese (0.2-8 mg), n=56 (overall similar to study 001)
     E2007-E044-002: MAD (1-4 mg, QD, 14 day; 4mgx7d followed by 6 mgx7d, QD), n=32 (steady state reached by Day 14. Accumulation ratio of AUC: 3.40-4.88)
     E2007-J081-026: MAD in Japanese (2mgx14d and 2mgx14d followed by 4mgx14d, QD), n=12 in each group
     E2007-E044-009 (part 2): Time of Dosing (6mgx7d followed by 8 mgx7d then 10mgx7d, QD, morning or evening dosing), n=8 in each group (Cmin not affected by time of dosing)
     E2007-E044-007: Mass Balance, SD 2 mg with ^{14}C-labeled microdose, N=8 (collected up to 41 days, Recovery=70%, 48% in feces and 22% in urine Little parent drug present in feces and urine, indicating almost complete Absorption in plasma, perampanel metabolites were not detected.)

  2. Patient PK and initial tolerability study reports: (2 studies)
     E2007-E049-203: MAD (1 or 2 mgx28d, QD) n=6 for each group (steady state reached within 21 days of dosing; Accumulation ratio: 2.53-3.35)
     E2007-J081-231: MD in Japanese (efficacy study, initiated at a dose of 2mg QD and increased weekly in 2 mg increments up to 12 mg QD) n=30

  3. Intrinsic factors: (2 studies)
     E2007-E044-004: Elderly population. SD 1 or 2 mg, n=8 for each group, age 65-76 yr
     E2007-E044-015: Hepatic impaired population. SD 1 mg in mild and moderate hepatic insufficient patient (Child-Pugh A and B), n=6 in each group (fu,p at 2 h was increased by 27.3% and 73.5% in Child-Pugh A and B subjects, respectively, vs. their respective control groups. For Child-Pugh A subjects, Cu,2 h was 1.26-fold higher, t1/2 was 2.4-fold longer, and unbound AUC(0-inf) was 1.8-fold higher. For Child-Pugh B subjects, Cu,2 h was 1.18-fold higher, t1/2 was 2.1-fold longer, and the unbound AUC(0-inf) was 3.3-fold higher.

4. Extrinsic factors: (6 studies)
   E2007-E044-005: DDI, SD 1 mg alone vs. ketoconazole 400 mg QD x 10 days + SD 1 mg on Day 3 N=26, (AUC of perampanel increased by 20%)
   E2007-E044-006: DDI, SD 2 mg vs. Carbamazepine 300 mg BID x 17 days (Day 25-41) + SD 2 mg on Day 32, N=20
   (AUC of perampanel decreased by 67%, $t_{1/2}$ reduced by ~50%)
   E2007-E044-025: MD 4 mg x 19 days + Levodopa SD 100 mg, N=59 (no effect on levodopa)
   E2007-A001-014: DDI, MD 6mg x 20 days QD + SD 4 mg midazolam, N=35 (<20% effect)
   E2007-E044-019: DDI, MD 4mg x 21 days QD + OC (ethinylestradiol 30 µg and levonorgestrel 150 µg) 21 days QD, N=24 (No effect on either component of OC)
   E2007-E044-029 (Part A): MD 35 days, titration to 8 or 12 mg, QD + OC Single dose, N=28
   (8 mg had no effect on OC; 12 mg reduced Cmax of ethinylestradiol by <20%; 12 mg perampanel decreased levonorgestrel Cmax and AUC by ~40%)
   (Part B): SD 6 mg + OC QD 21 days, N=24 (OC had no effect on perampanel)

5. Population PK (4 reports)
   CPMS-E2007-2011-002: a pooled analysis of the data obtained in 19 Phase 1 studies
   EMFFR2008/06/00: a pooled analysis of data obtained in two Phase 2 studies
   CPMS-E2007-2011-003: a pooled analysis of data from 3 pivotal Phase 3 studies (all patients)
   CPMS-E2007-2011-004: a pooled analysis of data from 3 pivotal Phase 3 studies (adolescent)

- **Human Pharmacodynamic studies (5 studies):**
  1. Healthy PD and PK/PD:
     E2007-E044-030: Alcohol, effect on psychomotor function and cognition.
     E2007-A001-013: QT, moxifloxacin used as positive control (Linear PK from 6 to 12 mg)
     E2007-E044-020: Phototoxic Potential
     E2007-A001-023: Abuse potential
     E2007-A001-024: Abuse potential

  2. Patient PD and PK/PD – Population PK/PD: (3 reports)
     EMFFR2008/06/00, CPMS-E2007-2011-003, CPMS-E2007-2011-004:
     Modeling of the exposure-response relationship

- **Efficacy and safety studies (9 studies):**
  1. Phase 2 trials: (3 studies) 206, 208, 231
  2. Phase 3 pivotal trials (3 studies): 304, 305, 306
  3. Open-label extension: (3 studies) 207, 233 and 307

- **In vitro studies pertinent to PK using human biomaterials (20 studies):**
  1. Plasma protein binding: (2 studies) B00033 and AE-4737-G (fu,p ~5%)
  2. Blood to Plasma ratio: B06013 (B/P: 0.55-0.59)
  3. Hepatic metabolism and drug interaction: (8 studies)
     B04006, B07001, B06012, B00030, GE-0045, AE-4739-G, XT095036, XT093050
     (mainly via CYP3A4/5, not inhibitor of major CYP450 isoenzymes except CYP2C8, no or weak inhibitor of 3A4 though time-dependent inhibitor of 3A4, not inducer of 1A2, weak inducer of 3A4 and 2B6)
  4. Metabolite isolation and identification: (5 studies) C07139, B03033, B05007, L07002, B08002
  5. Transporter: (4 studies) GE-0258-G, B06015, GE-0404-G, DMPK2011-002
     (not substrate of P-gp, BCRP, OATs, OCTs and OATP1B1 and 1B3
     Weak inhibitor of P-gp, BCRP, OAT1, OAT3, OCT1 and OCT3)

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	16		
I. Clinical Pharmacology				
Mass balance:	x	1		
Isozyme characterization:	x	3		
Transporters:	x	4		
Blood/plasma ratio:	x	1		
Plasma protein binding:	x	2		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	1		
multiple dose:	x	1		
Patients-				
single dose:				
multiple dose:	x	2		One in Japanese
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	3		
In-vivo effects of primary drug:	x	4		
In-vitro:	x	5		
Subpopulation studies -				
ethnicity:	x	2		Japanese, SAD and MAD
gender:				
pediatrics:				
geriatrics:	x	1		
renal impairment:				
hepatic impairment:	x	1		Mild and moderate
Obese subject:				
PD -				
Phase 2:	x	3		Study 206, 208, 231
Phase 3:	x	3		Study 304, 305, 306
PK/PD -				
Phase 1 and/or 2, proof of concept:	x	3		Study 206, 208, 231
Phase 3 clinical trial:	x	3		Study 304, 305, 306
Population Analyses -				
Data rich:	x	1		
Data sparse:	x	3		
II. Biopharmaceutics				
Absolute bioavailability	x	1		
Relative bioavailability -	x	1		[redacted] (b) (4) to Tablet
solution as reference:				

alternate formulation as reference:				
Bioequivalence studies -	x	5		
traditional design; single / multi dose:	x	5		
replicate design; single / multi dose:				
Food-drug interaction studies	x	2		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics	x	1		Morning vs. Evening dosing
Pediatric development plan				
Literature References				
Total Number of Studies				
	24 PK + 4 Pop PK/PD + 1 QTc+ 20 in vitro+ 16 Assay Validation + Literature		**24 PK + 4 Pop PK/PD + 20 in vitro+ 16 Assay Validation Reports Reviewed**	

Filability and QBR comments

	"X" if yes	**Comments**
Application filable?	X	
Comments sent to firm?		
QBR questions (key issues to be considered)	• Are there exposure (dose) – response (efficacy and safety) relationships? • Is dose adjustment necessary for concomitant use of AEDs which induced perampanel clearance? • Is severe renal impairment study needed? • Sample collection period for one of the food effect studies was only 24hr. • Is drug-drug interaction study needed for PPIs, considering pH dependent solubility and dissolution of perampanel?	
Other comments or information not included above		
Primary reviewer Signature and Date	Xinning Yang	
Secondary reviewer Signature and Date	Angela Men	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	No pre-NDA meeting
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		x		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
____Yes____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

Appendix 2. Clinical Pharmacology Studies: Overview of Study Design and Results

Study No.	Study Design and Objective	Treatments	Subjects	Key PK/PD Results/Conclusions
Studies in Healthy Subjects: Studies with Single-Dose PK/PD Data Only				
E2007-E044-001	Randomized (within group), double-blind, placebo-controlled, sequential ascending single-dose study to evaluate safety, tolerability, and PK	Single oral doses: Perampanel tablets (N=42) (Formulation A) 0.2 mg (n=6) 0.5 mg (n=6) 1 mg (n=6) 2 mg (n=6) 4 mg (n=6) 6 mg (n=6) 8 mg (n=6) Placebo tablets (N=13)	55 healthy males age range, 18 – 45 y	At dose levels of 0.2 to 8 mg, perampanel was rapidly absorbed and following C_{max} appeared to be eliminated in a tri-exponential manner, with a long apparent terminal disposition phase. Across the dose groups 0.2 mg to 8 mg, mean apparent terminal half-life values ranged from approximately 50 to 120 h. Perampanel elimination by the renal route was minimal, with less than 0.12% of the dose eliminated unchanged in urine. Sedation increased in a dose dependent manner at doses of 2 mg and higher. Levels of sedation did not prevent subjects from performing the test battery. At the highest dose, sedation was rated as similar to a therapeutic dose of a benzodiazepine. The safety, tolerability and pharmacokinetics of perampanel did not appear to be affected in poor metabolizers of CYP2D6 and CYP2C19.
E2007-E044-003	Open-label, randomized, single-dose, two-way crossover study to evaluate the effect of food on PK and PD	1 mg oral tablet (Formulation A); fasting 1 mg oral tablet (Formulation A); fed	24 healthy adults (12 males/12 females) age range, 19 – 41 y	The rate, but not the extent (AUC), of perampanel exposure was affected by administration in the fed vs. fasted state. C_{max} was reduced by approximately 40% and t_{max} was increased by 2 h in fed vs. fasted subjects. Exposure in terms of AUC was approximately 20 to 30% greater in females compared to males in both the fasted and fed states. Half-life was 45 to 65% longer in females compared to males in both the fasted and fed states. Exposure in terms of C_{max} was similar in males and females in both the fasted and fed states. There were no clinically relevant gender differences in the measures of sedation. Measures of the magnitude of sedation, in particular decreases in PSV, tended to parallel plasma perampanel concentrations.
E2007-E044-007	Open-label study to obtain information on the absorption, metabolism, and elimination of ^{14}C-perampanel	2 mg oral tablet (Formulation B) to which was applied a ^{14}C-perampanel solution (200 nCi)	8 healthy elderly adults (4 males/4 females) age range, 65 – 79 y	Mean recovery of ^{14}C radioactivity = 70.1%, with approximately 70% excreted in the feces and 30% in the urine. No parent drug was recovered in the feces; thus, perampanel appeared to be completely absorbed following oral administration. PK profile of ^{14}C-perampanel was similar to that of the parent compound: both radiolabeled and unlabeled perampanel were rapidly absorbed, with average maximum plasma concentrations achieved within the first hour after drug administration. The median half-life of ^{14}C was longer and the total exposure (AUC) slightly greater than the respective values for perampanel.

Study No.	Study Design and Objective	Treatments	Subjects	Key PK/PD Results/Conclusions
E2007-A001-008	Open-label, randomized, two-period, two-sequence crossover study to evaluate BE of two oral tablet formulations	2 × 1 mg oral tablets (Formulation A; reference) 2 × 1 mg oral tablets (Formulation B; test)	34 healthy adults (23 males/11 females) age range, 18 – 45 y	2 mg oral doses (2 × 1 mg tablets) of the test (Formulation B) and reference (Formulation A) tablets were bioequivalent when administered to healthy men and women
E2007-J081-010	Randomized (within group), double-blind, placebo-controlled, sequential ascending single dose study to evaluate safety, tolerability, PK, and PD	Single oral doses: Perampanel tablets (N=56) (Formulation B) 0.25 mg (n=6) 0.5 mg (n=6) 1 mg (n=6) 2 mg (n=6) 4 mg (n=6) 6 mg (n=6) 8 mg (n=6) Placebo tablets (N=14)	56 healthy Japanese males age range, 20 – 44 y	At dose levels of 0.25 mg to 8 mg, perampanel was rapidly absorbed and following C_{max} appeared to be eliminated in a biexponential manner, with a long apparent terminal phase. Across the dose groups 0.25 mg to 8 mg, mean apparent terminal half-life values ranged from approximately 61 to 95 h. At doses ≥4 mg, perampanel reduced PSV in a dose-related manner and maximal effects were apparent at times corresponding to maximum plasma concentrations.
E2007-E044-016	Open-label, randomized, crossover study to establish dose strength equivalence	2 × 2 mg oral tablets (Formulation C) 1 × 4 mg oral tablet (Formulation C)	24 healthy adults (12 males/12 females) age range, 20 – 55 y	BE demonstrated for the two dose strengths based on rate and extent of exposure
E2007-E044-017	Open-label study to determine absolute oral BA and investigate metabolite profile	IV solution of ^{14}C-perampanel (10 µg/200 nCi) + oral dose of perampanel 8 mg (2 × 4 mg tablets, Formulation C)	10 healthy males (age range, 18 – 55 y)	Due to analytical problems, only five of ten subjects provided concentration-time profile of unchanged ^{14}C-perampanel. Using these data, the estimated mean (SD) absolute bioavailability was 116% (9.4%). Based on quantitative and specific assays for known perampanel metabolites (M1, M2, M3, M4, M5, and M7 and their glucuronides) for practical purposes, perampanel metabolites were not observed in plasma and unchanged perampanel is the only observable circulating compound. Additional LC/MS/MS and LC with AMS profiling confirm this result. The main metabolic pathway of perampanel is primarily oxidation at the pyridine, benzene, or benzonitrile ring, and subsequent conjugation.
E2007-E044-028	Open-label, two-period, two-sequence crossover study to determine the relative BA of two oral formulations	4 mg oral perampanel tablet (Formulation C) 4 mg dose of perampanel oral suspension	16 healthy adults (9 males/7 females) age range, 20 – 53 y	The oral suspension and the tablet had similar bioavailability in terms of extent of exposure as measured by $AUC_{(0-72h)}$ and $AUC_{(0-t)}$. However, the rate of absorption for the suspension was slower than that of the tablet as shown by a prolonged t_{max} and an associated reduction in C_{max} compared with the tablet formulation.

Study No.	Study Design and Objective	Treatments	Subjects	Key PK/PD Results/Conclusions
E2007-E044-037	Open-label, two-period, two-sequence crossover study to evaluate BE between oral tablet Formulations C and D	6 × 2 mg oral tablets (Formulation C) 1 × 12 mg oral tablet (Formulation D)	28 healthy adults (21 males/7 females) age range, 21 – 54 y	BE demonstrated for the two formulations based on AUC, but not C_{max} (90% CI: 78.4, 95.3). C_{max} (mean ± SD) of the 12 mg tablet (285 ± 68.5 ng/mL) was slightly lower than that of 6 x 2 mg tablets (335 ± 83.4 ng/mL).
E2007-A001-039	Open-label, two-period, two-sequence crossover study to evaluate BE between oral tablet Formulations C and D	3 × 2 mg oral tablets (Formulation C) 1 × 6 mg oral tablet (Formulation D)	54 healthy adults (34 males, 20 females) age range, 18 – 55 y	Based on rate and extent of exposure, BE was demonstrated for one 6 mg tablet of Formulation D and 3 × 2 mg tablets of Formulation C.
E2007-A001-040	Open-label, two-period, two-sequence crossover study to evaluate BE between oral tablet Formulations C and D	6 × 2 mg oral tablets (Formulation C) 1 × 12 mg oral tablet (Formulation D)	54 healthy adults (32 males/22 females) age range, 18 – 54 y	Based on rate and extent of exposure, BE was demonstrated for one 12 mg tablet of Formulation D and 6 × 2 mg tablets of Formulation C.
Studies in Healthy Subjects: Studies with Multiple-Dose PK/PD Data				
E2007-E044-002	Double-blind, randomized, placebo-controlled, ascending-dose study to determine the safety, tolerability, PK, and PD of multiple oral doses	Multiple daily oral doses: Perampanel tablets (N=24) (Formulation A) 1 mg/day × 14 days (n=6) 2 mg/day × 14 days (n=6) 4 mg/day × 14 days (n=6) 4 mg/day × 7 days, then 6 mg/day × 7 days (n=6) Placebo tablets × 14 days (N=8)	32 healthy males, age range 19 - 45 y	At dose levels of 1 to 4 mg/day, perampanel was rapidly absorbed, and following C_{max} was eliminated with an apparent harmonic mean $t_{1/2}$ ranging from 66 – 90 h. At steady-state, C_{max} and $AUC_{(0-\tau)}$ increased in a dose-proportional manner, indicating linear PK over the dose range tested (1 to 4 mg/day). Less than 0.2% of the dose was eliminated in the urine as unchanged perampanel. Reductions in PSV, indicative of sedation, were observed at all doses. Significant sedation, which was correlated with perampanel plasma levels, was observed at 4 and 6 mg/day. No changes in cognitive performance were observed.

Study No.	Study Design and Objective	Treatments	Subjects	Key PK/PD Results/Conclusions
E2007-E044-009	Single-dose phase; Part 1 Single-dose, randomized, active, and placebo-controlled parallel group, double-blind, double-dummy study to evaluate the impact of food on PK and PD	6 mg perampanel (3 × 2 mg oral tablets, Formulation B); fasting 6 mg perampanel (3 × 2 mg oral tablets, Formulation B); fed Oral placebo; fasting or fed Oral diazepam 5 mg	8 healthy adults (7 males/1 female) 8 healthy adults (7 males/1 female) 8 healthy adults (6 males/2 females) 7 healthy adults (6 males/1 female)	Peak perampanel exposure (C_{max}) was 28% lower and occurred 3 h later (t_{max}) when a 6 mg dose was given with a high-fat meal vs. after an overnight fast. The extent of perampanel exposure ($AUC_{(0\text{-}24\ h)}$) showed no noteworthy difference in the fed vs. fasted subjects. Consistent with the PK findings, administration of perampanel with food vs. in the fasting condition delayed the onset but did not alter the extent of sedation.
	Multiple-dose phase; Part 2 Repeated-dose, randomized, placebo-controlled parallel group, double-blind study to identify a dosing regimen suitable to achieve supratherapeutic plasma concentrations and to evaluate the effect of morning vs. evening dosing on tolerability, PK, and PD	2 mg perampanel oral tablets (Formulation B) for 21 days as follows: 6 mg/day (Days 1-7), 8 mg/day (Days 8-14), 10 mg/day (Days 15-21) Morning dosing (n=8) Evening dosing (n=8) Daily oral placebo (Days 1-21) (N=8)	8 healthy adults (4 males/4 females) 8 healthy adults (4 males/4 females) 4 healthy adults (2 males/2 females)	Perampanel exposure after repeated dosing appeared unaffected by the time of drug dosing. The PK profile after repeated dosing was uniform across the dosing interval and peak to trough fluctuations were small (PTF ratio = 0.38–0.22 across the dose range tested). Perampanel exposure appeared similar among men and women. PSV parameters measured in the morning after evening dosing were less affected than after morning dosing of perampanel. Mean changes from baseline in QT interval duration and categorical analysis of absolute QT interval duration and changes from baseline did not show any clear relationship with treatment group or perampanel dose.
E2007-J081-026	Step 1: QD dosing (Day1-14) Step 2: QD dosing (Days 1-14) QD dosing (Days 15-28)	Formulation C: Perampanel 2 mg QD Placebo 2 mg QD Perampanel 2 mg QD Placebo 2 mg QD Perampanel 4 mg QD Placebo 4 mg QD	healthy Japanese men: n=9 n=3 n=9 n=3 (age range, 20 – 44 y)	After oral single and repeated daily doses of 2 mg and 4 mg, perampanel PK were characterized by rapid absorption (average t_{max} of 0.75 to 1.50 h) followed by biphasic elimination. At steady state (by Day 14), the mean half-life was 101.7 h and 63.9 h for the 2 mg QD and 4 mg QD doses, respectively. Compared with placebo, perampanel did not show any notable changes from pretreatment VAMS anxiety, dysphoria, or sedation subscores. In contrast, perampanel administration was associated with decreases from pretreatment values of PSV; these changes were greater for perampanel 4 mg vs. 2 mg doses. The decreases in PSV were greatest at approximately 1 h postdosing; thereafter, PSV gradually returned to pretreatment values. At both the 2 mg and 4 mg doses, plasma perampanel concentrations showed an inverse correlation with PSV.

Study No.	Study Design and Objective	Treatments	Subjects	Key PK/PD Results/Conclusions
Studies in Epileptic Patients				
E2007-E049-203	Randomized, double-blind, placebo-controlled, parallel-group study to evaluate safety, tolerability, and PK in epileptic patients with partial and generalized seizures	Perampanel oral tablets QD × 28 days (Formulation B): 1 mg (N=6) 2 mg (N=6) Placebo QD × 28 days (N=6)	Patients with epilepsy (age range, 20 – 52 y) 5 males/1 female 3 males/3 females 3 males/3 females	Perampanel PK were characterized by rapid absorption followed by multiphasic disposition. Perampanel exposure was substantially higher after repeated dosing vs. single dosing. Steady state was not achieved after 14 days of dosing. Perampanel exposure tended to be lower in patients taking anti-epileptic drugs known to induce cytochrome P450. Perampanel had no apparent effect upon plasma levels of carbamazepine, phenytoin, or valproate.
E2007-J081-231	Open-label study to evaluate safety, tolerability, and PK in Japanese epileptic patients with partial and generalized seizures	Perampanel oral tablets QD × 10 weeks (Formulation C) (N=30) 2 mg QD (initial dose), titrated weekly in 2 mg increments to a maximum dose of 12 mg QD	Japanese patients with epilepsy (age range, 20 – 62 y) 16 males/14 females	Subjects taking carbamazepine had lower plasma perampanel concentrations compared subjects who received phenytoin or phenobarbital. Perampanel administration had no apparent effect on the plasma concentration of other AEDs.
Effects of Intrinsic Factors on PK: Studies in Special Populations				
E2007-E044-004	Randomized, double-blind, placebo-controlled, single ascending dose, parallel-group study to evaluate the safety, tolerability, and PK profile in healthy elderly subjects	Perampanel oral tablet, single dose (Formulation A) 1 mg (N=8) 2 mg (N=8) Placebo (N=8)	Healthy elderly subjects (age range, 65-76 y) 4 males/4 females 4 males/4 females 4 males/4 females	At both dose levels, perampanel was rapidly absorbed and, following C_{max}, was eliminated with an apparent harmonic mean half-life of 93 h (1 mg dose) or 100 h (2 mg dose). Increases in C_{max}, $AUC_{(0\text{-}t)}$, and $AUC_{(0\text{-}inf)}$ were dose proportional. There were no noteworthy gender differences in the PK of perampanel. There was no evidence of significant sedation following administration of single doses of perampanel 1 or 2 mg.
E2007-E044-015	Open-label, parallel, four group study to determine the effect of hepatic impairment on PK in subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment and demographically matched subjects with normal hepatic function (Normal A and Normal B, respectively.	Perampanel 1 mg oral tablet, single dose (Formulation B)	Four groups of adults (age range, 33-69 y): Normal A (4 males/2 females) Child-Pugh A (4 males/2 females) Normal B (5 males/1 female) Child-Pugh B (5 males/1 female)	The fraction of perampanel unbound (f_u) in plasma at 2 h was increased by 27.3% and 73.5% in hepatically impaired Child-Pugh A and Child-Pugh B subjects, respectively, vs. their respective control groups. In the hepatically impaired subjects, half-life was longer, AUC was increased, and CL/F was decreased. The levels of unbound perampanel were higher in the subjects with hepatic impairment compared with subjects with normal hepatic function, and as a result unbound V_d/F as well as total V_d/F were increased and unbound C_{max} was decreased in the hepatically impaired subjects. Unbound AUC and unbound CL/F were increased and decreased respectively in subjects with hepatic impairment compared to subjects with normal hepatic function.

Study No.	Study Design and Objective	Treatments	Subjects	Key PK/PD Results/Conclusions
Effects of Extrinsic Factors on PK: Drug-Drug Interaction Studies				
E2007-E044-005	Randomized, open-label, two period, two treatment, two-way crossover study to determine the effect of ketoconazole on perampanel PK.	Perampanel 1 mg oral tablet, single dose (Formulation A) Ketoconazole 400 mg/d (Days 1-10) + Perampanel 1 mg oral tablet, single dose (Formulation A) on Day 3	26 healthy men (age range, 20 – 32 y)	Statistically significant increases in the AUC and half-life of perampanel were observed when perampanel was administered with ketoconazole. However, differences in plasma levels of perampanel in the perampanel alone group vs. the perampanel + ketoconazole group were generally less than 20%.
E2007-E044-006	Open-label, three treatment, fixed sequence, three-way crossover study to determine the effects of carbamazepine on the PK, PD, and safety and tolerability of perampanel.	Perampanel 2 mg single oral dose (Formulation A) Perampanel 2 mg (Day 1) Carbamazepine dosing: 100 mg BID (Days 11-17) 200 mg BID (Days 18-24) 300 mg BID (Days 25-31) 300 mg BID (Days 32-41) Perampanel 2 mg (Day 32)	20 healthy men (age range, 18–51 y) N=20 N=16 N=14 N=14	Co-administration of carbamazepine with perampanel caused an increase in CL/F and a corresponding reduction in perampanel exposure. Perampanel peak and total exposure from a single 2 mg dose was 26% and 67% lower, respectively, when co-administered with steady state carbamazepine 300 mg BID than when administered alone. Differences in perampanel exposure reflected a 203% increase in apparent oral clearance and a 56% reduction in terminal half-life in the presence of carbamazepine. Co-administration of carbamazepine had no significant effect on the t_{max} of perampanel. Both perampanel alone and carbamazepine alone reduced PSV and increased sedation scores, but co-administration of carbamazepine and perampanel caused greater effects than either drug administered alone.
E2007-A001-014	Open-label, non-randomized, fixed sequence crossover study to investigate the effect of steady state perampanel on the PK of midazolam	Perampanel 2 mg tablets (Formulation C) Midazolam 4 mg (Day 1) Perampanel 6 mg QD (Days 2 – 21) Midazolam 4 mg + Perampanel 6 mg (Day 22)	35 healthy subjects, 25 males/10 females, (age range, 20 – 55 y) N=35 N=35 N=30	The effect of perampanel on midazolam elimination and overall extent of exposure did not reach the level of clinical significance. The 90% CIs for the ratio of CL/F, V_d/F, $AUC_{(0-inf),}$, and $AUC_{(0-t)}$ were all contained within the 0.8-1.25 bioequivalence limit. Mean half-life values were also comparable. The effect of perampanel on midazolam rate of absorption, specifically C_{max}, though statistically significant, is likely small.

Study No.	Study Design and Objective	Treatments	Subjects	Key PK/PD Results/Conclusions
E2007-E044-019	Open-label, three treatment, fixed sequence crossover study to investigate the effect of perampanel on the PK of the combined ethinylestradiol and levonorgestrel oral contraceptive (OC) pill (Microgynon® 30 ED)	Perampanel 2 mg tablets (Formulation B) OC QD (Days 1 – 21) OC placebo + perampanel 2 mg QD (Days 22 – 28) OC pill + perampanel 4 mg QD (Days 29 – 49)	Healthy pre-menopausal females (age range, 19 – 40 y) N=24 N=21 N=20	Perampanel 4 mg had no effect on the plasma levels or PK of either component of the OC.
E2007-E044-025	Open-label non-randomized, fixed sequence crossover study to investigate the effect of steady state perampanel on the PK of levodopa	Perampanel 2 mg tablets (Formulation C) Levodopa 100 mg (Day 1) Perampanel 4 mg QD (Days 2 – 20) Levodopa 100 mg (Day 21)	60 healthy subjects 43 males/17 females (age range, 19 – 54 y) N=59 N=59 N=59	Geometric mean $AUC_{(0\text{-inf})}$, C_{max} and $AUC_{(0\text{-t})}$ following dosing with perampanel plus levodopa were comparable to values following levodopa alone. Median t_{max} values were the same following perampanel plus levodopa and levodopa alone. Geometric mean $t_{½}$ values were similar following perampanel plus levodopa and levodopa alone. The 90% CIs for both $AUC_{(0\text{-inf})}$ and C_{max} were within the limit of 0.75 to 1.33 indicating that there was no evidence of an interaction between levodopa and perampanel when co-administered.
E2007-E044-029	Open-label non-randomized, fixed sequence study to investigate the effect of steady state perampanel on the PK of single dose of the combined ethinylestradiol and levonorgestrel oral contraceptive (OC) pill (Microgynon® 30 ED (Part A), and the effect of repeated dosing of the OC on the PK of a single dose of perampanel (Part B). Effect of perampanel on QT interval duration was also assessed (Part A)	Perampanel 2 mg tablets (Formulation C) Part A: Period 1: OC single dose Period 2: Perampanel QD for 35 days (doses titrated to a maximum of 12 mg QD Single dose of OC on last treatment day. Part B: Period 1: perampanel 6 mg single dose Period 2: OC QD × 21 days. Single perampanel 6 mg dose on Day 21	Healthy pre-menopausal females N=28 (age range, 21 – 43 y) N=24 (age range, 20 – 42 y)	Steady-state concentrations of perampanel following multiple doses of 8 mg perampanel had no statistically significant effect on the PK (C_{max} and $AUC_{(0\text{-24h})}$) of ethinylestradiol and levonorgestrel compared to the OC administration alone. Steady-state concentrations of perampanel following multiple doses of 12 mg perampanel induced a decrease of C_{max} and $AUC_{(0\text{-24h})}$ of levonorgestrel to 58% and 60% compared with OC administration alone. For ethinylestradiol only C_{max} was lowered by less than 20% whereas perampanel had no effect on $AUC_{(0\text{-24})}$ of ethinylestradiol compared with OC administration alone. The combined effects of perampanel on ethinylestradiol and levonorgestrel suggest that 12 mg QD of perampanel induced metabolism of levonorgestrel, but the induction did not appear to be CYP3A4-dependent. The PK of a single dose of perampanel 6 mg did not differ when it was administered alone or in combination with an OC at steady state. Visual inspection of QTcF data did not reveal any clinically relevant findings following treatment with perampanel.

Study No.	Study Design and Objective	Treatments	Subjects	Key PK/PD Results/Conclusions
E2007-E044-030	Two-part study to investigate the safety, tolerability, psychomotor effects, and cognitive effects of perampanel (single and multiple doses) when a single dose of alcohol (40% vodka to achieve a blood alcohol level of 80 - 100 mg/100 mL) was administered 75 min post perampanel administration	Perampanel 2 mg tablets (Formulation C) Part A: single dose First treatment: Placebo, then alcohol Second treatment: Perampanel Cohort 1, 4 mg Cohort 2, 8 mg Cohort 3, 12 mg then alcohol (all cohorts) Part B: QD dosing Treatment A: perampanel 4 mg QD (Days 1-7), 8 mg QD (Days 8-14), 12 mg QD (Days 15-34) Treatment B: placebo QD (Days 1-34) Treatments A and B: Alcohol on Day 34 75 min post perampanel dosing	Healthy adults N=35 (22 males/ 13 females), (age range, 18 – 49 y) N=35 N=12 N=12 N=11 N=24 (18 males, 6 females), (age range, 20 – 47 y) N=18 N=6	No formal PK analysis was performed. No consistent effect on cognitive function was found after single or multiple dosing of perampanel with up to 12 mg QD. Single or multiple doses of perampanel 4 mg were relatively devoid of psychomotor effects and did not impair simple psychomotor tasks, complex driving performance, or sensori-motor coordination. After single dosing and after 7 days of QD dosing, perampanel 8 mg and 12 mg produced dose-related impairment of simple psychomotor performance. Car handling ability was impaired after multiple dosing of perampanel 12 mg QD to steady state, but no evidence was found of increased risk taking or unusual driving behavior. Multiple dosing of perampanel 12 mg QD did not significantly impair postural stability. Vigilance and alertness were reduced by all doses of perampanel, and this effect may have contributed to the general psychomotor slowing observed in the psychomotor test battery. Perampanel 12 mg was associated with small but statistically significant increased tension and anger, increased feelings of depression and confusion, reduced vigor, and increased fatigue. Perampanel in combination with alcohol consistently impaired simple psychomotor performance at all dose levels after single dosing and after multiple dosing of 12 mg QD to steady state. In many cases, the effects of alcohol were additive to those of perampanel but in some cases there was evidence of a supra-additive effect. When administered with alcohol, perampanel 12 mg (steady-state) impaired working memory and executive function to an extent greater than the effects of perampanel or alcohol administered alone. Psychomotor performance returned to normal within two weeks of perampanel withdrawal. Though effects were relatively small, alertness levels were reduced up to four weeks after treatment cessation

Study No.	Study Design and Objective	Treatments	Subjects	Key PK/PD Results/Conclusions
Special Studies in Healthy Subjects				
E2007-A001-013	Double-blind, active- and placebo-controlled, combined fixed sequence, parallel group study to evaluate the effect of perampanel on QT interval duration and explore the relationship between perampanel plasma concentrations and QT interval duration.	Perampanel group: Perampanel 6 mg QD (Days 1-7) Perampanel 8 mg (Day 8) Perampanel 10 mg (Day 9) Perampanel 12 mg QD (Days 10 – 16) Moxifloxacin placebo (Day 16) Placebo group: Perampanel placebo QD (Days 1 – 16) Moxifloxacin placebo (Day 16) Moxifloxacin group: Perampanel placebo QD (Days 1 - 16) Moxifloxacin 400 mg (Day 16)	257 healthy subjects, 129 males/128 females (age range, 18 – 55 y) N=107 N=75 N=75	Drug accumulation was observed with multiple-dose administration of both perampanel 6 mg and perampanel 12 mg. The exposure parameters, $AUC_{(0-12)}$ and C_{max}, following 7 days of perampanel 6 mg administration were representative of the exposure at the therapeutic dose of perampanel in Parkinson's disease patients. Exposure appeared to increase proportionally across the 6-mg to 12-mg daily dose levels. Assay sensitivity to detect a drug effect on QTc interval was validated by the administration of a single 400-mg moxifloxacin dose on Day 16 which caused a peak ΔΔQTcF effect of approximately 12 msec 4 h postdose that subsequently declined with lower one-sided 95% CL exceeding 5 msec at all time points. Administration of 6-mg and 12-mg doses of perampanel for seven days did not show effects on cardiac repolarization (upper one-sided 95% CL of ΔΔQTcF <10 msec). Similar results were observed with ΔΔQTci and ΔΔQTcB. Outlier analysis of absolute QTcF and ΔQTcF was consistent with the absence of an effect. Exploratory graphical evaluation showed no relationship between perampanel plasma concentrations and baseline-adjusted QTc. The PK/PD analyses evaluating effect of perampanel concentrations on QT intervals demonstrated that perampanel did not have any effect on heart rate or any of the heart-rate corrected QT intervals (QTcF, QTcB, QTci and QTcSS). Administration of a single dose of 400 mg moxifloxacin (positive control) increased the population QT interval by more than 8 msec, taking into account diurnal variations and the effects of placebo and study time.
E2007-E044-020	Randomized, placebo- and active-controlled, parallel group study to investigate the phototoxic potential of perampanel in healthy volunteers.	Perampanel 2 mg tablets (Formulation C) 10 days of treatment with: Placebo QD Perampanel 6 mg QD Ciprofloxacin 500 mg BID (single evening dose on Day 1)	36 healthy subjects, 30 males/6 females (age range, 19 – 54 y) N=12 N=12 N=12	There was no evidence of a difference in phototoxic index (PI) between perampanel and placebo at any wavelength. There was a significant difference between ciprofloxacin and placebo for delayed phototoxicity at the 335 (± 30) and the 365 (± 30) indicating that assay sensitivity was achieved. This study found no evidence that dosing healthy volunteers at 6 mg of perampanel induces skin phototoxicity to ultraviolet or visible light.

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