

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202834Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

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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4. APPENDICES

4.4 INDIVIDUAL STUDY REVIEW

4.4.1. Individual Study Review for *In Vitro* Studies

Study B00033: Protein Binding of E2007 in Rat, Dog and Human Plasma (Study Period: Nov 2, 2000 -Jan 18, 2001)

Methods: Equilibrium dialysis. Plasma was obtained from male Sprague-Dawley rats, male beagle dogs and male healthy volunteers (age: 30-37 years) under fasted condition. Plasma samples spiked with E2007 at 20, 200 and 2000 ng/mL were dialyzed against 1/15 mol/L phosphate buffer (pH7.4) containing 50 mM NaCl for 1 day at 37°C. The concentrations of E2007 in plasma and phosphate buffer were determined by an HPLC-Fluorescence method. The assay method was validated in the range of 0.3 to 3000 ng/mL using 0.1 mL of rat, dog and human plasma and phosphate buffer for extraction. Protein binding of E2007 in plasma was calculated as follows:

$$\text{Protein binding(\%)} = (\text{Conc.}_{\text{plasma}} - \text{Conc.}_{\text{buffer}}) / \text{Conc.}_{\text{plasma}} \times 100$$

Results: The protein binding of E2007 in plasma was constant from 20 to 2000 ng/mL. Among species tested, E2007 exhibited the highest protein binding in human (95.3-95.8 %), followed by dog (88.8-90.1 %) and rat (86.8-87.5 %).

Table 1. Plasma protein binding of E2007 in rat, dog and human plasma

Species	Added conc. (ng/mL)	Plasma protein binding (%)			
		No.1	No.2	No.3	Mean \pm SEM
Rat	20	88.3	87.0	87.3	87.5 \pm 0.4
	200	88.0	87.0	87.2	87.4 \pm 0.3
	2000	87.3	86.6	86.4	86.8 \pm 0.3
Dog	20	90.9	90.2	89.2	90.1 \pm 0.5
	200	89.6	89.8	89.7	89.7 \pm 0.1
	2000	88.9	88.9	88.5	88.8 \pm 0.1
Human	20	95.3	96.4	95.8	95.8 \pm 0.3
	200	95.7	94.7	95.8	95.4 \pm 0.4
	2000	95.5	94.9	95.4	95.3 \pm 0.2

Study AE-4737-G: Protein Binding of ^{14}C -E2007 to Human Serum Protein (*in vitro*) (Study Period: December 1, 2005- March 7, 2006)

Objective: to clarify protein binding of ^{14}C -E2007 in human serum albumin (HSA), human γ -globulin (HG) and human α 1-acid glycoprotein (α ₁-AGP) by equilibrium dialysis.

Method: Equilibrium dialysis. HSA, HG and α 1-AGP were dissolved in phosphate buffered saline (PBS, pH 7.4) to prepare 40 mg/mL of HSA solution, 15 mg/mL of HG

solution and 1 mg/mL of α_1 -AGP solution, respectively. The human serum protein solutions spiked with ^{14}C -E2007 at final concentrations of 20, 200 and 2000 ng/mL were dialyzed against PBS at 37°C for 24 h. From the measured radioactivity values, the radioactivity concentrations in the protein solution and PBS were determined, and protein binding ratio was calculated.

Results: There was no extensive adsorption of ^{14}C -E2007 to equilibrium dialyzer (adsorption ratio: 6.0-7.9%). The radiochemical purity of ^{14}C -E2007 in the human serum protein solutions and PBS ranged from 96.5% to 99.2% after incubation. The equilibrium state was achieved after 12 hr incubation.

The protein binding ratios of ^{14}C -E2007 to HSA, HG and α_1 -AGP were 74%, 8.8-10.6% and 58.2-77.8%, respectively. The protein binding ratio in α_1 -AGP decreased with increase of ^{14}C -E2007 concentration, but there were no marked changes in HSA and HG between the concentration of 20 and 2000 ng/mL. These results indicated that ^{14}C -E2007 mainly bound to HSA and α_1 -AGP, and partially to HG in human serum. Saturable binding was found in α_1 -AGP.

Table 2. Protein binding of ^{14}C -E2007 in HSA, HG and α_1 -AGP

Added conc. (ng/mL)	Protein binding (%)		
	HSA	HG	α_1 -AGP
20	74.1 ± 0.5	9.6 ± 0.4	77.8 ± 3.2
200	74.1 ± 0.3	8.8 ± 1.0	66.5 ± 3.3
2000	74.0 ± 0.1	10.6 ± 0.6	58.2 ± 1.6

Data are expressed as the mean values ± S.E.M. of three experiments.

Study B06013: Blood to Plasma Concentration Ratio of ^{14}C -E2007 in Rat, Dog, Monkey and Human (Study Period: September 19, 2006 - February 27, 2007)

Method: Blood was obtained from male Sprague-Dawley rats, male beagle dogs, male cynomolgus monkeys and male healthy volunteers under fasted condition. Blood samples spiked with ^{14}C -E2007 at the final concentration of 20, 200 and 2000 ng/mL were incubated at 37°C for 5, 15 and 30 min. Plasma and red blood cells (RBC) were obtained after centrifugation of the blood samples. The radioactivity in blood, plasma and RBC were measured using a liquid scintillation counter. Blood to plasma concentration ratio (Rb) of ^{14}C -E2007 was calculated as follows.

$$\text{Rb} = \text{radioactivity in blood} / \text{radioactivity in plasma}$$

Results: There was no difference among Rb values obtained after incubating 5 min to 30 min, suggesting rapid distribution of E2007 into RBC. Rb values were constant between 20 and 2000 ng/mL. Among the species tested, ^{14}C -E2007 exhibited the highest Rb in monkey (0.90-0.99), followed by rat (0.76-0.81), dog (0.67-0.72) and human (0.55-0.59).

Table 3. Rb Values of ^{14}C -E2007 in Rat, Dog Monkey and Human

Incubation time	Add conc. (ng/mL)	Rat			Dog			Monkey			Human		
		mean	±	S.E.M.	mean	±	S.E.M.	mean	±	S.E.M.	mean	±	S.E.M.
5 min	20	0.80	±	0.03	0.67	±	0.04	0.99	±	0.06	0.56	±	0.02
	200	0.77	±	0.02	0.70	±	0.02	0.99	±	0.07	0.55	±	0.01
	2000	0.78	±	0.03	0.71	±	0.02	0.95	±	0.04	0.59	±	0.01
15 min	20	0.81	±	0.03	0.71	±	0.03	0.96	±	0.04	0.57	±	0.03
	200	0.78	±	0.01	0.71	±	0.02	0.97	±	0.06	0.55	±	0.00
	2000	0.76	±	0.01	0.70	±	0.01	0.92	±	0.05	0.59	±	0.01
30 min	20	0.78	±	0.03	0.68	±	0.04	0.93	±	0.06	0.56	±	0.01
	200	0.78	±	0.02	0.72	±	0.01	0.94	±	0.05	0.55	±	0.01
	2000	0.76	±	0.01	0.72	±	0.01	0.90	±	0.06	0.58	±	0.02

Each value represents the mean ± S.E.M. of three samples.

Study B04006: Estimation of human CYP Isoforms Responsible for E2007 Metabolism (Study Period: March 15, 2004- November 9, 2004)

Objective: to identify human CYP isoforms involved in E2007 metabolism by quantifying the unchanged amount of E2007 in microsomal incubation mixtures containing recombinant human CYP (rCYP).

Method: Responsible rCYP isoforms for E2007 metabolism were estimated by quantifying the unchanged amount of E2007 after 30-min incubation at 37°C of 10 ng/mL E2007 with microsomal incubation mixture containing 200 pmol/mL for each rCYP. A microsomal matrix contained 0.1 mM EDTA, 100 mM phosphate buffer (pH 7.4), 25 µL of NADPH generating system, E2007 and rCYP microsomes in a final volume of 250 µL. NADPH generating system was prepared as a mixture containing 3.3 mM β-NADP⁺, 80 mM G6P (Glucose 6-phosphate), 60 mM MgCl₂ and 1 unit/mL G6PDH (6-phosphate dehydrogenase). E2007 was measured with HPLC-Fluorescence (LLOQ: 1 ng/mL). The residual percent of E2007 after each incubation was calculated. In addition, the first order disappearance rate constant (*k*) was estimated by the time-course experiments using 10, 30 and 100 ng/mL of E2007 and 200 pmol/mL rCYP3A4.

Results: After incubation with NADPH generating system, the residual percent of E2007 in each rCYP was more than 93% compared to time zero except CYP3A4 (75.4%), suggesting that among the enzymes examined CYP3A4 is the major one responsible for E2007 metabolism.

Reviewer's Comment: Other CYP enzymes may also contribute to E2007 metabolism considering that: First, E2007 seems to be slowly metabolized. In this study, the incubation time of E2007 with microsomes was 30 min, which may not be long enough to detect the maximal effect of an enzyme; Secondly, even for CYP3A4, there was only 25% reduction in E2007 amount. Thus, the relatively small decreases seen for some other enzymes can not be ignored; Lastly, though the activity of each microsome has been validated by the vendor (b) (4) using probe substrate, the sponsor did not validate the enzyme activity of microsome preparations in house. Such a possibility that the

microsomes used in these experiments had inadequate activities could not be excluded. Insufficient activity of rCYP would impair its ability to metabolize substrates.

Table 4. Residual percent of E2007 in rCYP

CYP Isozymes	Residual Percentage of Perampanel	
	with NADPH Generating System	without NADPH Generating System
CYP1A2	93.9	98.6
CYP2A6	102.3	101.9
CYP2B6	96.3	99.1
CYP2C8	94.3	97.6
CYP2C9	101.0	102.0
CYP2C19	97.6	101.0
CYP2D6	93.1	98.2
CYP2E1	94.8	96.2
CYP3A4	75.4	99.5

The k values in 200 pmol/mL protein rCYP3A4 were 0.0112, 0.0104 and 0.0108 min^{-1} at the concentrations of 10, 30 and 100 ng/mL, respectively, suggesting that the enzymatic reaction of E2007 in rCYP3A4 was linear between 10 and 100 ng/mL.

Table 5. First Order Rate Constant (k) and Extrapolated Initial Concentration (A) of E2007 calculated in rCYP3A4

Concentration of E2007	k (min^{-1})	A (ng/mL)
10 ng/mL	0.0112	10.5
30 ng/mL	0.0104	31.4
100 ng/mL	0.0108	104.5

rCYP3A4 concentration: 200 pmol/mL, Incubation time: 0, 10 and 20 min

Study B06012: Assessment of E2007 Metabolism by Recombinant Human CYP3A5 (Study Period: June 22, 2006 - November 27, 2006)

Objective: to assess the involvement of CYP3A5 in E2007 metabolism by quantitating the unchanged amount of E2007 in microsomal incubation mixtures containing rCYP3A5.

Method: The metabolism of E2007 (10, 30 and 100 ng/mL) in rCYP3A5 (200 pmol/mL) was estimated by quantifying the residual amount of E2007 after a 30-min incubation using HPLC-fluorescence (LLOQ: 1 ng/mL). The residual percent of E2007 after incubation was calculated and the first order disappearance rate constant (k) was estimated by the remaining E2007 concentration-time curve. The intrinsic clearance of E2007 (CL_{int}) in rCYP3A5 was calculated using k value.

Results: The residual percent of E2007 compared to time zero was 68.9%-75.1% and 93.5%-101% with and without NADPH generating system, respectively, after 30 min-incubation, indicating that E2007 is metabolized by CYP3A5 *in vitro*. The k (min^{-1}) values were 0.0129, 0.0098 and 0.0138 at the concentrations of 10, 30 and 100 ng/mL E2007, respectively, suggesting that enzyme reaction of E2007 in rCYP3A5 was linear over the range of 10 to 100 ng/mL.

Table 6. Residual Percent of E2007 in rCYP3A5

E2007 concentration (ng/mL)	Residual percent (%)				
	0 min	10 min	20 min	30 min	30 min (GS (-))
10	100.0	90.7	76.9	74.1	93.5
30	100.0	89.8	82.5	75.1	101.0
100	100.0	86.3	76.1	68.9	99.7

rCYP3A5 concentration: 200 pmol/mL; Incubation: 0, 10, 20 and 30 min at 37°C; GS (-): without NADPH generating system

Table 7. First order rate constant (k), extrapolated initial concentration (A) of E2007 and intrinsic clearance (CL_{int}) calculated in rCYP3A5

E2007 concentration (ng/mL as free base)	A (ng/mL)	k (min ⁻¹)	CL_{int} (mL/min/nmol CYP)
10	10.9	0.0129	0.065
30	29.9	0.0098	0.049
100	103.1	0.0138	0.069

$CL_{int} = k / \text{rCYP3A5 concentration (0.2 nmol/mL)}$

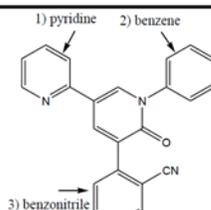
The calculated CL_{int} values of rCYP3A5 were 0.049-0.069 mL/min/nmol CYP, similar to that of rCYP3A4. CL_{int} values calculated from the k values of rCYP3A4 were 0.052-0.056 mL/min/nmol CYP. The expression of CYP3A5 is polymorphic, therefore CYP3A5 might contribute to inter-individual variation of E2007 clearance to some extent *in vivo*.

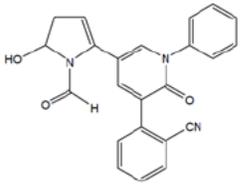
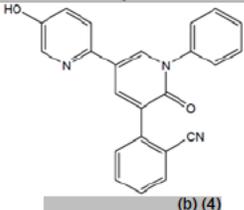
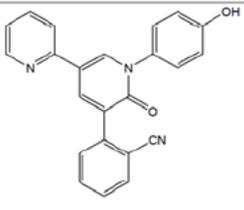
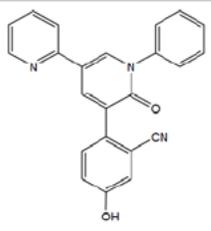
Study B05007: Structural Analysis of E2007 Metabolites Produced by Human Liver Microsomes (Study Period: March 15, 2005 - August 21, 2006)

Objective: to estimate the chemical structures of E2007 metabolites produced by CYP dependent metabolism.

Method: The metabolites were generated by incubating 60 µg/mL E2007 in 2 mg/mL protein human liver microsomes at 37°C for 2 hr, in the presence of NADPH. The chemical structures of metabolites were analyzed by LC-MS/MS, and further confirmed by comparing the synthetic reference compounds.

Results: Twelve metabolites (HM1-12) were detected. The proposed structures of metabolites in human liver microsomes are shown below.

Metabolite	[M+H] ⁺	Structure	
		(Form)	(Metabolized moiety)
E2007	<i>m/z</i> 350	Unchanged	

Metabolite	[M+H] ⁺	Structure	
		(Form)	(Metabolized moiety)
HM1	<i>m/z</i> 384	Dihydrogenated-dihydroxylated	2) benzene
HM2	<i>m/z</i> 384	Dihydrogenated-dihydroxylated	3) benzonitrile
HM3	<i>m/z</i> 384	Rearrangement of pyridine (DM1)	
HM4	<i>m/z</i> 382	Dihydroxylated	1) pyridine or 3) benzonitrile
HM5	<i>m/z</i> 382	Dihydroxylated	2) benzene
HM6	<i>m/z</i> 382	Dihydroxylated	3) benzonitrile
HM7	<i>m/z</i> 366	Hydroxylated (Metabolite 1)	 (b) (4)
HM8	<i>m/z</i> 366	Hydroxylated (Metabolite 3)	 (b) (4)
HM9	<i>m/z</i> 366	Hydroxylated	3) benzonitrile
HM10	<i>m/z</i> 366	Hydroxylated	2) benzene
HM11	<i>m/z</i> 366	Hydroxylated (Metabolite 4)	 (b) (4)
HM12	<i>m/z</i> 366	Hydroxylated	2) benzene

Study B07001: Effect of Ketoconazole and CYP3A4 Antibody on the Formation of E2007 Metabolites in Human Liver Microsomes (Study Period: February 20, 2007 - July 23, 2007)

Objective: The purpose of this study is to evaluate the effect of ketoconazole and anti-human CYP3A4 antibody on the formation of E2007 metabolites, in order to confirm E2007 is metabolized by CYP3A4/5 in human liver microsomes. [*Note:* According to the sponsor, the decrease of unchanged E2007 was not quantifiable in human liver microsomes (Study #B05007, data not provided). This was considered probably due to low specific content of CYPs in human liver microsomes to metabolize E2007, however some metabolites were generated.]

Method: The formation of metabolites of E2007 (1 µg/mL) in 0.2 mg/mL protein human liver microsomes (pooled from 50 humans) was assessed in the presence or absence of ketoconazole (0.03, 0.3 and 3 µM) and anti-human CYP3A4 antibody (20 µL Rabbit serum containing anti-human CYP3A4 antibody, supplied by (b) (4)). After 20-min incubation at 37°C, the metabolites formed were monitored using LC-MS method with selected ion recording (SIR). Four synthetic reference compounds, (b) (4) were used as metabolite standards. Peak area ratios of each metabolite to the IS (internal standard, (b) (4)) were calculated, and the effect of ketoconazole and CYP3A4 antibody were assessed.

Results: Four metabolites at m/z 366 were observed in human liver microsomes without ketoconazole and anti-human CYP3A4 antibody. Among these, three metabolites consisted with the synthetic metabolite standards that are E2007 hydroxylated metabolites ((b) (4)/HM7/Metabolite 1, (b) (4)/HM8/Metabolite 3, and (b) (4)/HM11/metabolite 4). The other one was identified as HM12 or Metabolite 19. Ketoconazole reduced the metabolites generation with dose dependent manner, and 0.3 µM ketoconazole reduced the formation of the metabolites to 30-40% of those in the absence of ketoconazole. The formation of the metabolites was decreases to 30-40% in the presence of anti-human CYP3A4 antibody compared to that without the antibody.

Table 8. Effect of ketoconazole or anti-CYP3A4 antibody on the formation of metabolites of m/z 366 in human liver microsomes

Metabolite	Control (no inhibitor)	Ketoconazole			Anti-CYP3A4 Antibody
		0.03 µmol/L	0.3 µmol/L	3 µmol/L	
M1	100.0	67.7	35.7	15.5	42.7
M3	100.0	70.9	38.1	30.6	40.5
M4	100.0	72.4	40.7	21.3	41.8
M19	100.0	68.0	30.8	15.8	29.9

Each value represents percentage of metabolites formed compared to those in control (the absence of ketoconazole or anti-CYP3A4 antibody).

Three minor metabolites at m/z 384 (HM1/Metabolite 7, HM2/Metabolite 8 and HM3/Metabolite 6) were also found in human liver microsomes, and their formation

were decreased by ketoconazole and anti-human CYP3A4 antibody. However, quantitative results were not available.

Reviewer's Comments:

1. Ketoconazole inhibits CYP3A5 as well as CYP3A4 and the specificity of anti-human CYP3A4 antibody against CYP3A5 is not clear. According to a poster from Inveresk Research Ltd. (web source: <http://www.cypex.co.uk/presentationpdfs/InvereskAb.pdf>), while the anti-human CYP3A4 antibody used was selective for CYP3A isoforms, it was found to cross-react with CYP3A5. (b) (4)

Thus, the contribution of CYP3A4 versus CYP3A5 to E2007 metabolism in human liver microsomes could not be differentiated in this study. Overall, these results indicate that E2007 is metabolized by CYP3A4/5 in human liver microsomes.

2. It is also noted that the effect of anti-CYP3A4 antibody on E2007 metabolism was similar to that of 0.3 μM ketoconazole, but less than 3 μM ketoconazole. One of the possible reasons may be that ketoconazole at a concentration of 3 μM inhibits not only CYP3A4 but also other CYP isoforms. For example, a literature study using human liver microsome showed that CYP2B6-mediated bupropion hydroxylation was reduced to 62% of control by 1 μM ketoconazole and 51% of control by 2.5 μM ketoconazole (Hesse LM, et al. *Drug Metab Dispos.* 2000 Oct;28(10):1176-83). Later on, a study determined the IC_{50} and K_i of ketoconazole on bupropion hydroxylation in human liver microsomes as 2.3 μM and 1.4 μM , respectively (Perloff ES, et al. *Xenobiotica.* 2009 Feb;39(2):99-112). These results suggest that ketoconazole at 3 μM could inhibit CYP2B6 activity. In addition, ketoconazole has the potential to inhibit CYP2C8, CYP2C9, and perhaps also CYP2C19 (Stresser DM, et al. *Drug Metab Dispos.* 2004 Jan;32(1):105-12; Lee CA, et al. *Drug Metab Dispos.* 2012 May;40(5):943-51). It is recognized that only small percentages of E2007 were metabolized in CYP2B6, CYP2C8 and CYP2C19 microsome incubations (Table 4). However, as discussed previously, the possibility of larger contribution of these enzymes to E2007 metabolism can not be excluded due to the caveats of Study B04006.

3. It should also be aware that even with the presence of 3 μM ketoconazole there was still some extent of metabolite formation (15-30% of control for M1, M3, M4 and M19). One of possible explanations is that there are other enzymes involved in the formation of these metabolites, which can not be inhibited by ketoconazole. Study B04006 showed that CYP1A2 and CYP2D6 each can metabolize about 5% of E2007, i.e, one-fifth relative to the metabolism mediated by CYP3A4. Ketoconazole at 3 μM concentration did not inhibit CYP2D6-mediated dextromethorphan O-demethylation to any extent in human liver microsomes (Delaporte E, et al. *J Biomol Screen.* 2001 Aug;6(4):225-31). The IC_{50} or K_i of ketoconazole on phenacetin-O-deethylation ranges from 26 to 55 μM , indicating ketoconazole does not inhibit CYP1A2 at a concentration of 3 μM (von Moltke LL, et al, *Psychopharmacology (Berl).* 1996 Dec;128(4):398-407).

4. There are several other metabolites (e.g, M5 and M15) for which the effect of ketoconazole and anti-CYP3A4 antibody has not been evaluated. The mass-balance study

(E2007-E044-007) showed that feces represented a major elimination pathway for E2007 metabolites, as 48% of radiolabeled dose was excreted into feces (the total recovery of administered dose in urine and feces was 70%). Based on the metabolic profiling results of the absolute bioavailability study (E2007-E044-017), M5 is present in feces to some extent. Since the extraction ratio of feces samples in this study was only 20-30%, it is impossible to reliably quantitate the amount of each metabolite in feces as % of dose administered. Therefore, it is unknown which metabolite represents the major metabolic pathway of E2007.

In summary, there are two limitations with the current study: first, involvement of CYP3A4/5 in E2007 metabolism was evaluated based on the formation of several E2007 metabolites but not for all the identified metabolites; secondly, the contribution of any other CYP enzyme (except CYP3A4/5) to the formation of any E2007 metabolite has not been evaluated.

Study B00030: Kinetic and Inhibition Studies Using Human Liver Microsomes with E2007 (Study Period: October 20, 2000 - April 27, 2001)

Objective: To examine the effect of E2007 on CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 in human liver microsomes.

Method: The activities of CYP isozymes in human liver microsomes (pooled from 10 humans) have been estimated by HPLC methods using marker substrates.

CYP Isozyme		Compound Name	Kinetic (Substrate final conc., μM)
1A2	Substrate	Phenacetin	5, 10, 30, 100, 300, 1000, 3000
	Metabolite	Acetaminophen	
	IS	(b) (4)	
2A6	Substrate	Coumarin	1, 2.5, 5, 10, 50, 100, 500
	Metabolite	7-Hydroxycoumarin	
2B6	Substrate	7-Benzoyloxyresorufin	1, 1.5, 3, 6, 10, 12, 15, 18, 20
	Metabolite	Resorufin	
2C9	Substrate	Tolbutamide	3, 10, 30, 100, 300, 1000, 3000
	Metabolite	Hydroxytolbutamide	
	IS	(b) (4)	
2C19	Substrate	S(+)-Mephenytoin	10, 20, 50, 100, 200, 500, 1000
	Metabolite	(\pm)-4'-Hydroxymephenytoin	
	IS	(b) (4)	
2D6	Substrate	Bufuralol	20, 30, 40, 60, 100, 200, 600, 2000
	Metabolite	1'-Hydroxybufuralol	
2E1	Substrate	Chlorzoxazone	5, 10, 50, 100, 200, 500, 1000, 2000
	Metabolite	6-Hydroxychlorzoxazone	
	IS	(b) (4)	
3A4	Substrate	Nifedipine	3, 6, 10, 30, 60, 100, 300
	Metabolite	Oxidized nifedipine	
	IS	(b) (4)	

(b) (4)

The % inhibition was calculated as follows:

$$\text{Inhibition \%} = (1 - v_{E2007} / \text{mean } v_{\text{control}}) \times 100$$

where v_{E2007} is the initial velocity of the formation of the marker metabolite in the presence of 30 μM E2007 and v_{control} is the mean initial velocity of triplicate control samples. The mean of inhibition % with the standard error of the mean was then calculated. Michaelis-Menten kinetic parameters for the formation of each metabolite were also determined.

Results: E2007 at 30 μM has no or little inhibition effect on CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 in human liver microsomes. E2007 seemed to stimulate the activity of CYP2B6 at 30 μM . The CYP2B6 activity was increased to 2.2- or 3.57-fold of that in the control groups. The effects of E2007 at lower concentrations on CYP2B6 activity have not been evaluated.

Table 9. CYP Inhibition of E2007 at 30 $\mu\text{mol/L}$ in Human Liver Microsomes

P450 isozyme	1A2	2A6	2B6	2C9	2C19	2D6	2E1	3A4
Km ($\mu\text{mol/L}$)	269.2 ^a , 3873.7 ^b	7.1	7.1	548.8	107.9	22.2	139.1	14.6
Inhibition (%)	9.5 \pm 2.4 (10)	13.5 \pm 2.7 (1)	-256.5 \pm 20.2 (1)	16.9 \pm 1.9 (100)	-26.2 (10)	-2.7 \pm 1.3 (20)	-32.8 \pm 1.9 (10)	5.0 \pm 2.2 (6)
	8.0 \pm 5.9 (30)	10.6 \pm 0.8 (5)	-120.1 \pm 6.8 (3)		-4.9 (1000)	-13.0 \pm 2.3 (60)	-23.2 \pm 5.6 (50)	1.7 \pm 1.1 (10)

The inhibition % was shown as the mean \pm SEM of 3 samples except for CYP2C19 (n=2).

The values in the parentheses are substrate concentrations (μM) used in the corresponding enzyme inhibition experiments.

a: Km1, b: Km2

Study AE-4739-G: Inhibitory Study of E2007 for CYP Isoforms Using Human Liver Microsomes (Study Period: October 5, 2005 - March 28, 2006)

Objective: to investigate enzyme inhibitory effect of E2007 on human CYP isoforms (CYP2C8 and CYP3A4) using human liver microsomes.

Method: CYP2C8 and CYP3A4 activities in pooled human liver microsomes (0.1 mg protein/mL for midazolam and testosterone, or 0.5 mg protein/mL for paclitaxel and nifedipine) were determined by measuring the metabolite formation of marker substrates using HPLC, with or without presence of E2007 (0, 3, 10, and 30 μM). Time-dependent inhibition for CYP3A4 was also evaluated with or without pre-incubation (at 37°C for 0 or 30 min) of E2007 (0, 0.3, 3, and 30 μM).

Isoform	Model substrate	Final concentration (μmol/L)	Incubation time (min)	Internal standard (concentration) ^{(b) (4)}
CYP2C8	Paclitaxel ¹⁾	10	20	
CYP3A4	Midazolam ²⁾	10	10	
CYP3A4	Testosterone ³⁾	120	30	
CYP3A4	Nifedipine ³⁾	30	5	

The corresponding metabolites measured were 6α-hydroxypaclitaxel, 1'-Hydroxymidazolam, 6β-Hydroxytestosterone and oxidized nifedipine, respectively.

For time-dependent inhibition, the rate constant of activity disappearance was calculated with the following equation.

$$k_{\text{obs}} \text{ (the initial rate constant for inactivation)} = (\text{Ln A} - \text{Ln B}) / 30$$

A: % of control without pre-incubation

B: % of control after pre-incubation for 30 min

The K_I and k_{inact} were calculated from the relationship between the concentration of E2007 and the k_{obs} using the following equation.

$$E = (E_{\text{max}} \times C) / (C + EC_{50})$$

E: k_{obs} (min^{-1})

E_{max} : k_{inact} (the maximum rate constant for inactivation, min^{-1})

C: Concentration of E2007 (μM)

EC_{50} : K_I (E2007 concentration at 50% of k_{inact} , μM)

Results: The inhibition percent of E2007 at 3, 10, and 30 μM was 6.0%, 18% and 40.7%, respectively, for CYP2C8. The inhibition percent of E2007 at 30 μM for CYP3A4 using midazolam, testosterone and nifedipine as substrates were 14.0%, 7.6% and 2.1%, respectively. For the time-dependent inhibition of CYP3A4, after pre-incubation for 0 and 30 min, the inhibition percent of E2007 was 3.4% and 5.7% at 0.3 μM , 4.1% and 10.8% at 3 μM , and 20.0% and 49.4% at 30 μM , respectively. It was suggested that E2007 has an irreversible inhibitory effect or metabolites inhibition for CYP3A4. k_{inact} and K_I were estimated to be 0.036 min^{-1} and 40.6 μM , respectively.

Table 10. Remaining activity (inhibition percent) of E2007 on the metabolism of model substrates for each cytochrome P450 isoforms in human liver microsomes

Cytochrome P450	Remaining activity (inhibition percent) of E2007 (%)				Positive control
	0	3	10	30	
CYP2C8	100.0 (0.0)	94.0 (6.0)	82.0 (18.0)	59.3 (40.7)	31.3 (68.7)
CYP3A4 (Midazolam)	100.0 (0.0)	91.6 (8.4)	94.7 (5.3)	86.0 (14.0)	8.7 (91.3)
CYP3A4 (Testosterone)	100.0 (0.0)	99.2 (0.8)	101.4 (-1.4)	92.4 (7.6)	5.9 (94.1)
CYP3A4 (Nifedipine)	100.0 (0.0)	104.8 (-4.8)	104.5 (-4.5)	97.9 (2.1)	7.0 (93.0)

Figures in parentheses are expressed as inhibition percent.

Concentration of positive control: CYP2C8, quercetin (10 μM); CYP3A4, ketoconazole (1 μM)

Table 11. Time-dependent inactivation of the midazolam metabolism in human liver microsomes, as a function of pre-incubation time in Exp. 3

Compound	Conc. ($\mu\text{mol/L}$)	% of control		% of inhibition	
		0 min	30 min	0 min	30 min
E2007	0	100.0	100.0	0.0	0.0
	30	86.7	53.6	13.3	46.4
Positive control		92.9	48.3	7.1	51.7

Concentration of positive control: CYP3A4, troleandomycin (1 μM)

Table 12. Time- and concentration-dependent inactivation of the midazolam metabolism in human liver microsomes, as a function of pre-incubation time in Exp. 4

Compound	Conc. ($\mu\text{mol/L}$)	% of control		% of inhibition	
		0 min	30 min	0 min	30 min
E2007	0	100.0	100.0	0.0	0.0
	0.3	96.6	94.3	3.4	5.7
	3	95.9	89.2	4.1	10.8
	30	80.0	50.6	20.0	49.4
Positive control		87.5	43.6	12.5	56.4

Concentration of positive control: CYP3A4, troleandomycin (1 μM)

Reviewer's Comment: Using PK parameters derived from the Phase 1 population PK analysis (study CPMS-E2007-2011-002) for E2007 given under fasting conditions, a steady-state C_{max} of 661 ng/mL (i.e, 1.89 μM) is simulated for E2007 administered following the dosing regimen proposed for clinical use, i.e, 2 mg \times 7 days \rightarrow 4 mg \times 7 days \rightarrow 6 mg \times 7 days \rightarrow 8 mg maintained. Thus, E2007 is not expected to significantly inhibit CYP2C8 *in vivo*. Effect of E2007 on CYP3A4 substrates was evaluated in a drug-drug interaction study between E2007 and midazolam (study E2007-A001-014). Please refer to that study review for details.

Study XT095036: *In Vitro* Evaluation of E2007 as a Direct Inhibitor of UGT Enzymes in Human Liver Microsomes (Study Period: October 27, 2009 - January 21, 2010)

Objective: to evaluate the ability of E2007 to inhibit select uridine diphosphate glucuronosyltransferase (UGT) enzymes in human liver microsomes (UGT1A1, UGT1A4, UGT1A6, UGT1A9 and UGT2B7).

Method: Pooled human liver microsomes (16 individuals) were incubated with marker substrates, at concentrations approximately equal to their apparent K_m or S_{50} , in the presence or absence of E2007 (0.03 to 30 μM). A known direct-acting inhibitor of UGT enzymes, troglitazone, was included as a positive control. Incubations were conducted at approximately 37°C in 200- μL or 400- μL incubation mixtures containing water, Tris-HCl (100 mM, pH 7.7), MgCl_2 (10 mM), EDTA (1 mM, pH 7.4), saccharic acid 1,4-lactone (0.1 mM) and UDPGA (20 mM) at the final concentrations indicated. All analyses were performed with HPLC/MS/MS.

Enzyme	Enzyme reaction	Substrate concentration (μM)	Substrate solvent (% v/v)	Incubation volume (μL)	Protein ^a ($\mu\text{g/mL}$)	Incubation time (min)	E2007	
							Target concentrations (μM)	Solvent volume ^b (μL)
UGT1A1	17 β -Estradiol 3-glucuronidation	9	Methanol (1%)	200	100	5	0, 0.03, 0.1, 0.3, 1, 3, 10, 30	2
UGT1A4	Trifluoperazine glucuronidation	12	Methanol (0.5%)	400	100	5	0, 0.03, 0.1, 0.3, 1, 3, 10, 30	4
UGT1A6	1-Naphthol glucuronidation	1	Methanol (1%)	200	5	5	0, 0.03, 0.1, 0.3, 1, 3, 10, 30	2
UGT1A9	Propofol glucuronidation	20	Methanol (1%)	200	100	5	0, 0.03, 0.1, 0.3, 1, 3, 10, 30	2
UGT2B7	Morphine 3-glucuronidation	400	Water (NA)	200	100	5	0, 0.03, 0.1, 0.3, 1, 3, 10, 30	2

a The human liver microsomal sample used for these experiments was a pool of 16 individuals

b Methanol was the solvent used to dissolve the test article.

NA Not applicable

v/v Volume/volume

It should be noted that the methods described in this study did not use activators, such as alamethicin or CHAPS which is commonly used to improve cofactor (UDPGA) access to UGT enzymes, for the following reasons:

1. UGT activity in untreated (or native) liver microsomes is sufficient to measure UGT inhibition.
2. It is possible that 50% of the microsomal vesicles may be inside out; therefore, sufficient enzyme activity may be achieved without the use of activators.
3. Activators such as alamethicin or CHAPS may have unforeseen interactions with inhibitors and/or drug candidates.

The IC_{50} of E2007 on each UGT enzyme was estimated by fitting the data to Levenberg-Marquardt algorithm:

$$\text{fit} = \text{background} + \frac{(\text{range} - \text{background})}{\left(1 + \left(\frac{x}{\text{IC}_{50}}\right)^{\text{slope}}\right)}$$

Background was set = 0 and range to 100, as percent of control values are utilized.

Results: E2007 inhibited UGT1A9 and UGT2B7, as about 44% and 13% inhibition (respectively) was observed at 30 μ M E2007. The IC₅₀ values for these enzymes were reported as greater than 30 μ M, thus significant *in vivo* inhibition of these enzymes by E2007 is not expected. There was little or no inhibition of UGT1A4 and UGT1A6 by E2007. Increase in UGT1A1 activity was observed with increasing E2007 concentrations (0.1 - 30 μ M). At 0.3, 1, 3, 10 and 30 μ M E2007, UGT1A1 activity was 109%, 116%, 122%, 160% and 173% of solvent control, respectively.

Reviewer's Comment: As C_{max} of E2007 at the recommended maintenance dose level (8 mg) is predicted to be around 1.89 μ M, no significant increase of UGT1A1 activity by E2007 is expected *in vivo*.

Table 13. *In vitro* evaluation of E2007 as an inhibitor of human UGT enzymes

Enzyme	Enzyme reaction	Direct inhibition	
		IC ₅₀ (μ M) ^a	Maximum inhibition at 30 μ M (%) ^b
UGT1A1	17 β -Estradiol 3-glucuronidation	>30	NA
UGT1A4	Trifluoperazine glucuronidation	>30	NA
UGT1A6	1-Naphthol glucuronidation	>30	NA
UGT1A9	Propofol glucuronidation	>30	44
UGT2B7	Morphine 3-glucuronidation	>30	13

a Average data (i.e., percent of control activity) obtained from duplicate samples for each test article concentration were used to calculate IC₅₀ values.

b Maximum inhibition (%) is calculated as following and data for the highest concentration of test article evaluated: Maximum inhibition (%) = 100% – Percent solvent control.

NA Not applicable. No value was obtained as the rates at the highest concentration of E2007 evaluated (30 μ M) were higher than the control rates.

Study GE-0045: Enzyme Induction Study of E2007 in Primary Cultured Human Hepatocytes (Study Period: April 15, 2002 - September 26, 2002)

Objective: To clarify the induction potency of E2007 for drug-metabolizing enzymes.

Methods: Fresh primary cultured human hepatocytes were incubated for 48 and 72 hr before CYP1A2 and CYP3A4 enzyme activity assay, respectively, and for 24 and 48 hr before CYP1A2 and CYP3A4/5 mRNA assay, respectively. Medium was changed every 24 hrs. 0.1% DMSO was used as vehicle and 20 μ M β -naphthoflavone (β -NF) and 10 μ M rifampicin (RIF) were used as positive controls for CYP1A2 and CYP3A4/5, respectively. For enzyme activity assay, after the induction treatment, the culture medium containing inducer was removed from each well, 0.5 mL of the enzyme reaction mixture was immediately added, and incubated at 37°C. The enzyme reaction time was 2 hr for CYP1A2 and 1 hr for CYP3A4. The enzyme activities (pmol/hr/mg protein) of CYP1A2 and CYP3A4 were measured by using specific substrates, phenacetin (10 μ M) and midazolam (10 μ M), respectively, and each metabolite formed were assayed by LC/MS/MS. The mRNA levels of CYP1A2 and CYP3A4/5 were determined by branched DNA assay using specific probes for each mRNA and the luminescence probe, where (b) (4) was used as the internal standard. The assay value of each gene (CYP1A2,

CYP3A4/5 and (b) (4) after subtraction of background value was normalized with the value of (b) (4)

$$\text{Enzyme induction ratio} = \frac{\text{Enzyme activity after exposure of E2007 or positive control}}{\text{Enzyme activity of Solvent control}}$$

$$\text{mRNA induction ratio} = \frac{\text{Normalized luminescence after exposure of E2007 or positive control}}{\text{Normalized luminescence of Solvent control}}$$

Results: E2007 up to 30 µM had no induction potency for CYP1A2 in primary cultured human hepatocytes. In contrast, the positive control, β-naphthoflavone, greatly induced CYP1A2 mRNA expression and increased its activity. Actually, E2007 decreased CYP1A2 activity rather than increased. It remains unknown as to the possible reasons for decreased CYP1A2 activity in hepatocytes after treatment with E2007. As shown in the previous study using human liver microsomes (Study B00030), E2007 did not inhibit phenacetin O-deethylation activity up to 30 µM. Though decreased mRNA expression of CYP1A2 was observed in two livers (lot No. 40 and 41), mRNA levels in the E2007 exposure groups in the other two livers (lot No. 39 and 43) were comparable or higher than those in solvent control group. It is also noted that the tendency of decrease in CYP1A2 activity was not concentration-dependent.

Table 14. Effect of E2007 on Phenacetin O-deethylation in primary cultured human hepatocytes

CYP1A2	Induction ratio(relative to Solvent control)					Mean	S.D.
	Lot No.39	Lot No.40	Lot No.41	Lot No.43			
Solvent control	1.00	1.00	1.00	1.00	1.00	0.00	
0.03 µmol/L E2007	0.74	0.58	0.91	0.46	0.67	0.20	
0.3 µmol/L E2007	0.74	0.96	0.87	0.44	0.75	0.23	
3 µmol/L E2007	0.87	0.55	0.90	0.50	0.71	0.21	
30 µmol/L E2007	0.59	0.76	0.87	0.55	0.69	0.15	
Positive control	15.2	20.1	15.9	6.17	14.3	5.86	

Table 15. Effect of E2007 on CYP1A2 mRNA expression in primary cultured human hepatocytes

CYP1A2	Induction ratio(relative to Solvent control)					Mean	S.D.
	Lot No.39	Lot No.40	Lot No.41	Lot No.43			
Solvent control	1.00	1.00	1.00	1.00	1.00	0.00	
0.03 µmol/L E2007	0.90	0.83	0.71	0.90	0.84	0.09	
0.3 µmol/L E2007	1.05	0.90	0.67	1.04	0.92	0.18	
3 µmol/L E2007	1.14	0.74	0.73	1.31	0.98	0.29	
30 µmol/L E2007	1.37	0.68	0.72	1.49	1.07	0.42	
Positive control	17.3	8.34	10.4	5.32	10.3	5.09	

Solvent control: 0.1% DMSO; Positive control: 20 µM β-naphthoflavone (β-NF)

CYP3A4/5 was induced by E2007 at a concentration of 3 µM or more. The induction ratio of enzyme activity by 30 µM E2007 was about 1/7 to 1/3 of that in the positive

control (10 μ M RIF) exposure group and the mRNA induction ratio was 1/3 to 1/2 of that in the positive control group.

Table 16. Effect of E2007 on Midazolam 1'-hydroxylation in primary cultured human hepatocytes

CYP3A4	Induction ratio(relative to Solvent control)					Mean*	S.D.*
	Lot No.39	Lot No.40	Lot No.41	Lot No.43			
Solvent control	1.00	1.00	1.00	1.00	1.00	0.00	
0.03 μ mol/L E2007	1.07	0.87	1.10	1.02	0.99	0.10	
0.3 μ mol/L E2007	1.27	1.04	0.92	1.02	1.11	0.14	
3 μ mol/L E2007	3.42	3.45	0.95	1.57	2.81	1.08	
30 μ mol/L E2007	4.89	4.37	0.71	2.75	4.00	1.12	
Positive control	14.9	13.3	2.14	20.6	16.3	3.84	

Table 17. Effect of E2007 on CYP3A4/5 mRNA expression in primary cultured human hepatocytes

CYP3A4/5	Induction ratio(relative to Solvent control)					Mean*	S.D.*
	Lot No.39	Lot No.40	Lot No.41	Lot No.43			
Solvent control	1.00	1.00	1.00	1.00	1.00	0.00	
0.03 μ mol/L E2007	1.13	0.98	0.89	1.50	1.20	0.27	
0.3 μ mol/L E2007	1.36	0.84	0.97	1.48	1.23	0.34	
3 μ mol/L E2007	6.46	3.11	2.25	7.45	5.67	2.27	
30 μ mol/L E2007	19.1	3.66	4.66	31.9	18.2	14.1	
Positive control	38.6	6.44	6.32	90.6	45.2	42.5	

Solvent control: 0.1% DMSO; Positive control: 10 μ M rifampicin (RIF)

* Mean and S.D. were calculated from values of hepatocytes Lot No. 39, 40 and 43. Since the enzyme activity for CYP3A4 in the hepatocytes Lot No. 41 showed only slight increase by RIF, this lot was judged to be excluded for the evaluation of CYP3A4/5 induction.

Reviewer's Comment: The newly updated FDA Drug-Drug Interaction Guidance (draft, 2012 version) recommends changes in the mRNA level of the target gene be used as an endpoint to judge the *in vivo* induction potential of a compound. A pre-defined threshold for increase in mRNA of CYP3A4 was not proposed by the sponsor, nor were induction parameters (E_{max} and EC_{50}) measured. A recently published paper introduced a simple algorithm with 98% sensitivity and 69% specificity and having minimal false negative prediction (Fahmi O, et al. *Drug Metab Dispos.* 2010 Sep;38(9):1605-11). The algorithm is based on fold induction of target gene relative to vehicle control and applies a 4-fold cut-off. Utilizing this method, E2007 at concentrations around 3 μ M and above will be expected to have *in vivo* induction effect on CYP3A4/5, since more than 4-fold induction of CYP3A4/5 mRNA was seen in two livers (6.46-fold in lot No. 39 and 7.45-fold from lot No. 43) after treatment with 3 μ M E2007. However, it should be noted that induction effect of E2007 on CYP3A4/5 mRNA dramatically decreased when its concentration drops to 0.3 μ M, with none of the livers having induction fold over 4-fold cut-off. As previously mentioned, a steady-state C_{max} of 661 ng/mL (i.e., 1.89 μ M) was simulated for E2007 administered as once daily 8 mg dose after titration. Average concentration (C_{avg}) was predicted as 512 ng/mL (1.46 μ M). Also, considering that induction effect of E2007 on CYP3A4 activity at a concentration of 3 μ M was less than 20% of the effect of

positive control (rifampicin), E2007 is expected to be a weak inducer on CYP3A4/5 at the recommended maintenance dose levels.

Study XT093050: *In Vitro* Evaluation of E2007 as an Inducer of Cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT) Expression in Cultured Human Hepatocytes (Study Period: October 27, 2009 - March 30, 2010)

Objective: to investigate the effects of treating primary cultures of fresh human hepatocytes with E2007 on the expression of CYP enzymes and UGT enzymes.

Method: Three preparations of cultured human hepatocytes from 3 donors were treated once daily for three consecutive days with DMSO (0.1% v/v, vehicle control), E2007 (0.03, 0.3 or 3 and 30 μ M) or one of five known CYP and UGT inducers, namely, 3-methylcholanthrene (2 μ M), β -naphthoflavone (33 μ M), omeprazole (100 μ M), phenobarbital (750 μ M) and rifampin (10 μ M). After treatment, the cells were harvested to isolate microsomes for the analysis of bupropion hydroxylation (marker for CYP2B6), 17 β -Estradiol 3- β -D-glucuronidation (marker for UGT1A1), trifluoperazine glucuronidation (marker for UGT1A4), 1-naphthol glucuronidation (marker for UGT1A6), propofol glucuronidation (marker for UGT1A9) and morphine 3 β -D-glucuronidation (marker for UGT2B7) by LC/MS/MS. Additional hepatocytes from the same treatment groups were harvested to isolate RNA, which was analyzed by qRT-PCR (quantitative reverse transcription-polymerase chain reaction) to assess the effect of E2007 on CYP2B6, UGT1A1, UGT1A4, UGT1A6, UGT1A9 and UGT2B7 mRNA levels. Viability of hepatocytes was evaluated by monitoring the morphology of cells with light microscopy.

To measure CYP enzyme activity, microsomal incubations were conducted at 37 °C in 200- μ L incubation mixtures (pH 7.4) containing water, potassium phosphate buffer (50 mM), MgCl₂ (3 mM), EDTA (1 mM), an NADPH generating system (mixture of NADP [1 mM], glucose-6-phosphate [5 mM], glucose-6-phosphate dehydrogenase [1 Unit/mL]), and marker substrate at the final concentrations indicated.

To measure UGT enzyme activity, microsomal incubations were conducted at 37 °C in 200- μ L incubation mixtures containing Tris-HCl (100 mM, pH 8.0), MgCl₂ (10 mM), EDTA (1 mM), D-saccharic acid 1,4-lactone (100 μ M), UDPGA (8 mM) and marker substrate at the final concentrations indicated.

Enzyme	Substrate	Substrate concentration (μ M)	Protein concentration (μ g/mL) ^a	Incubation time (min)
CYP2B6	Bupropion	500	40	30
UGT1A1	β -Estradiol	100	20	10
UGT1A4	Trifluoperazine	25	200	5
UGT1A6	Naphthol	500	10	10
UGT1A9	Propofol	50	50	10
UGT2B7	Morphine	1000	20	10

a. Incubation volume = 200 μ L

Fold increases were determined by dividing the enzymatic rate for each treatment group by that of the vehicle control. For CYP2B6, the percent of positive control was further calculated with the following equation:

$$\text{Percent positive control} = \frac{(\text{activity of test article treated cells} - \text{activity of vehicle control})}{(\text{activity of positive control} - \text{activity of vehicle control})} \times 100$$

For enzyme expression measured as mRNA level, PCR product quantities for both the target genes and the endogenous controls ((b) (4)) in all samples were determined from the standard curve. The target gene quantity was then normalized to the endogenous control in all samples, and the target gene quantity in the treated samples was divided by the target gene quantity in the untreated control. The result represents a fold change in gene expression. For CYP2B6, the level of mRNA expression relative to the positive control is calculated as follows:

$$\text{Percent positive control} = \frac{[(\text{fold change in treated sample}) - 1]}{[(\text{fold change in positive control}) - 1]} \times 100$$

Results: Treatment of hepatocyte cultures H948 and H949 with up to 30 µM E2007 caused no or little increase (< 2-fold) in CYP2B6 activity. In human hepatocyte preparation H950, E2007 caused a concentration-dependent increase in CYP2B6 activity (up to 3.96-fold). But it was less than 20% as effective as phenobarbital at inducing CYP2B6 activity (percentage of positive control is 17.7%).

Table 18. CYP and UGT activity fold increase: The effects of treating cultured human hepatocytes with E2007 or prototypical inducers on microsomal CYP and UGT enzyme activity

Treatment	Concentration	Fold Increase ^a					
		Bupropion hydroxylation (CYP2B6)	17β-Estradiol 3-β-D-glucuronidation (UGT1A1)	Trifluoperazine glucuronidation (UGT1A4)	1-Naphthol glucuronidation (UGT1A6)	Propofol glucuronidation (UGT1A9)	Morphine 3β-D-glucuronidation (UGT2B7)
Dimethyl sulfoxide	0.1% (v/v)	1.00 ± 0.42	1.00 ± 0.35	1.00 ± 0.26	1.00 ± 0.30	1.00 ± 0.43	1.00 ± 0.17
E2007	0.03 µM	0.935 ± 0.086	0.923 ± 0.114	0.964 ± 0.221	0.850 ± 0.163	0.889 ± 0.227	0.899 ± 0.102
E2007	0.3 µM	1.14 ± 0.18	0.996 ± 0.028	1.05 ± 0.02	1.01 ± 0.14	0.951 ± 0.084	1.01 ± 0.07
E2007	3 µM	1.66 ± 0.39	1.13 ± 0.17	1.32 ± 0.31	1.00 ± 0.12	0.840 ± 0.254	1.10 ± 0.25
E2007	30 µM	2.18 ± 1.61	1.25 ± 0.16	1.84 ± 0.57	0.981 ± 0.226	0.780 ± 0.090	1.03 ± 0.11
3-Methylcholanthrene	2 µM	1.37 ± 0.47	1.29 ± 0.03	1.33 ± 0.06	1.09 ± 0.11	0.920 ± 0.055	1.08 ± 0.04
β-Naphthoflavone	33 µM	4.35 ± 1.80	1.64 ± 0.34	1.60 ± 0.50	1.13 ± 0.28	0.930 ± 0.233	1.19 ± 0.36
Omeprazole	100 µM	8.14 ± 2.94	1.89 ± 0.12	2.01 ± 0.49	1.13 ± 0.17	0.968 ± 0.073	1.18 ± 0.18
Phenobarbital	750 µM	13.3 ± 4.3	1.30 ± 0.26	1.90 ± 0.54	1.02 ± 0.32	0.821 ± 0.053	1.15 ± 0.33
Rifampin	10 µM	6.00 ± 1.29	1.46 ± 0.07	2.35 ± 0.80	1.14 ± 0.23	0.882 ± 0.131	1.23 ± 0.07

a. Values are the mean ± standard deviation of three determinations (human hepatocyte preparations H948, H949 and H950).

Table 19. Fold increase of CYP2B6 activity in the presence of E2007 or prototypical inducers

Treatment	Concentration	Bupropion hydroxylation ^a		
		H948	H949	H950
Dimethyl sulfoxide	0.1 % (v/v)	1.00	1.00	1.00
E2007	0.03 µM	0.916	1.03	0.860
E2007	0.3 µM	0.952	1.30	1.16
E2007	3 µM	1.22	1.77	1.98
E2007	30 µM	0.829	1.75	3.96
3-Methylcholanthrene	2 µM	0.932	1.31	1.87
β-Naphthoflavone	33 µM	4.38	2.54	6.14
Omeprazole	100 µM	6.27	6.62	11.5
Phenobarbital	750 µM	9.11	13.0	17.7
Rifampin	10 µM	4.79	5.86	7.37

a. Fold increase = activity of test article treated cells / activity of vehicle control

In general, CYP2B6 mRNA expression levels in hepatocytes treated with up to 30 μM E2007 were similar to the trends observed in H950 CYP2B6 activity levels, which was a concentration-dependent increase, up to 2.66-fold on average. However, the effects of E2007 at 3 and 30 μM were small relative to the effect of phenobarbital (percentage of positive control: 24.6 \pm 10.1% at 30 μM , 18.3 \pm 5.0% at 3 μM).

Reviewer's Comment: The induction of CYP2B6 mRNA were less than 4-fold of DMSO group in all three preparations of hepatocytes treated with 30 μM E2007, indicating that there may not be significant induction of CYP2B6 *in vivo* by E2007 (Fahmi O, et al. *Drug Metab Dispos.* 2010 Sep;38(9):1605-11). In contrast, phenobarbital induced CYP2B6 mRNA more than 4-fold of vehicle control in all the three hepatocytes.

Table 20. mRNA fold increase: The effects of treating cultured human hepatocytes with E2007 or prototypical inducers on microsomal CYP and UGT mRNA levels as determined by qRT-PCR

Treatment	Concentration	Fold Increase ^a					
		CYP2B6	UGT1A1	UGT1A4	UGT1A6	UGT1A9	UGT2B7
Dimethyl sulfoxide	0.1% (v/v)	1.00 \pm 0.00	1.00 \pm 0.00	1.00 \pm 0.00	1.00 \pm 0.00	1.00 \pm 0.00	1.00 \pm 0.00
E2007	0.03 μM	1.10 \pm 0.08	0.975 \pm 0.052	0.911 \pm 0.026	1.18 \pm 0.47	1.03 \pm 0.11	1.01 \pm 0.06
E2007	0.3 μM	1.32 \pm 0.23	1.76 \pm 1.51	0.764 \pm 0.234	1.30 \pm 0.59	1.01 \pm 0.13	1.09 \pm 0.24
E2007	3 μM	2.36 \pm 0.73	3.95 \pm 4.50	1.40 \pm 0.49	1.62 \pm 0.69	1.07 \pm 0.27	1.38 \pm 0.21
E2007	30 μM	2.66 \pm 0.61	3.18 \pm 1.16	2.65 \pm 1.52	1.45 \pm 0.43	0.907 \pm 0.302	1.21 \pm 0.26
3-Methylcholanthrene	2 μM	1.04 \pm 0.14	2.47 \pm 0.54	1.52 \pm 0.41	1.22 \pm 0.09	1.02 \pm 0.28	1.60 \pm 0.31
β -Naphthoflavone	33 μM	2.26 \pm 1.02	1.20 \pm 0.59	1.08 \pm 0.37	1.09 \pm 0.04	0.827 \pm 0.140	1.69 \pm 0.18
Omeprazole	100 μM	3.75 \pm 1.56	3.21 \pm 2.63	3.49 \pm 1.56	1.01 \pm 0.25	0.871 \pm 0.262	1.57 \pm 0.28
Phenobarbital	750 μM	9.74 \pm 7.39	5.32 \pm 6.01	5.88 \pm 4.04	1.56 \pm 0.45	0.810 \pm 0.267	2.14 \pm 0.24
Rifampin	10 μM	4.42 \pm 1.04	4.23 \pm 3.67	5.34 \pm 3.38	1.58 \pm 0.68	0.641 \pm 0.255	1.98 \pm 0.50

a. Values are relative to (b) (4) and are the mean \pm standard deviation of three determinations (human hepatocyte preparations H948, H949 and H950).

Table 21. mRNA fold increase of CYP2B6

Treatment	Concentration	CYP2B6 mRNA levels (fold increase) ^a		
		H948	H949	H950
Dimethyl sulfoxide	0.1 % (v/v)	1.00	1.00	1.00
E2007	0.03 μM	1.02	1.18	1.08
E2007	0.3 μM	1.16	1.58	1.22
E2007	3 μM	1.69	3.14	2.23
E2007	30 μM	2.12	3.32	2.53
3-Methylcholanthrene	2 μM	1.20	0.912	1.02
β -Naphthoflavone	33 μM	1.66	3.43	1.69
Omeprazole	100 μM	2.63	5.53	3.09
Phenobarbital	750 μM	4.37	18.2	6.68
Rifampin	10 μM	4.57	5.38	3.32

a. Values are relative to (b) (4) and are the average of triplicate determinations.

For UGT1A6, UGT1A9 and UGT2B7, there was no change in their activities in all three hepatocyte cultures in response to the prototypical inducers and E2007 (Table 18). These treatments slightly increased UGT1A1 activity, with more increases observed for UGT1A4 activity. After treatment with E2007, UGT1A4 activity was increased in a concentration-dependent manner, up to 1.84-fold on average, in response to 30 μM E2007 (Table 22).

Table 22. Fold increase of UGT1A4 activity in the presence of E2007 or prototypical inducers

Treatment	Concentration	Trifluoperazine glucuronidation ^a		
		H948	H949	H950
Dimethyl sulfoxide	0.1 % (v/v)	1.00	1.00	1.00
E2007	0.03 µM	1.21	0.900	0.781
E2007	0.3 µM	1.05	1.06	1.03
E2007	3 µM	1.69	1.13	1.15
E2007	30 µM	2.50	1.56	1.46
3-Methylcholanthrene	2 µM	1.39	1.31	1.28
β-Naphthoflavone	33 µM	2.06	1.07	1.68
Omeprazole	100 µM	2.57	1.69	1.76
Phenobarbital	750 µM	2.49	1.42	1.80
Rifampin	10 µM	3.25	2.12	1.70

a. Fold increase = activity of test article treated cells / activity of vehicle control

Table 23. Fold increase of UGT1A1 activity in the presence of E2007 or prototypical inducers

Treatment	Concentration	17β-Estradiol 3-glucuronidation ^a		
		H948	H949	H950
Dimethyl sulfoxide	0.1 % (v/v)	1.00	1.00	1.00
E2007	0.03 µM	1.06	0.859	0.857
E2007	0.3 µM	1.03	0.973	0.989
E2007	3 µM	1.33	1.03	1.03
E2007	30 µM	1.24	1.09	1.41
3-Methylcholanthrene	2 µM	1.29	1.26	1.32
β-Naphthoflavone	33 µM	1.90	1.25	1.76
Omeprazole	100 µM	1.96	1.75	1.95
Phenobarbital	750 µM	1.35	1.02	1.53
Rifampin	10 µM	1.53	1.44	1.39

a. Fold increase = activity of test article treated cells / activity of vehicle control

In general, effects of prototypical inducers and E2007 on mRNA expression of UGTs were higher than those on UGT activities (Table 18 and Table 20), especially for UGT1A1, where more prominent increases (3.95- and 3.18-fold) in mRNA expression levels were observed following treatment with 3 µM and 30 µM E2007, respectively. On average, effects of E2007 on UGT1A1 mRNA level at these concentrations were just slightly lower than those of rifampicin (4.23-fold). In contrast, effects of E2007 on UGT1A4 mRNA level were weaker (1.40 ± 0.49 fold at 3 µM, 2.65 ± 1.52 fold at 30 µM), while rifampicin increased UGT1A4 mRNA to 5.34 ± 3.38 fold.

Table 24. mRNA fold increase of UGT1A4

Treatment	Concentration	UGT1A4 mRNA levels (fold increase) ^a		
		H948	H949	H950
Dimethyl sulfoxide	0.1 % (v/v)	1.00	1.00	1.00
E2007	0.03 µM	0.924	0.928	0.882
E2007	0.3 µM	0.672	0.591	1.03
E2007	3 µM	1.31	0.963	1.93
E2007	30 µM	4.30	1.30	2.34
3-Methylcholanthrene	2 µM	1.97	1.18	1.39
β-Naphthoflavone	33 µM	0.796	0.939	1.50
Omeprazole	100 µM	5.30	2.62	2.55
Phenobarbital	750 µM	10.5	3.77	3.34
Rifampin	10 µM	9.23	3.59	3.20

Table 25. mRNA fold increase of UGT1A1

Treatment	Concentration	UGT1A1 mRNA levels (fold increase) ^a		
		H948	H949	H950
Dimethyl sulfoxide	0.1 % (v/v)	1.00	1.00	1.00
E2007	0.03 μ M	1.03	0.952	0.939
E2007	0.3 μ M	0.765	3.50	1.01
E2007	3 μ M	1.30	9.15	1.42
E2007	30 μ M	4.31	3.21	2.00
3-Methylcholanthrene	2 μ M	2.46	3.01	1.94
β -Naphthoflavone	33 μ M	1.10	0.666	1.84
Omeprazole	100 μ M	5.98	0.764	2.89
Phenobarbital	750 μ M	12.3	1.56	2.14
Rifampin	10 μ M	8.43	2.64	1.62

a. Values are relative to (b) (4) and are the average of triplicate determinations.

Reviewer's Comment: At concentrations of 3 μ M and above, E2007 induced expression of UGT1A1 mRNA. Though effect of E2007 on UGT1A1 activity was small, it should be noted that the positive controls (rifampicin and phenobarbital) also just showed small effects (1.46 ± 0.07 and 1.30 ± 0.26 fold of induction, respectively). Similar effect (1.6-fold after two-day treatment) has been reported for higher concentration of phenobarbital (2 mM) in literature (Ramírez J, et al. *Pharmacogenet Genomics*. 2006 Feb;16(2):79-86).

E2007 induced expression of UGT1A4 mRNA to a lesser extent. E2007 (3 μ M) only had a small induction effect on UGT1A4 activity (1.32 ± 0.31 fold of vehicle control) compared to phenobarbital and rifampicin (1.90 ± 0.54 and 2.35 ± 0.80 fold, respectively). Similar induction effects for these positive controls have been reported in literature (Argikar UA, et al. *Xenobiotica*. 2009 Nov;39(11):826-35).

Since prototypical inducers examined in this study did not show induction effect on mRNA expression or activity of UGT1A6, UGT1A9 and UGT2B7, it is difficult to make definite conclusions about effects of E2007 on these enzymes.

Study GE-0258-G: Cellular Transport Study of E2007 Using MDR1 Expressing Cell (Study Period: November 4, 2005 - May 31, 2006)

Objective: to investigate whether E2007 is a substrate of MDRI or not. The effect of E2007 on digoxin transport mediated by MDRI was also investigated. The effect of E2007 on passive diffusion or paracellular transport was further investigated by using propranolol or mannitol.

Method: The permeability of ¹⁴C-E2007 across the MDR1 expressing cells (LLC-PK1-MDR1 cells) and control cells (porcine kidney epithelial LLC-PK1 cells) was examined to clarify the involvement of MDR1 in membrane permeation of E2007. LLC-PK1 and LLC-PK1-MDR1 cells were seeded at density of 4×10^4 cells/insert in plates (area: 0.3 cm² and pore size: 3 μ m), and grew for 7 or 8 days to prepare cell monolayers. When monolayers were formed, the apical (100 μ l) or basal side (600 μ l) was replaced with HBSS solution (pH 7.4) containing ¹⁴C-E2007 (1, 3, and 10 μ M), and the cells were

incubated at 37°C. After incubation for 1 and 2 hr, 50 µL of the HBSS solution was collected from the opposite compartment of that spiked with ¹⁴C-E2007 or reference compound. To compensate for the collection volume, 50 µL of pre-warmed HBSS was added immediately. After incubation for 4 hr, 50 µL of the HBSS solution was collected in the same way. The radioactivity of collected sample was measured using a liquid scintillation counter. The permeated amount of E2007 from the apical to basal side or the basal to apical side was determined.

To clarify the inhibitory effect of E2007 on MDR1, the digoxin transport mediated by MDR1 was examined in the absence or presence of E2007. In the plates seeded with LLC-PK1-MDR1 and LLC-PK1 cells, both apical and basal side was pre-incubated with HBSS solution containing E2007 (0, 1, 3, and 10 µM) or positive control (30µM Verapamil) for 1 h at 37°C prior to the incubation. Then, the apical (100 µl) or basal (600 µl) side was replaced with the model substrate ³H-digoxin (1 µM) plus E2007 (0, 1, 3, and 10 µM) or verapamil, and the cells were incubated at 37°C. After incubation for 2 h, 50 µL HBSS solution was collected from the opposite compartment of that spiked with ³H-digoxin, and the radioactivity was measured using a liquid scintillation counter. The permeated amount of ³H-digoxin from the apical to basal side or the basal to apical side was determined.

To more clarify the effect on digoxin transport, a higher concentration of E2007 (30 µM) was used. Furthermore the effect of E2007 on cellular transport was investigated by using ³H-propranolol (1 µM) or ¹⁴C-mannitol (1 µM) as a substrate for passive diffusion or paracellular transport. The effect of E2007 (0, 0.3, 1, 3, 10 and 30 µM) on transport of ³H-digoxin, ³H-propranolol or ¹⁴C-mannitol was examined with same procedure described above. Considering that 2-hr incubation might be too long to assess the initial velocity of the propranolol transport, the effect of E2007 on the ³H-propranolol transport was further examined after incubation for shorter times (20, 40 and 60 minutes).

Calculation of Cleared Volume: Permeated amounts across monolayers of LLC-PK1 and LLC-PK1-MDR1 were calculated from permeation concentration (concentration of the receiver side) of the test substance after incubation for the defined time multiplied by the volume.

Permeated amount from the apical to basal side: $X_{A \text{ to } B} = 600/50$

Permeated amount from the basal to apical side: $X_{B \text{ to } A} = 100/50$

Permeated amount at 1 h or 20 min after the start of incubation

= Radioactivity in the collected HBSS solution (50 µL) at 1 h or 20 min after the start of incubation (a) × $X_{A \text{ to } B}$ OR $X_{B \text{ to } A}$

Permeated amount at 2 h or 40 min after the start of incubation

= Radioactivity in the collected HBSS solution (50 µL) at 2 h or 40 min after the start of incubation (b) × $X_{A \text{ to } B}$ OR $X_{B \text{ to } A}$ + (a)

Permeated amount at 4 h or 60 min after the start of incubation

= Radioactivity in the collected HBSS solution (50 µL) at 4 h or 60 min after the start of incubation × $X_{A \text{ to } B}$ OR $X_{B \text{ to } A}$ + (a) + (b)

Cleared volume = Permeated amount / Initial concentration (µL/well)

$$\text{Cleared volume ratio} = \frac{\text{Basal to apical cleared volume}}{\text{Apical to basal cleared volume}}$$

The radioactive concentrations in the spiked compartment before the incubation (observed value) were used as the initial concentration.

Calculation of IC₅₀:

% of control was calculated from the cleared volume ratio of digoxin across LLC-PK1-MDR1 cells using the following equation,

$$\% \text{ of control} = \frac{\text{Cleared volume ratio in the presence of 0.3 to 30 } \mu\text{mol/L E2007} - 1}{\text{Cleared volume ratio in the absence of E2007} - 1} \times 100$$

IC₅₀ value of E2007 for MDR1-mediated digoxin transport was calculated using the following equation,

$$\% \text{ of control} = \frac{\text{IC}_{50}}{\text{IC}_{50} + I} \times 100$$

I: E2007 concentration

[Note: Herein, I_{max} seems to be assumed as 1, i.e, the function of MDR1 will be completely inhibited at the presence of high enough concentration of E2007.]

Results: As the results of examination of the permeability of ¹⁴C-E2007, the cleared volume ratios across LLC-PK1 cells after incubation for 2 h at 1 to 10 μM were 1.1 to 1.2. The ratios across the LLC-PK1-MDR1 cells were 1.2 to 1.4. There was no difference in the permeability of ¹⁴C-E2007 between the control cells and MDR1 expressing cells. Incubation time of 2 hr was chosen for calculation because permeation of ¹⁴C-E2007 showed linearity across both cells up to 2 h. In contrast, the ratios of digoxin were much higher in MDR1 expressing cells than control cells, as expected for a MDR1 substrate. These results suggest that E2007 is not a substrate of MDR1 (P-glycoprotein, P-gp).

Table 26. Cellular transport of ¹⁴C-E2007 across control cell and MDRI expressing cell monolayers

Compounds	Conc. (μmol/L)	Incubation time (h)	Control cells			MDR1 expressing cells		
			Apical to basal	Basal to apical	Cleared volume ratio	Apical to basal	Basal to apical	Cleared volume ratio
¹⁴ C-E2007	1	1	41.2 ± 2.9	39.8 ± 1.2	1.0	38.8 ± 3.2	44.8 ± 3.0	1.2
		2	64.0 ± 3.7	73.5 ± 3.2	1.1	59.6 ± 3.9	79.5 ± 6.4	1.3
		4	76.7 ± 2.9	116 ± 4	1.5	79.2 ± 5.1	126 ± 12	1.6
	3	1	39.4 ± 4.1	43.9 ± 2.3	1.1	40.9 ± 0.8	49.1 ± 1.6	1.2
		2	63.0 ± 0.8	76.3 ± 4.4	1.2	62.2 ± 1.9	86.0 ± 1.6	1.4
		4	80.5 ± 3.8	119 ± 6	1.5	81.2 ± 0.8	132 ± 3	1.6
	10	1	40.9 ± 3.8	43.5 ± 1.9	1.1	42.6 ± 1.3	42.7 ± 4.2	1.0
		2	65.7 ± 2.1	78.3 ± 1.4	1.2	64.4 ± 2.9	78.5 ± 4.5	1.2
		4	84.4 ± 2.3	119 ± 2	1.4	80.9 ± 1.3	124 ± 6	1.5
³ H-Digoxin	1	1	1.50 ± 0.23	1.89 ± 0.15	1.3	0.629 ± 0.102	11.3 ± 0.6	18.0
		2	2.95 ± 0.31	4.31 ± 0.28	1.5	1.19 ± 0.24	24.7 ± 1.8	20.8
		4	6.76 ± 0.41	12.2 ± 0.6	1.8	2.57 ± 0.37	50.6 ± 3.4	19.7
¹⁴ C-Mannitol	1	1	0.649 ± 0.278	0.718 ± 0.076	1.1	1.24 ± 0.80	1.04 ± 0.04	0.8
		2	0.873 ± 0.103	1.31 ± 0.07	1.5	2.08 ± 1.08	2.26 ± 0.34	1.1
		4	2.67 ± 0.57	2.78 ± 0.32	1.0	4.06 ± 0.96	4.96 ± 0.45	1.2

Each value represents the mean ± SD of three samples.

For the inhibitory effect of E2007 on digoxin transport mediated by MDR1, the cleared volume ratio of digoxin decreased with increase of E2007 concentration. Therefore, E2007 has an inhibitory effect on digoxin transport mediated by MDR1 and the IC₅₀ value was estimated as 12.8 μM.

Reviewer's Comment: Using PK parameters from the Phase 1 population PK analysis (study CPMS-E2007-2011-002) for E2007 given under fasting conditions, a steady-state C_{max} of 661 ng/mL (i.e, 1.89 μM) is simulated for E2007 administered as 8 mg once daily, i.e., the recommended maintenance dose. Based on this estimated C_{max}, the [I]₁/IC₅₀ ratio is estimated as 0.15, just slightly higher than a cut-off value of 0.1. The gut concentration of E2007 is estimated as [I]₂= Dose of inhibitor (in mol)/250 mL. A dose of 8 mg E2007 results an [I]₂ of 91 μM. The [I]₂/IC₅₀ ratio is 7.1, less than a cut-off value of 10. Overall, these estimates suggest a low potential of clinically significant P-gp inhibition by E2007.

Table 27. Inhibitory effect of E2007 on the Digoxin transport across control cell and MDR1 expressing cell monolayers

Compounds	Conc. (μmol/L)	Control cells			MDR1 expressing cells		
		Apical to basal	Basal to apical	Cleared volume ratio	Apical to basal	Basal to apical	Cleared volume ratio
Inhibitor (-)	0	2.46 ± 0.20	3.37 ± 0.48	1.4	1.28 ± 0.05	23.4 ± 1.4	18.3
E2007	1	2.49 ± 0.10	3.34 ± 0.27	1.3	1.29 ± 0.04	24.1 ± 1.0	18.7
	3	3.46 ± 0.12	3.54 ± 0.18	1.0	1.88 ± 0.22	24.0 ± 0.5	12.8
	10	3.66 ± 0.20	3.81 ± 0.24	1.0	2.94 ± 0.36	22.1 ± 1.1	7.5
Verapamil	30	4.03 ± 0.16	4.03 ± 0.18	1.0	5.58 ± 0.28	10.5 ± 0.8	1.9
¹⁴ C-Mannitol	1	0.995 ± 0.587	1.39 ± 0.12	1.4	1.58 ± 0.43	2.89 ± 0.33	1.8

Each value represents the mean ± SD of three samples.

Compound	Conc. (μmol/L)	Control cells			MDR1 expressing cells		
		Apical to basal	Basal to apical	Cleared volume ratio	Apical to basal	Basal to apical	Cleared volume ratio
E2007	0	2.51 ± 0.30	3.33 ± 0.10	1.3	1.18 ± 0.25	21.2 ± 2.3	18.0
	0.3	2.31 ± 0.19	3.76 ± 0.28	1.6	0.913 ± 0.111	20.3 ± 1.7	22.2
	1	2.77 ± 0.22	4.69 ± 2.06	1.7	1.04 ± 0.12	21.5 ± 1.5	20.7
	3	3.12 ± 0.07	2.99 ± 0.32	1.0	1.11 ± 0.14	22.4 ± 1.0	20.2
	10	3.70 ± 0.41	4.60 ± 0.32	1.2	2.28 ± 0.24	18.1 ± 0.4	7.9
	30	4.30 ± 0.18	4.94 ± 0.41	1.1	4.04 ± 0.26	14.0 ± 0.1	3.5

Each value represents the mean ± SD of three samples.

The basal to apical and apical to basal permeation of ³H-propranolol and ¹⁴C-mannitol across both cells were not significantly changed by E2007. Though the apical to basal cleared volumes of propranolol in LLC-PK1-MDR1 cells tended to decrease with increase of E2007 concentration, and the cleared volumes of mannitol from the apical to basal side in MDR1 expressing cells tended to increase with increase of E2007 concentration, these changes were small and the cleared volume ratios of ³H-propranolol and ¹⁴C-mannitol in both control and the MDR1 expressing cells were almost constant at E2007 concentrations between 0 to 30 μM. Overall, these results suggest that E2007 does not affect passive diffusion or paracellular transport of compounds.

Table 28. Influence of E2007 to Propranolol permeation

Compound	Conc. (μmol/L)	Control cells			MDR1 expressing cells		
		Cleared volume (μL/well)		Cleared volume ratio	Cleared volume (μL/well)		Cleared volume ratio
		Apical to basal	Basal to apical		Apical to basal	Basal to apical	
E2007	0	34.3 ± 0.8	30.0 ± 0.8	0.9	28.3 ± 2.4	21.9 ± 0.7	0.8
	0.3	32.0 ± 1.0	30.6 ± 2.2	1.0	27.7 ± 0.6	20.5 ± 1.9	0.7
	1	32.5 ± 1.7	29.3 ± 1.3	0.9	26.2 ± 0.3	18.3 ± 3.1	0.7
	3	29.5 ± 1.4	28.7 ± 0.3	1.0	26.7 ± 0.2	23.3 ± 3.1	0.9
	10	31.1 ± 2.0	31.0 ± 2.4	1.0	25.3 ± 1.9	19.7 ± 0.2	0.8
	30	31.5 ± 0.7	32.3 ± 1.0	1.0	24.9 ± 0.4	21.3 ± 2.2	0.9

Each value represents the mean ± SD of three samples.

Table 29. Influence of E2007 to Mannitol permeation

Compound	Conc. (μmol/L)	Control cells			MDR1 expressing cells		
		Cleared volume (μL/well)		Cleared volume ratio	Cleared volume (μL/well)		Cleared volume ratio
		Apical to basal	Basal to apical		Apical to basal	Basal to apical	
E2007	0	1.84 ± 0.59	1.29 ± 0.08	0.7	2.05 ± 0.08	2.58 ± 0.04	1.3
	0.3	1.62 ± 0.85	1.21 ± 0.21	0.7	2.28 ± 0.19	2.57 ± 0.21	1.1
	1	1.52 *	1.36 ± 0.35	0.9	2.25 ± 0.62	3.07 ± 0.52	1.4
	3	1.96 ± 1.18	1.47 ± 0.21	0.8	2.53 ± 0.02	2.86 ± 0.07	1.1
	10	1.85 ± 0.33	1.22 ± 0.07	0.7	3.25 ± 1.91	2.25 ± 0.80	0.7
	30	1.80 ± 0.60	1.35 ± 0.25	0.8	3.13 ± 0.67	3.36 ± 0.60	1.1

Each value represents the mean ± SD of three samples.

*: Mean value of duplicate

Study DMPKT2011-002: Transport of E2007 across Human Breast Cancer Resistance Protein (BCRP)-Expressed Cell Monolayer and the Inhibition Potency of E2007 on BCRP (Study Period: Sep 1, 2010 - Jan 25, 2011)

Objective: to clarify whether E2007 is a substrate and/or inhibitor of BCRP

Method: BCRP- and vector-transfected MDCKII cells were seeded in the apical side of 24-well transwell insert system with 100 μL of the culture medium at density of 1.4×10^5 cells/well, and 600 μL of medium was added to the basal side (Day 1). Transcellular transport studies were conducted on Day 7. Transport of E2007, 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP, 1 μM , a typical BCRP substrate), and Lucifer Yellow (30 μM , a paracellular marker) was determined in the apical to basal (A to B) and basal to apical (B to A) directions across BCRP- and vector-MDCKII cell monolayers at 37 $^{\circ}\text{C}$ for 2 hours. E2007 and PhIP were subject to LC/MS/MS analyses, while Lucifer Yellow was measured with a plate reader. Flux ratio, which is the ratio of B to A transport to A to B transport of a tested compound, was used as an index of transport activity of BCRP.

$$\text{Flux ratio} = \frac{P_{\text{app}}(\text{A to B})}{P_{\text{app}}(\text{B to A})} \quad \text{CFR} = \frac{\text{Flux ratio in BCRP}}{\text{Flux ratio in vector}} \quad (\text{CFR: corrected flux ratio})$$

To examine the inhibitory effect of E2007 on BCRP, transcellular transport of PhIP (1 μM) across BCRP- and vector-MDCKII cell monolayers was examined at 37 $^{\circ}\text{C}$ for 2 hours in the presence and absence of E2007 (0, 0.1, 1, 10, and 100 μM). Data were presented as % of control,

$$\% \text{ of control} = \frac{(\text{Flux ratio in BCRP}) - (\text{Flux ratio in vector})}{(\text{Flux ratio in BCRP}_{\text{control}}) - (\text{Flux ratio in vector}_{\text{control}})} \times 100$$

where Flux ratios in BCRP and in vector represent flux ratios of PhIP with E2007 in BCRP- and vector-MDCKII cells, respectively. Flux ratios in BCRP_{control} and in vector_{control} represent flux ratios of PhIP without E2007 in BCRP- and vector-MDCKII cells, respectively. IC₅₀ of E2007 for BCRP was determined using the following equation,

$$\% \text{ of control} = \frac{1}{1 + \left(\frac{I}{\text{IC}_{50}} \right)} \times P$$

where I represents concentrations of E2007. The initial estimate of P was set to be 100%.

Results: Papp values of a paracellular marker, Lucifer Yellow, ranged from 0.32 to 2.29 $\times 10^{-6}$ cm/s, indicating that cell monolayer integrities were adequate throughout the studies. Flux ratio of E2007 in BCRP-MDCKII cells was 0.84, almost same as that in vector-MDCKII cells (0.89), and CFR of E2007 was close to unity (0.94). In contrast, flux ratio of PhIP was approximately 30-fold greater in BCRP-MDCKII cells than that in vector-MDCKII cells. These results indicated that E2007 was not a substrate of BCRP. In addition, E2007 has a relative high passive permeability (23.68 – 29.68 $\times 10^{-6}$ cm/sec), indicating that its transport is less likely to be limited by transporter.

Table 30. Transcellular Transport of PhIP and E2007 across BCRP- and Vector-MDCKII Cell Monolayers

Substrate ($\mu\text{mol/L}$)	BCRP-MDCKII cells			Vector-MDCKII cells			CFR
	$P_{\text{app}} (\times 10^{-6} \text{ cm/s})$		Flux ratio	$P_{\text{app}} (\times 10^{-6} \text{ cm/s})$		Flux ratio	
	A to B	B to A		A to B	B to A		
PhIP (1)	0.73	24.92	34.14	12.40	14.27	1.15	29.69
E2007 (1)	28.09	23.68	0.84	29.68	26.41	0.89	0.94

E2007 inhibited BCRP-mediated PhIP transport in a concentration-dependent manner with the IC_{50} of 18.5 μM . No positive control of inhibitor (i.e, known BCRP inhibitor) was included in this study.

Table 31. Inhibitory Effect of E2007 on BCRP-mediated PhIP Transport

Substrate ($\mu\text{mol/L}$)	Inhibitor ($\mu\text{mol/L}$)	BCRP-MDCKII cells			Vector-MDCKII cells			$(\text{FR}_{\text{BCRP}})$ $-(\text{FR}_{\text{vector}})$	% of control
		$P_{\text{app}} (\times 10^{-6} \text{ cm/s})$		FR	$P_{\text{app}} (\times 10^{-6} \text{ cm/s})$		FR		
		A to B	B to A		A to B	B to A			
PhIP (1)	-	1.03	22.64	21.98	12.73	11.34	0.89	21.09	100.0
PhIP (1)	E2007 (0.1)	0.72	22.50	31.25	11.61	12.78	1.10	30.15	143.0
PhIP (1)	E2007 (1)	0.78	22.74	29.15	11.04	13.78	1.25	27.90	132.3
PhIP (1)	E2007 (10)	1.45	24.17	16.67	12.13	13.18	1.09	15.58	73.9
PhIP (1)	E2007 (100)	2.74	18.69	6.82	12.75	12.21	0.96	5.86	27.8

Reviewer's Comment: As mentioned previously, steady-state plasma C_{max} of E2007 after doses of 8 mg is estimated to be 1.89 μM , resulting in an $[\text{I}]_1/\text{IC}_{50}$ ratio of 0.10, on the border of a cut-off value of 0.1. The $[\text{I}]_2/\text{IC}_{50}$ ratio is 4.9, below the cut-off value of 10. Thus, E2007 is not expected to significantly inhibit BCRP *in vivo*.

Study GE-0404-G: Transport Study of E2007 Using OATP1B1 and OATP1B3 Expressing Oocytes (Study Period: February 1, 2007 - June 27, 2007)

Objective: Transport study of E2007 was conducted using human organic anion transporting polypeptides (OATP1B1 and OATP1B3) expressing oocytes to assess whether E2007 is a substrate or inhibitor of OATP1B1 and OATP1B3.

Method: OATP1B1 and OATP1B3 expressing oocytes, and control oocytes were mixed with 150 μL Na^+ buffer (pH 7.4) containing 1 μM ^{14}C -E2007, and the mixtures were incubated at room temperature for 30, 60, and 120 min. After incubation for the designated periods, the oocytes were collected and dissolved with a solubilizer. The radioactivity was measured using a liquid scintillation counter to determine uptake amount of E2007, and the cleared volume was calculated as

$$\text{Cleared volume} = \text{Uptake amount into oocyte (dpm)} / \text{Initial concentration (dpm}/\mu\text{L)}$$

Transporter-mediated cleared volume = Cleared volume in oocyte expressing transporter
– Mean cleared volume in control Oocytes

To clarify the inhibitory effect of E2007 on OATP1B1 and OATP1B3, ³H-estrone 3-sulfate sodium (³H-E3S, 50 nM) transport mediated by OATP1B1 and ³H-β-estradiol-17β-D-glucuronide sodium (³H-E₂G, 50 nM) transport mediated by OATP1B3 were examined in the absence or presence of E2007. OATP1B1 and OATP1B3 expressing oocytes, and control oocytes were mixed with Na⁺ buffer solutions containing each substrate and E2007 (0, 0.3, 3, and 30 μM) or rifampicin (100 μM, as positive control). The mixtures were incubated at room temperature for 60 min, then the oocytes were collected and dissolved with a solubilizer. The radioactivity was measured using a liquid scintillation counter to determine uptake amounts of E3S and E₂G, and the cleared volumes were calculated. Data were presented as % of control.

$$\% \text{ of control} = \frac{\text{Transporter-mediated cleared volume in the presence of the test substance}}{\text{Transporter-mediated cleared volume in the absence of the test substance}} \times 100$$

Results: No significant difference was observed in ¹⁴C-E2007 uptake between the OATP1B1 or OATP1B3 expressing oocytes and control oocytes. In contrast, after incubation of ³H-E3S with the OATP1B1 expressing oocytes and control oocytes for 60 min, the cleared volumes were 4.30 and 0.0216 μL/oocyte, respectively. The cleared volumes of ³H-E₂G the OATP1B3 expressing oocytes and control oocytes were 0.412 and 0.00631 μL/oocyte, respectively. These results suggest that ¹⁴C-E2007 is not a substrate of OATP1B1 or OATP1B3. The uptake of ¹⁴C-E2007 into control oocytes was much higher than that of positive reference compounds, supporting that the passive diffusion is a main permeation mechanism of ¹⁴C-E2007.

Table 32. Uptake of ¹⁴C-E2007 in OATP1B1 and OATP1B3 expressing oocyte and control Oocyte

	Cleared volume (μL/oocyte)					
	30 min		60 min		120 min	
	mean	S.E.	mean	S.E.	mean	S.E.
Control	3.57	0.34	4.68	0.48	6.85	1.14
OATP1B1	3.23	0.31	4.90 ^a	0.39	6.63	0.82
OATP1B3	3.78	0.33	5.02	0.59	7.13	0.88

The ³H-E3S transport by OATP1B1 in the presence of E2007 at 0.3, 3, and 30 μM was 94.7%, 101.3%, and 79.0% of control, respectively. The ³H-E₂G transport by OATP1B3 was 75.1%, 77.7%, and 144.7% of control in the presence of 0.3, 3, and 30 μM E2007, respectively. In another experiment, the ³H-E₂G transport by OATP1B3 at E2007 concentrations of 0.3, 1, 3, 10, and 30 μM was 83.8%, 109.5%, 110.8%, 109.5%, and 88.9% of control, respectively. In contrast, positive reference compound rifampicin, a known inhibitor of OATP1B1 and OATP1B3, greatly inhibited transport of ³H-E3S and ³H-E₂G. These results suggested that E2007 did not inhibit OATP1B1 or OATP1B3.

Table 33. Inhibitory effect of E2007 on the ³H-Estrone sulfate uptake in OATP1B1 expressing oocyte and control Oocyte

Substrate	Inhibitor		Cleared volume (μL/oocyte)			
	Compound	Concentration (μmol/L)	Control		OATP1B1	
			mean	S.E.	mean	S.E.
³ H-Estrone sulfate	E2007	0	0.0222	0.0032	5.31	0.81
		0.3	0.0290	0.0066	5.04	0.88
		3	0.0416 ^a	0.0080	5.40	0.75
		30	0.0650	0.0068	4.25	0.83
	Rifampicin	100	0.0196	0.0024	1.36	0.28

Values are mean and S.E. of eight oocytes determination. (a: n=7)

Table 34. Inhibitory effect of E2007 on the ³H-Estradiol 17β-D-glucuronide uptake in OATP1B3 expressing oocyte and control oocyte

Substrate	Inhibitor		Cleared volume (μL/oocyte)			
	Compound	Concentration (μmol/L)	Control		OATP1B3	
			mean	S.E.	mean	S.E.
³ H-Estradiol 17β-D-glucuronide	E2007	0	0.00911	0.00120	0.206	0.033
		0.3	0.00831	0.00199	0.156	0.034
		3	0.00866	0.00187	0.162	0.080
		30	0.00817	0.00134	0.293 ^a	0.093
	Rifampicin	100	0.00386	0.00146	0.0262	0.0120

Substrate	Inhibitor		Cleared volume (μL/oocyte)			
	Compound	Concentration (μmol/L)	Control		OATP1B3	
			mean	S.E.	mean	S.E.
³ H-Estradiol 17β-D-glucuronide	E2007	0	0.0077	0.0021	0.303	0.029
		0.3	0.0117 ^a	0.0028	0.260	0.043
		1	0.0106	0.0010	0.334	0.027
		3	0.0192	0.0108	0.348	0.050
		10	0.00931	0.00171	0.333	0.042
		30	0.00973	0.00120	0.272	0.045
	Rifampicin	100	0.0106	0.0019	0.0408	0.0066

Values are mean and S.E. of eight oocytes determinations. (a: n=7)

In conclusion, E2007 is not a substrate or inhibitor of OATP1B1 or OATP1B3.

Study B06015: Characterization of E2007 Transport via Human Organic Anion and Organic Cation Transporters (Study Period: March 1, 2007 - September 28, 2007)

Objective: to evaluate the transport of E2007 mediated by human organic anion transporter 1 (hOAT1), hOAT2, hOAT3, hOAT4, and human organic cation transporter 1 (hOCT1), hOCT2 and hOCT3. In addition, inhibitory effect of E2007 on these transporters was examined.

Method: hOAT1-, hOAT2-, hOAT3-, hOAT4-, hOCT1-, hOCT2- and hOCT3-expressing cells (mice proximal tubular S2 cells transfected with vectors containing hOAT1, hOAT2, hOAT3, hOAT4, hOCT1, hOCT2 and hOCT3 cDNA, respectively) and mock cells (S2 cells transfected with vectors) were used. In uptake studies, the positive controls (known substrates of transporters) used for transport activities were [¹⁴C]*p*-aminohippuric acid (PAH), [³H]prostaglandin F2 α (PGF2 α), [³H]estrone sulfate (ES), [¹⁴C]tetraethylammonium (TEA), and [³H]histamine for OAT1, OAT2, OAT3 and OAT4, OCT1 and OCT2, and OCT3, respectively. In inhibition studies, unlabeled PAH, PGF2 α , ES, TEA, and histamine were used for positive controls (inhibitors for transporters).

Cells were seeded in 24-well culture plate with 1 mL of culture medium at density of 2 x 10⁵ cells/well on 2 days before uptake and inhibition studies. On the third day after seeding cells, uptake of ¹⁴C-E2007 and marker substrates into the cells was evaluated in triplicate. Cells were pre-incubated with DPBS (Dulbecco's phosphate buffered saline) solution at 37°C for 10 min. DPBS solution consists of NaCl (137 mmol/L), KCl (3 mmol/L), Na₂HPO₄ (8 mmol/L), KH₂PO₄ (1 mmol/L), MgCl₂ (0.5 mmol/L) and CaCl₂ (1 mmol/L). DPBS solution was then replaced with 400 μ L of radiolabeled substrate-containing dosage solution and incubated for 1, 5, 10 and 30 min at 37°C. At designated times, dosage solution was aspirated immediately, and cells were washed twice with ice cold DPBS solution to terminate the uptake. Cells were solubilized and radioactivity associated with cells was determined by liquid scintillation counter. Radioactivity in dosage solutions was also determined. Aliquots of neutralized cell lysate was used to determine the protein concentration by BCA Protein Assay Kit.

Uptake was calculated following equation:

$$\text{Uptake (}\mu\text{L/mg protein)} = \frac{\text{Radioactivity associated with cells (dpm}/\mu\text{L)}}{\text{Radioactivity concentration in dosage solution (dpm}/\mu\text{L)} \times \text{Protein concentration (mg protein}/\mu\text{L)}}$$

For inhibition studies, similar procedures were applied. Incubation time was set to be in the linear condition of the uptake for each marker substrate (1 min for OAT2, OAT4, OCT2 and OCT3, 5 min for OAT1 and OAT3, and 10 min for OCT1), and cells were incubated with buffer containing radiolabeled substrates in the presence and absence of E2007 (0, 1, 10 and 30 μ M). The data were shown as % of control calculated by using following equation:

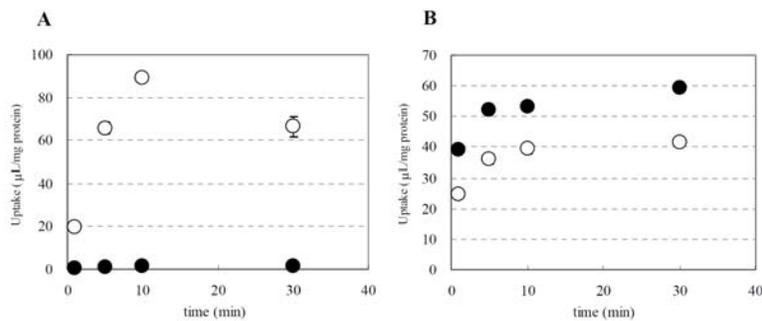
$$\% \text{ of control} = \frac{\text{Mean of CL}_{\text{uptake, OAT/OCT+I}} \text{ (}\mu\text{L/mg protein/min)} - \text{Mean of CL}_{\text{uptake, mock+I}} \text{ (}\mu\text{L/mg protein/min)}}{\text{Mean of CL}_{\text{uptake, OAT/OCT}} \text{ (}\mu\text{L/mg protein/min)} - \text{Mean of CL}_{\text{uptake, mock}} \text{ (}\mu\text{L/mg protein/min)}} \times 100$$

Mean of uptake clearances were determined by dividing uptake value by incubation time in OAT- or OCT-expressing cells in the presence (+I) or absence of E2007. Inhibition constant (K_i) of E2007 was determined by least-squares regression analysis using the following equation:

$$\% \text{ of control} = \frac{I}{1 + \frac{I}{K_i}} \times 100$$

Results: The uptake of typical substrates was greater in transporter-expressing cells than that in mock cells, confirming the presence of transport activities. In contrast, the uptake of E2007 in transporter-expressing cells was not greater than that in mock cells, indicating that E2007 is not a substrate of OAT1, OAT2, OAT3, OAT4, OCT1, OCT2 or OCT3.

Figure 1. Time profiles of the uptake of [¹⁴C]PAH (3 μM) and ¹⁴C-E2007 (3 μM) by hOAT1-expressing cells and mock cells



Open circles represent transporter-expressing cells. Closed circles designate mock cells. Panel A shows the result for typical substrate of the transporter evaluated (positive control). Panel B represents the data for E2007. Each point represents the mean ± S.E.M. These legend apply to the below figures (Fig 2 – 7).

Figure 2. Time profiles of the uptake of [³H]PGF2α (0.03 μM) and ¹⁴C-E2007 (3 μM) by hOAT2-expressing cells and mock cells

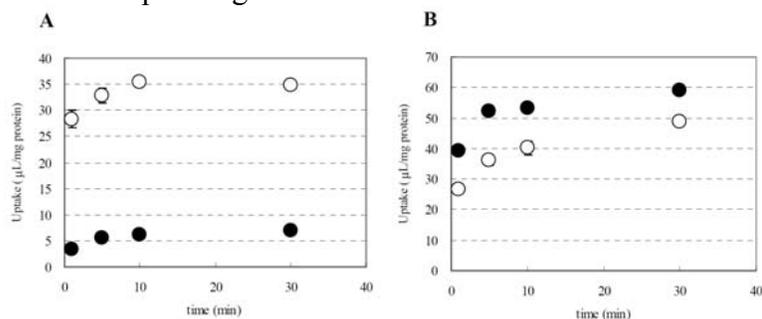


Figure 3. Time profiles of the uptake of [³H]ES (0.1 μM) and ¹⁴C-E2007 (3 μM) by hOAT3-expressing cells and mock cells

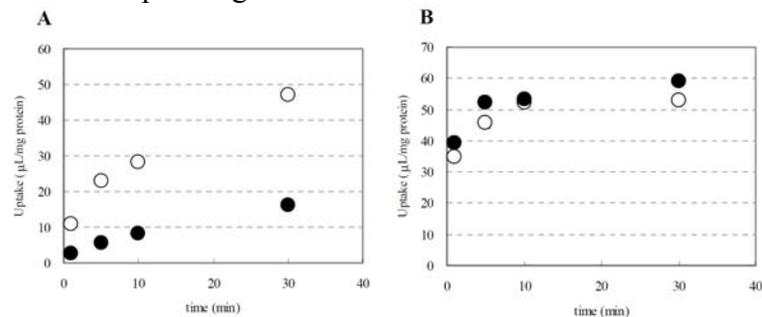


Figure 4. Time profiles of the uptake of [³H]ES (0.1 μM) and ¹⁴C-E2007 (3 μM) by hOAT4-expressing cells and mock cells

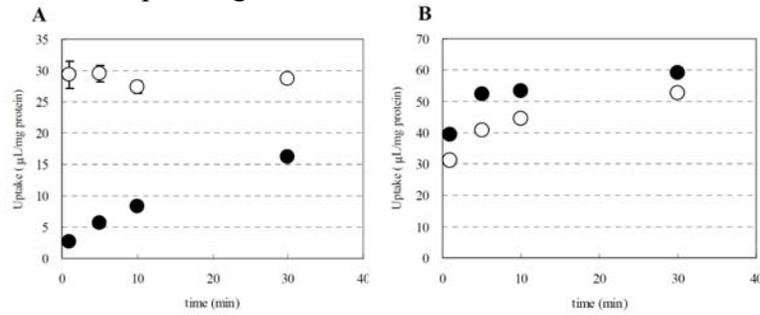


Figure 5. Time profiles of the uptake of [¹⁴C]TEA (5 μM) and ¹⁴C-E2007 (3 μM) by hOCT1-expressing cells and mock cells

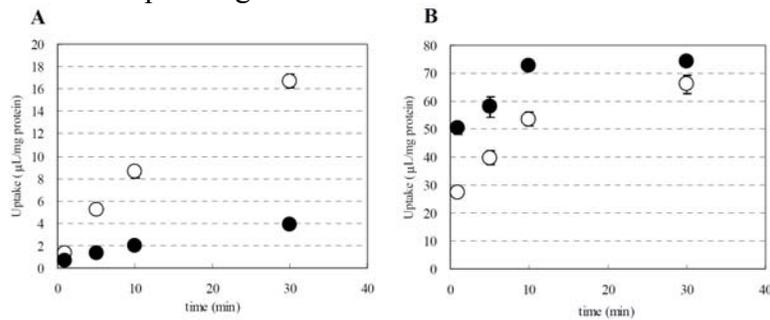


Figure 6. Time profiles of the uptake of [¹⁴C]TEA (5 μM) and ¹⁴C-E2007 (3 μM) by hOCT2-expressing cells and mock cells

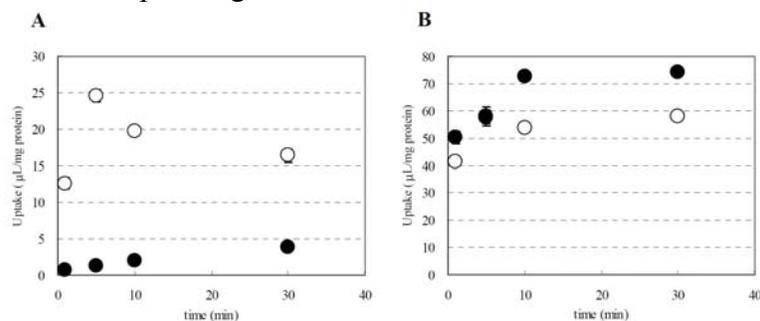
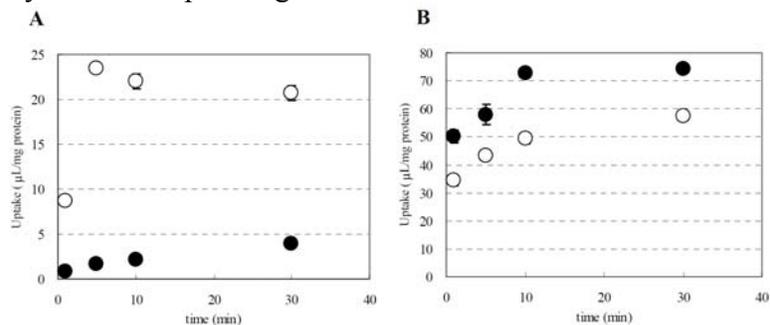
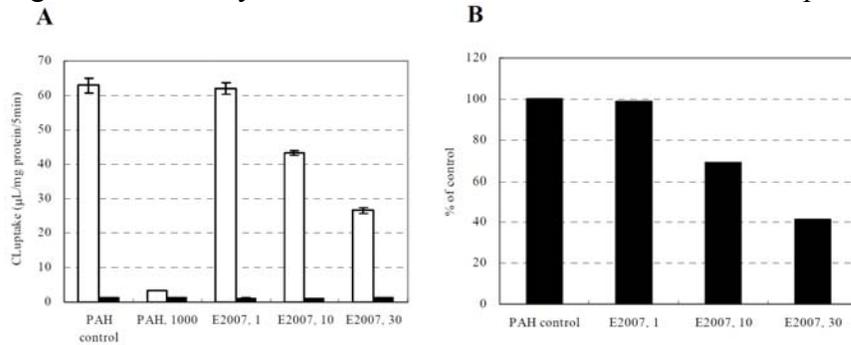


Figure 7. Time profiles of the uptake of [³H]Histamine (0.1 μM) and ¹⁴C-E2007 (3 μM) by hOCT3-expressing cells and mock cells



E2007 showed slight or no inhibition on OAT4 and OCT2. E2007 inhibited OAT1, OAT3, OCT1 and OCT3 in a concentration dependent manner, and OAT3 was the most sensitive to E2007 among them. K_i value of E2007 for OAT1, OAT3, OCT1 and OCT3 was calculated to be 21.9 ± 1.3 , (estimate value \pm S.D.), 8.5 ± 0.8 , 18.2 ± 3.6 and 40.5 ± 6.1 μ M, respectively. E2007 stimulated OAT2-mediated transport in a concentration dependent manner with approximately 140, 220 and 250% of control in the presence of 1, 10 and 30 μ M E2007, respectively.

Figure 8. Inhibitory effect of E2007 on the hOAT1-mediated uptake of [14 C]PAH (3 μ M)



Panel A: Open bars represent transporter-expressing cells. Closed bars designate mock cells. Excessive amount of unlabeled typical substrate was used as positive control for inhibitor of the transporter evaluated. Each bar represents the mean \pm S.E.M. (n = 3). Panel B: Inhibitory effect of E2007 on the transporter-mediated uptake of the typical substrate, expressed as percent of control. The legends apply to the rest figures (Fig 9 – 14).

Figure 9. Inhibitory effect of E2007 on the hOAT2-mediated uptake of [3 H]PGF2 α (0.03 μ M)

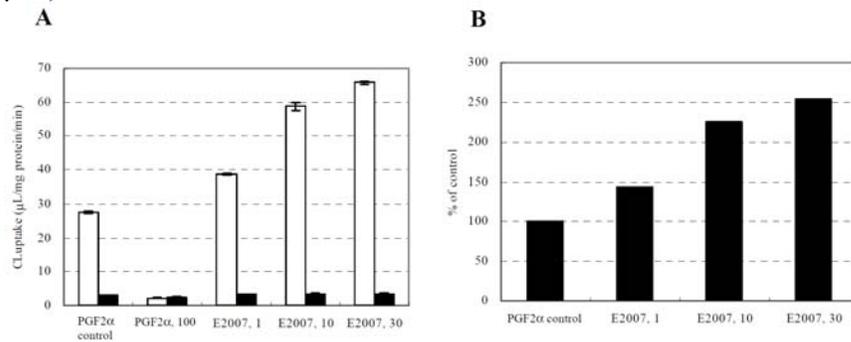


Figure 10. Inhibitory effect of E2007 on the hOAT3-mediated uptake of [3 H]ES (0.1 μ M)

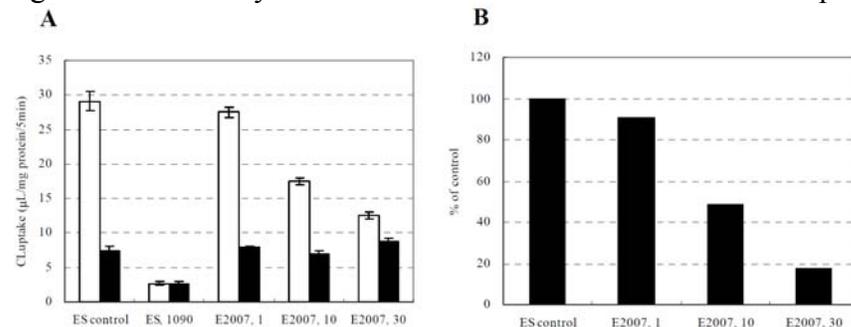


Figure 11. Inhibitory effect of E2007 on the hOAT4-mediated uptake of [³H]ES (0.1 μM)

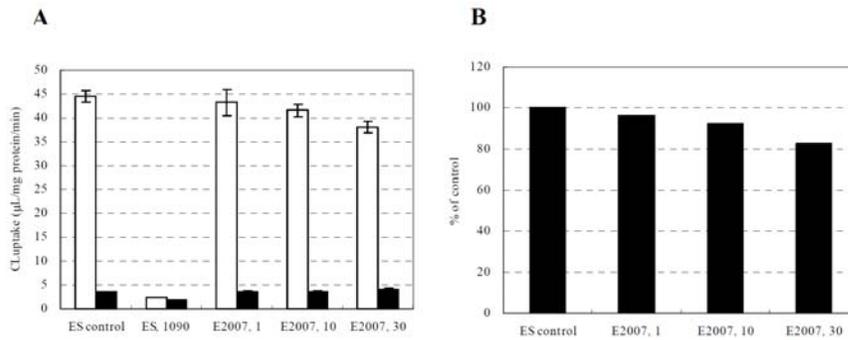


Figure 12. Inhibitory effect of E2007 on the hOCT1-mediated uptake of [¹⁴C]TEA (5 μM)

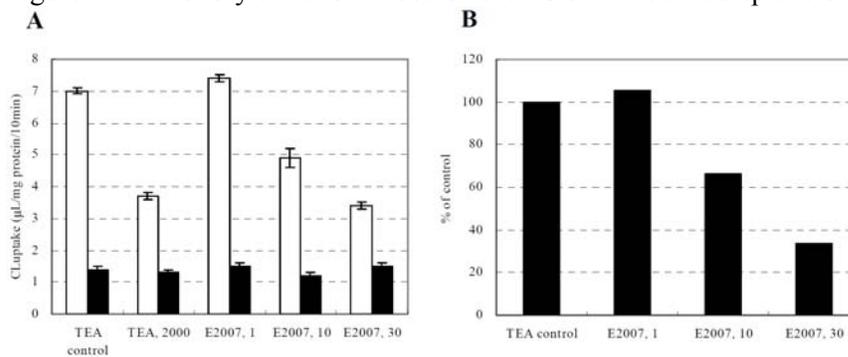


Figure 13. Inhibitory effect of E2007 on the hOCT2-mediated uptake of [¹⁴C]TEA (5 μM)

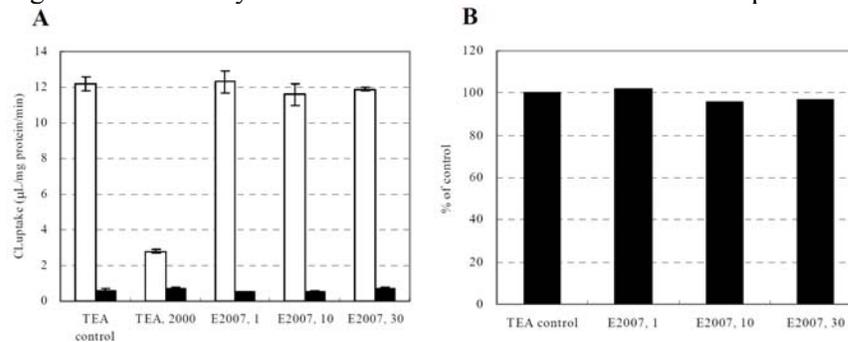
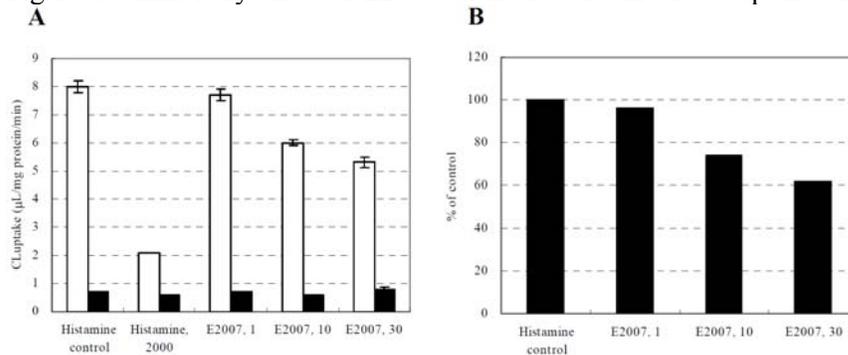


Figure 14. Inhibitory effect of E2007 on the hOCT3-mediated uptake of [³H]Histamine (0.1 μM)



Reviewer's Comment: In conclusion, E2007 is not a substrate of OAT1, OAT2, OAT3, OAT4, OCT1, OCT2 and OCT3. E2007 inhibits OAT1, OAT3, OCT1 and OCT3, with the lowest K_i value estimated for OAT3. Per the current Drug-Drug Interaction Guidance (draft, 2012 version), a cut-off value of 0.1 is applied to unbound C_{max}/IC_{50} ratio when assessing the inhibitory effect of a compound on OAT and OCT transporters. As mentioned earlier, a steady-state C_{max} of 661 ng/mL (i.e, 1.89 μ M) was predicted for E2007 given as 8 mg once daily after titration. The protein binding of E2007 was determined as 95.3-95.8%. Thus, the unbound C_{max} is about 0.09 μ M, much lower than 8.5 μ M. Therefore, E2007 is unlikely to inhibit OAT1, OAT3, OCT1 and OCT3 *in vivo*. E2007 stimulates OAT2 activity at concentrations of 1 μ M or above. Since the unbound concentration of E2007 is much lower, E2007 possess a minimal potential for increasing OCT2-mediated clearance in clinical setting.

4.4.2. Individual Study Review for *In Vivo* Studies

Study E2007-E044-001: Ascending single dose safety and tolerability study of E2007 in healthy male volunteers

Objective	<i>Primary objective:</i> To evaluate preliminary safety and tolerability of E2007 <i>Secondary objective:</i> To determine the pharmacokinetic profile of E2007		
Study Design	<p>This was a randomized, double-blind, placebo-controlled, sequential ascending single-dose study. E2007 was administered in the morning under fasted state.</p> <p>Group 1 – 0.2 mg E2007 (2 x 0.1 mg E2007 tablets) or placebo Group 2 – 0.5 mg E2007 (5 x 0.1 mg E2007 tablets) or placebo Group 3 – 1 mg E2007 (1 x 1 mg E2007 tablets) or placebo Group 4 – 2 mg E2007 (2 x 1 mg E2007 tablets) or placebo Group 5 – 4 mg E2007 (4 x 1 mg E2007 tablets) or placebo Group 6 – 8 mg E2007 (3 x 1 mg and 1 x 5 mg E2007 tablets) or placebo Group 7 – 15mg E2007 (3 x 5mg E2007 tablets) or placebo</p> <p><i>Note:</i> Following the safety assessment for Group 6 subjects (8 mg), the sponsor requested that Group 7 subjects should receive 6 mg E2007 or placebo rather than the planned 15 mg dose, as there were symptoms of light-headedness, dizziness or drowsiness reported by 5 of the 8 subjects at the 8 mg dose level.</p>		
Study Population	55 healthy male volunteers (age: 18-45 yr, weight: 58-93 kg, Race: 45 out of 55 Caucasians) were screened and randomized, with 6 subjects given E2007 and 2 subjects receiving placebo in each dose group (except in group 7 where 1 subject receiving placebo)		
PK & PD measurements	<p><i>Blood samples:</i> pre-dose and at 0.125, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 30, 36, 48, 72, 96 and 120 hours after drug administration. An additional timepoint of 168 hr post-dose was added for Groups 4 to 7 as amendment.</p> <p><i>Urine samples:</i> were collected at -1 hr predose-0, 0-6, 6-12, 12-24, 24-36, 36-48 hr post-dose.</p> <p><i>Pharmacodynamic:</i> The following procedures were performed pre-dose on Day 1 and at 2, 4, 8, 12, 24 and 30 hours post-dose: measurement of saccadic eye movements, Bond & Lader visual-analogue mood scale (VAMS), body sway, simple reaction time, choice reaction time and digit vigilance</p>		
Bioanalytical Method	Analyze	E2007 (plasma)	E2007 (urine)
	Method	HPLC-Fluorescence	HPLC-Fluorescence
	Internal Std.	(b) (4)	(b) (4)
	LOQ (ng/mL)	0.256	0.25
	Calibration Range (ng/mL)	0.256, 0.512, 2.05, 5.12 10.25, 51.2, 102.5	0.25, 0.5, 1.0, 5.0, 10, 50, 100
	QC (ng/mL)	0.72, 8.05, 80.5	0.72, 40.9, 81.8
	Accuracy	92 – 108.4%	93.7 – 112.7%
	Precision	0.6 – 4.6%	0.7 – 4.5%
PK & PD Assessments	PK parameters: C _{max} , t _{max} , λ _z , t _{1/2} , AUC _{0-t} , AUC ₀₋₄₈ , AUC _{0-∞} , Ae ₀₋₄₈ , CL _R , Vz/F and CL/F		

	PD parameters: peak saccadic velocity (PSV) and percentage failed saccades were determined for saccadic eye movements. Sub-scores for anxiety, sedation and dysphoria were calculated from the VAMS.
Safety Assessments	12-lead ECG, vital signs, laboratory safety tests, adverse events, physical and neurological examination
PK & PD Results	E2007

E2007 PK

E2007 was rapidly absorbed (median Tmax ranging from 0.5 – 1 hr). After reaching Cmax, E2007 concentrations declined in a multi-phasic manner, with a long terminal t1/2 (mean: 50 to 125 hr; harmonic mean: 40 to 95 hr). Oral clearance was low (11.7 – 18.7 mL/min) and apparent volume of distribution ranged from 51 to 96 L. Elimination of E2007 by the renal route was minimal, with < 0.12% of the dose excreted as unchanged drug into urine after 48 hours. Cmax and AUC of E2007 roughly increased in a dose-proportional manner within the dose range studied.

Figure 1. Mean (+SD) Plasma E2007 Profiles (0-48 hours) (linear scale)

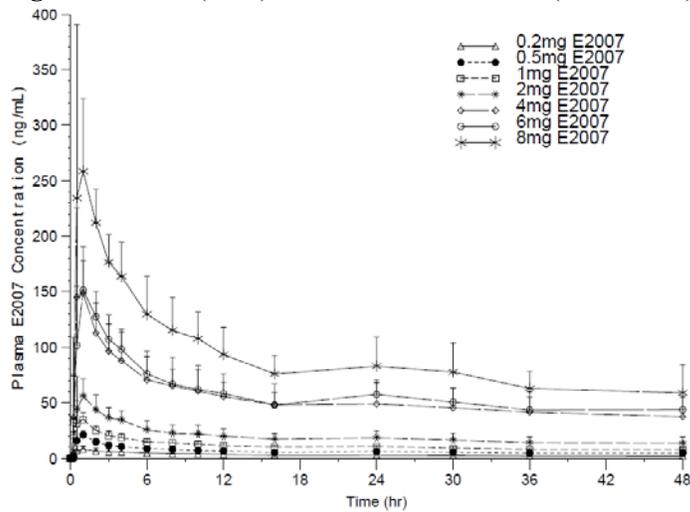


Figure 2. Mean (+SD) Plasma E2007 Profiles (0 - 168 hours) (semi-log scale)

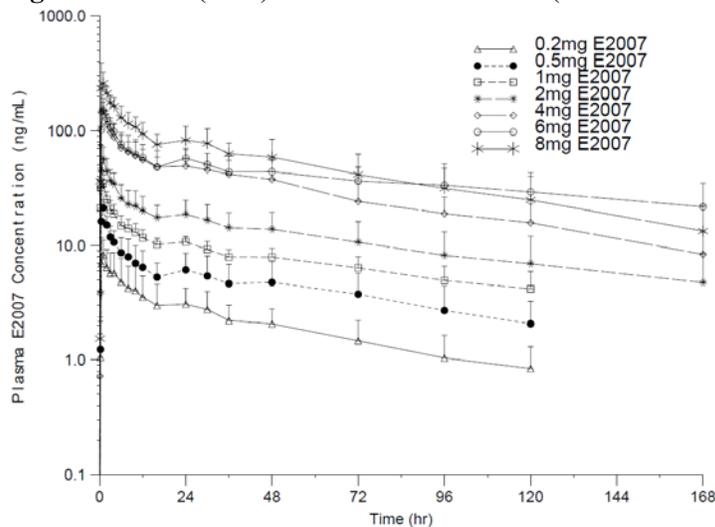


Table 1. Summary Pharmacokinetic Parameters of E2007

Parameter	Summary statistic	Dose of E2007 (mg)						
		0.2	0.5	1	2	4	6	8
C _{max} (ng/mL)	Mean	9.3	24.6	45.4	63.4	171.9	156.3	288.4
	SD	2.9	6.0	15.5	12.7	60.1	24.7	113.7
t _{max} (hr)	Median	1.00	1.00	0.54	0.75	0.79	1.00	1.00
	Range	0.50 - 1.12	0.50 - 1.02	0.25 - 1.12	0.50 - 1.03	0.50 - 2.00	0.50 - 1.02	0.50 - 2.00
AUC ₀₋₄₈ (ng·hr/mL)	Mean	155	308	544	938	2577	2773	4329
	SD	67	116	76	291	953	567	1135
AUC _{0-t} (ng·hr/mL)	Mean	247	545	961	1918	4816	6551	7999
	SD	86	246	169	864	1874	2007	3079
AUC _{0-∞} (ng·hr/mL)	Mean	317	766	1500	2557	5602	11379	9242
	SD	123	410	524	1488	2179	6723	4002
t _{1/2} (h)	Mean	52.5	67.2	79.5	71.0	58.7	122.8	55.4
	SD	23.2	17.2	29.9	34.9	17.3	72.4	19.0
	Harmonic mean	43.1	63.4	70.2	57.0	55.1	94.2	49.7
CL/F (mL/min)	Mean	12.43	13.37	12.33	18.65	13.49	11.71	16.85
	SD	6.44	6.14	4.26	12.82	5.28	6.56	7.17
V _z /F (L)	Mean	51.22	71.83	76.41	86.50	65.72	95.67	72.11
	SD	19.55	24.71	10.34	16.67	21.96	17.91	13.95
Ae ₀₋₄₈ (ng)	Mean	ND	ND	380	1931	4974	3999 ^a	9195 ^a
	SD	-	-	125	644	1112	1273	2574
CL _R (mL/min)	Mean	ND	ND	0.0117	0.0381	0.0361	0.0257 ^a	0.0350 ^a
	SD	-	-	0.0035	0.0201	0.0162	0.0111	0.0102

N = 6 in all cases, except ^a where N = 5

ND = Not determined, due to low or no quantified E2007 concentrations in urine

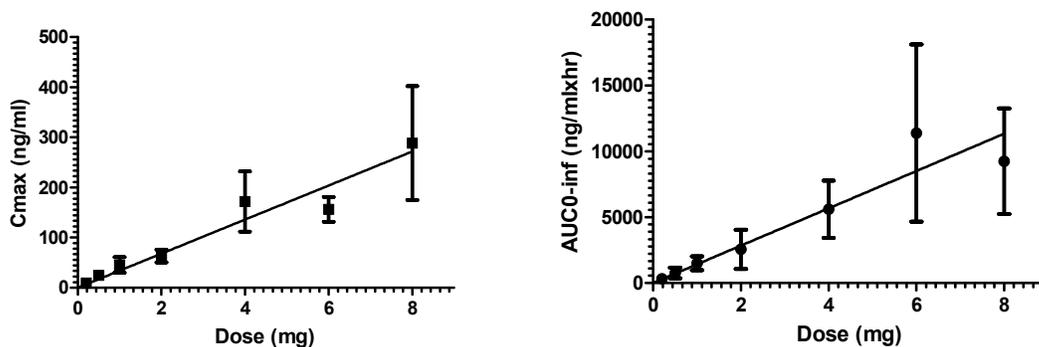
Table 2. Percentage of E2007 Dose Excreted Unchanged in Urine

E2007 Dose (mg)	N	Ae ₀₋₄₈ (ng)	% of Dose Excreted Unchanged in Urine
0.2	6	ND	-
0.5	6	ND	-
1	6	380	0.04
2	6	1931	0.10
4	6	4974	0.12
6	5	3999	0.07
8	5	9195	0.11

Table 3. Statistical Analysis for Dose Proportionality of E2007 using power model ($y = a \times \text{Dose}^b$, b was the slope in the Table)

Parameter	Slope (Least Squares Mean)	Slope 95% Confidence Intervals		p-value*
		Lower	Upper	
C _{max}	0.8812	0.8049	0.9575	0.0043
AUC _{0-t}	0.9771	0.8867	1.0674	0.3465
AUC ₀₋₄₈	0.9193	0.8446	0.9940	0.0393
AUC _{0-∞}	0.9632	0.8431	1.0834	0.3261

* test for slope significantly different from 1

Figure 3. Dose-Exposure Relationship of E2007 (Left panel: C_{max}; Right panel: AUC_{0-inf})

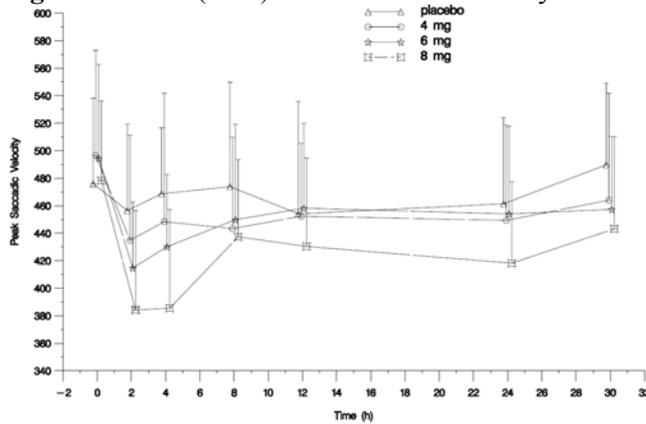
Pharmacodynamic:

Peak Saccadic Velocity (PSV):

Saccadic eye movement measurement is an objective and quantitative assessment of sedation of the central nervous system. Saccadic eye movements are rapid eye motions of the eyeballs to scan a suddenly appearing or shifting object. The motion of the eyeballs to catch the target accelerates gradually and attained the maximum velocity. In this study, the peak velocity of eye movement (PSV) is measured. The lower PSV measurements indicate stronger sedation effects.

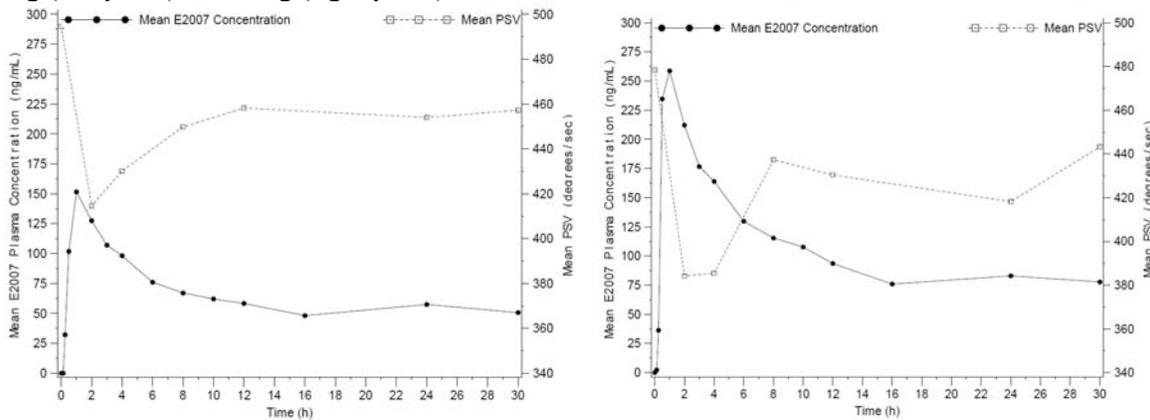
There were no clear changes in PSV at 0.2, 0.5 and 1 mg E2007 compared to placebo. However, PSV appeared to decrease in a dose dependent way at doses of 2 mg and above.

Figure 4. Mean (+SD) Peak Saccadic Velocity Following Single Oral Administration of E2007



A correlation between plasma E2007 concentrations and PSV is highlighted in the following plots.

Figure 5. Superimposed Plots of Mean Plasma Concentrations and Mean PSV Following E2007 6 mg (left panel) and 8 mg (right panel)

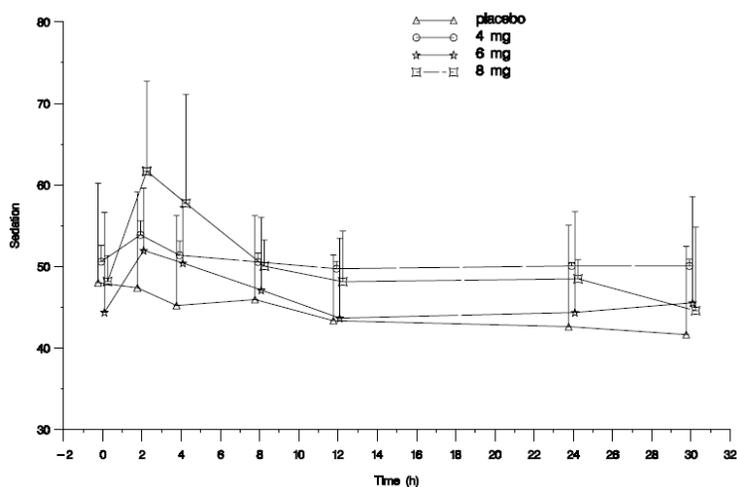


Bond and Lader Sedation Sub-score:

Bond & Lader visual-analogue mood scale (VAMS) is a 16-item, bipolar analogue scale by which a subject can self-rate their feelings by putting a perpendicular mark across each of the 16 lines (awaken \longleftrightarrow sleepy, calm \longleftrightarrow excited, energetic \longleftrightarrow depressed, confused \longleftrightarrow clear-headed, etc.) The midpoint of a line represents the usual feeling. The distance (mm) from the left-hand end (the right-hand end for some items) of each line to the mark was measured, and the sub-total scores of anxiety, dysphoria and sedation were determined using the pre-specified equations. This is a subjective and qualitative assessment of sedation of central nervous system.

There was no clear evidence of sedation at doses of 4 mg E2007 and lower. An increase in levels of sedation was noted for 6 and 8mg at the 2 and 4 hour timepoints with levels returning towards baseline by 8 hours.

Figure 6. Mean (+SD) Bond and Lader Sub-score Sedation Following Single Oral Administration of E2007 and Placebo



Safety Results

Most common adverse events following administration of E2007 were headache, dizziness, fatigue, somnolence and nasopharyngitis. All were mild or moderate in severity. In some subjects, transient symptoms of dizziness and drowsiness, occasionally accompanied by neurological symptoms were observed especially at the 6 and 8 mg dose levels. There were no clinically relevant changes in clinical pathology parameters, ECG, or physical examination.

Conclusions

- At dose levels of 0.2 to 8 mg, E2007 was rapidly absorbed (median T_{max} ranging from 0.5 to 1 hr) and following C_{max} concentrations of E2007 appeared to decline with multiple phases, with a long apparent terminal t_{1/2} (50 – 125 hrs). Oral clearance of E2007 was low (12 – 19 ml/min).
- Across the dose groups of 0.2 mg to 8 mg, increases of AUC and C_{max} of E2007 were approximately dose proportional.
- Elimination of E2007 by renal route was minimal, with < 0.12% of the dose eliminated as unchanged drug into urine within 48 hr after drug administration.
- E2007 showed sedation effect at higher doses as measured by PSV (≥ 2 mg) or by Bond and Lader sedation subscore (≥ 6 mg). There appeared to be correlation between plasma concentrations of E2007 and PSV.

Study E2007-E044-002: A double-blind, randomized study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple oral doses of E2007 as compared to placebo in healthy adult male subjects

Objective	To evaluate the safety, tolerability, PK and PD of multiple oral doses of E2007 as compared to placebo in healthy adult male subjects.		
Study Design	<p>This was a randomized, double-blind, placebo-controlled, multiple-dose, parallel group study. In each cohort, 6 subjects were randomized to receive E2007 and 2 subjects were randomized to receive placebo orally once daily, following overnight fast, for 14 days.</p> <p>Cohort A – 1 mg E2007 (1 x 1 mg E2007 tablets) or placebo Cohort B – 2 mg E2007 (2 x 1 mg E2007 tablets) or placebo Cohort C – 4 mg E2007 (4 x 1 mg E2007 tablets) or placebo Cohort D – 4 mg E2007 (4 x 1 mg E2007 tablets) or placebo on Days 1 to 7 followed by 6 mg E2007 (1 x 1 mg and 1 x 5 mg E2007 tablets) or placebo on Days 8 to 14. Cohort E – 6 mg E2007 (1 x 1 mg and 1 x 5 mg E2007 tablets) or placebo <i>Note:</i> Due to the two withdrawals in Cohort D, the sponsor decided not to continue dose escalation. Therefore, Cohort E was cancelled.</p>		
Study Population	32 healthy male volunteers (age: 19-45 yr, weight: 59-95 kg, Race: 29 out of 32 were Caucasians) were randomized into the study, of whom 30 completed the study.		
PK & PD Measurements	<p><i>Blood samples:</i> were taken at the following time points Day 1: Pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post-dose Days 2, 3: Pre-dose Day 7: Pre-dose and 0.5, 1, 1.5, 2, 4 and 8 hours post-dose Days 10, 12, 13: Pre-dose Day 14: Pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post-dose Days 15, 16, 17, 18, 19, 21, 23, 25: Pre-dose (i.e, 24, 48, 72, 96, 120, 168, 216, 264 hr post-dosing on Day 14) Day 28: Post-study medical (i.e, 336 hr post-dosing on Day 14)</p> <p><i>Urine samples:</i> was collected on Days 1 and 14 over 0 - 24 hours post-dose</p> <p><i>PD measurements:</i> Sedation was assessed using Bond and Lader visual analogue mood scales (VAMS), saccadic eye movements and neuropsychological tests at pre-dose and at 0.5, 1, 1.5, 2, 4, and 8 hours post-dose on Day 1, 7 and 14.</p>		
Bioanalytical Method	Analyze	E2007 (plasma)	E2007 (urine)
	Method	HPLC-Fluorescence	LC/MS/MS
	Internal Std.	E2007 associated substance	E2007 associated substance
	LOQ (ng/mL)	1	0.054
	Calibration Range (ng/mL)	1, 2, 5, 10, 50, 100, 151, 202, 348, 504	0.05, 0.07, 0.11, 0.18, 0.28, 0.37, 0.49, 0.65, 0.81, 1.0
	QC (ng/mL)	3.1, 154, 300, 429	0.153, 0.27, 0.50, 0.85
	Accuracy	91.2 – 118%	106.3 – 111.8%
	Precision	1.55 – 4.32%	2.3 – 10.9%

<p>PK & PD Assessments</p>	<p><i>Pharmacokinetics:</i> After single dose (Day 1): C_{max}, T_{max}, AUC₀₋₂₄, A_{e,0-24}, CL_r After repeated dosing (Days 7 and 14): C_{max,ss}, C_{min,ss}, T_{max,ss}, T_{rmin,ss}, C_{av}, λ_z (Day 14 only), t_{1/2} (Day 14 only), AUC_{0-τ}, A_e (Day 14 only), PTF (Peak-trough fluctuation, calculated as (C_{max,ss} – C_{min,ss})/C_{av} x 100%), Rac (Accumulation index, Day 14 only), CL_r (Day 14 only)</p> <p><i>Pharmacodynamic:</i> Peak saccadic velocity (PSV) and percentage of failed saccades were determined for saccadic eye movements. Sub-scores for anxiety, sedation and dysphoria were calculated from the VAMS.</p>
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<p>Safety Assessments</p>	<p>12-lead ECG, vital signs, laboratory safety tests, adverse events, physical and neurological examination</p>
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<p>PK & PD Results</p>	<p>E2007</p>
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E2007 PK

PK Profiles and Parameters

E2007 was rapidly absorbed with median of T_{max} ranging from 0.50 to 1.25 hr post-dose on Day 1 and Day 14. Following maximum concentrations after the last dose on Day 14, E2007 plasma concentrations declined with a long terminal disposition phase. Harmonic mean apparent terminal t_{1/2} values on Day 14 ranged from 66 to 106 hours (mean values ranging from 100 to 130 hr).

Figure 1. Geometric Mean Plasma E2007 Profiles on Day 1

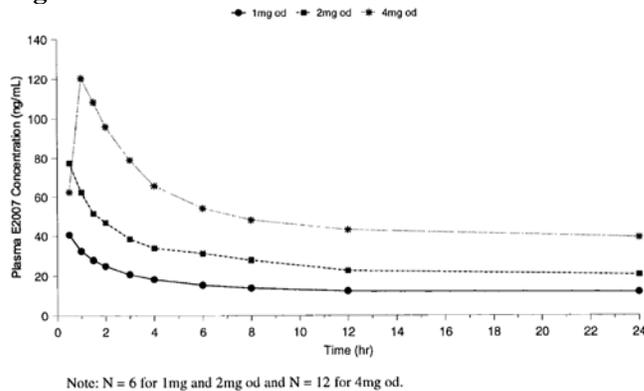
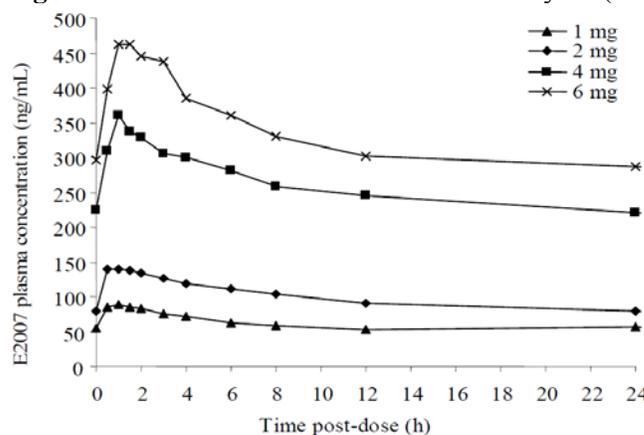


Figure 2. Mean Plasma E2007 Profiles on Day 14 (0-24 hr)



[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.]

Table 1. Summary Day 1 and Day 14 Pharmacokinetic Results of E2007

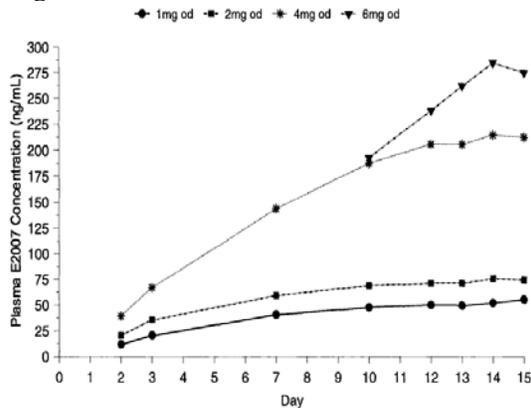
Day	Parameter	Summary Statistic	Dose of E2007 (mg)			
			1	2	4 ^a	6 ^b
1	C _{max} (ng/mL)	Arithmetic mean	42.30	79.15	131.44	-
		SD	13.24	14.64	38.24	-
		Geometric mean	40.60	78.01	126.30	-
	t _{max} (hr)	Median	0.50	0.55	1.00	-
		Range	0.50-0.55	0.50-1.00	0.50-1.83	-
	AUC ₀₋₂₄ (ng-hr/mL)	Arithmetic mean	370.0	695.6	1269.0	-
		SD	109.4	140.5	312.3	-
		Geometric mean	357.8	683.5	1233.2	-
	Ae ₀₋₂₄ (ng)	Arithmetic mean	246.33	625.86	1868.47	-
		SD	124.26	378.30	655.18	-
Geometric mean		207.12	527.86	1758.65	-	
CL _R (mL/min)	Arithmetic mean	0.01145	0.01530	0.02588	-	
	SD	0.00669	0.00849	0.01070	-	
	Geometric mean	0.00965	0.01287	0.02377	-	
14	C _{ss,max} (ng/mL)	Arithmetic mean	92.26	150.20	364.96	469.79
		SD	22.50	28.53	78.74	133.67
		Geometric mean	90.13	147.82	357.83	456.12
	t _{ss,max} (hr)	Median	0.77	0.55	1	1.26
		Range	0.50-2.00	0.50-1.50	0.50-1.50	1.00-3.00
	C _{ss,min} (ng/mL)	Arithmetic mean	50.77	76.32	221.35	286.96
		SD	11.64	26.89	70.66	98.37
		Geometric mean	49.67	72.58	212.38	274.87
	t _{ss,min} (hr)	Median	0	18	0	6
		Range	0.00-12.00	0.00-24.00	0.00-24.00	0.00-24.00
	t _{1/2z} (h)	Mean	99.84	72.09	129.45	121.06
		SD	31.59	21.33	145.96	49.52
		Harmonic mean	89.60	66.42	74.12	106.24
	AUC _τ (ng-hr/mL)	Arithmetic mean	1460.6	2365.2	6197.5	7939.8
		SD	326.8	786.3	1769.2	2562.8
		Geometric mean	1431.0	2265.2	5997.6	7651.3
	Ae _τ (ng)	Arithmetic mean	1409.78 ^c	1921.08	7010.56	8853.24
		SD	926.04 ^c	1283.64	3743.20	5209.85
		Geometric mean	1131.32 ^c	1587.57	6353.84	7811.28
	PTF (%)	Arithmetic mean	68.11	81.99	58.70	56.87
		SD	13.71	30.60	16.45	6.66
		Geometric mean	66.89	77.24	56.85	56.57
R _{ac}	Arithmetic mean	6.52	4.85	8.30	7.79	
	SD	1.89	1.28	8.77	2.97	
	Geometric mean	6.26	4.71	6.10	7.36	
CL _R (mL/min)	Arithmetic mean	0.01521	0.01513	0.01979	0.01863	
	SD	0.01047	0.01266	0.01097	0.00868	
	Geometric mean	0.01233	0.01168	0.01766	0.01702	

N = 6 in all cases, except ^a where N = 12 on Day 1, ^b where N = 4 and ^c where N = 5

Time to reach steady state

As shown in the following figure, concentrations of E2007 only increased slightly between Day 12 and Day 15 for 1, 2 and 4 mg groups, indicating that steady-state was approached around Day 14.

Figure 3. Geometric Mean Pre-dose Plasma E2007 Concentrations



[Note: At 6 mg, concentrations on Days 10, 11, 12, 13 and 14 are those following 6 mg E2007 q.d. for 3, 4, 5, 6 and 7 days, respectively.]

Accumulation after multiple dosing

The Rac (accumulation ratio) values listed in Table 1 were not the observed ones, but predicted values based on the apparent terminal t1/2 using the following equation,

$$R_{ac} = \frac{1}{[1 - e^{-(\lambda, \tau)}]}$$

Reviewer's Comment: With this equation, it is assumed that the PK profile of the compound is mono-exponential, which is apparently not consistent with the multi-phasic PK profile of E2007. Observed Rac calculated as $AUC_{0-\tau, \text{Day 14}}/AUC_{0-\tau, \text{Day 1}}$ ($\tau=24\text{hr}$) were 4.15, 3.41 and 4.52, respectively, for dose groups of 1, 2 and 4 mg. The reason of predicted values being higher than observed ones is that the predicated values are calculated based on an assumption that the entire dose was eliminated during the terminal phase, whereas E2007 was eliminated during both distribution phase and terminal elimination phase. Based on the observed Rac, effective t1/2 for E2007 was estimated as 60, 48 and 67 hr, for dose groups of 1, 2 and 4 mg, respectively.

The accumulation ratio for Cmax ($C_{\text{max,Day 14}}/C_{\text{max,Day 1}}$) was lower than those for AUC, being 2.32, 1.96 and 2.58, for dose groups of 1, 2 and 4 mg, respectively.

Fluctuation Index

The FI% value, calculated as $(C_{\text{max,ss}} - C_{\text{min,ss}})/C_{\text{av}} \times 100\%$, was 68%, 82% and 59%, for dose groups of 1, 2 and 4 mg, respectively.

Dose Proportionality

Based on power-model analysis ($y = a \times \text{Dose}^b$, b is the slope in the Table below), AUC0- τ and Cmax of E2007 after multiple dosing increased in a dose-proportional manner.

Parameter	Slope (Least Squares Mean)	95% Confidence Interval	
		Lower	Upper
C _{ss,max}	0.9946	0.7896	1.1996
AUC _{τ}	1.0337	0.7729	1.2945

Urine Excretion

Less than 0.2% of dose administered was excreted into urine as unchanged drug during 24 hr post-dose on Day 1 or Day 14.

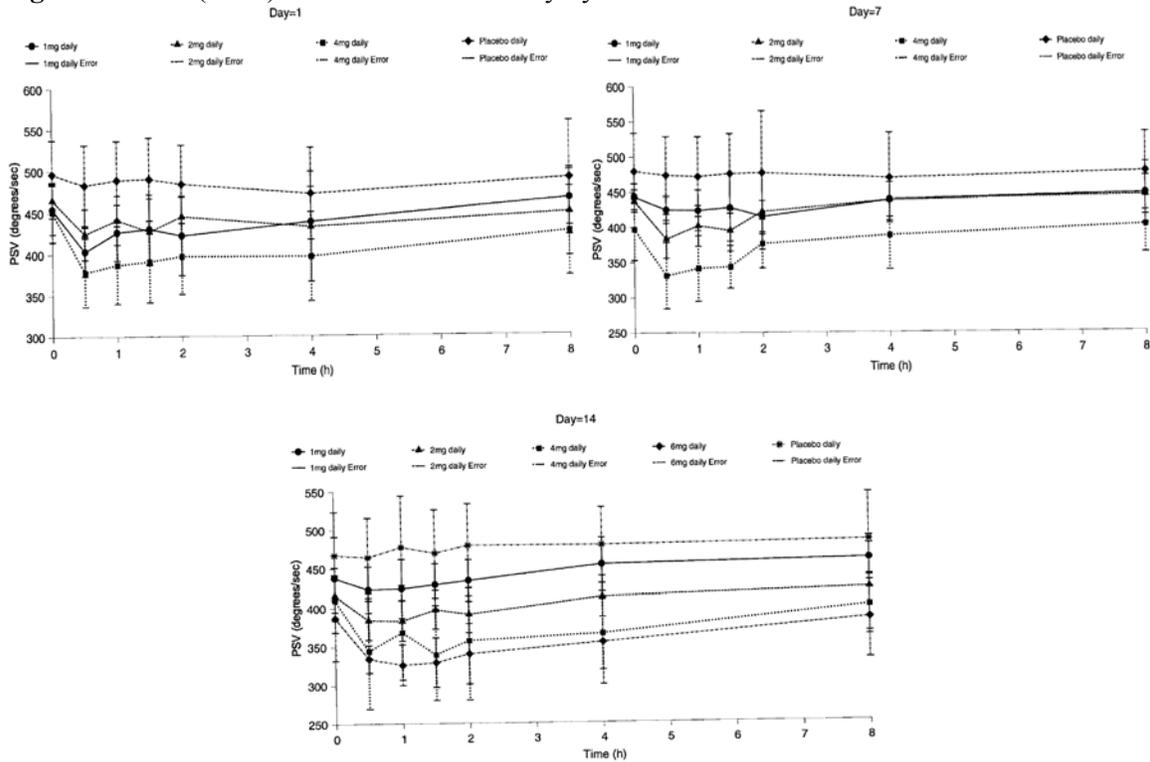
Table 2. Mean Percentage of E2007 Dose Excreted Unchanged in Urine

E2007 Dose (mg)	N	Day 1		Day 14	
		Ac ₀₋₂₄ (ng)	% of Dose Excreted Unchanged in Urine	Ac _{τ} (ng)	% of Dose Excreted Unchanged in Urine
1		246.33	0.02	1409.78	0.14
2		625.86	0.03	1921.08	0.10
4 (Cohort C and D)		1865.47	0.05	-	-
4 (Cohort C)		-	-	7010.56	0.18
6 (Cohort D)		-	-	8853.24	0.15

Pharmacodynamics:

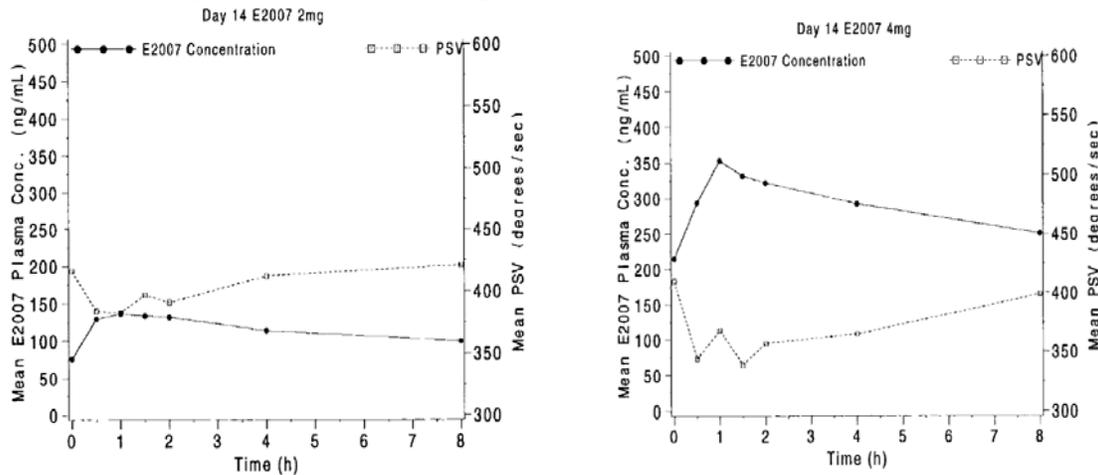
Peak Saccadic Velocity (PSV): Dose-dependent decreases in PSV were observed on day 1 and more obviously on Day 7 and Day 14. Pre-dose PSV values measured for 4 mg dose group declined between Day 1 and Day 7, suggesting that sedation was increasing with repeated administration, while there was no apparent difference between Day 7 and Day 14.

Figure 4. Mean (\pm SD) Peak Saccadic Velocity by Treatment



A correlation between E2007 plasma concentrations and PSV was observed.

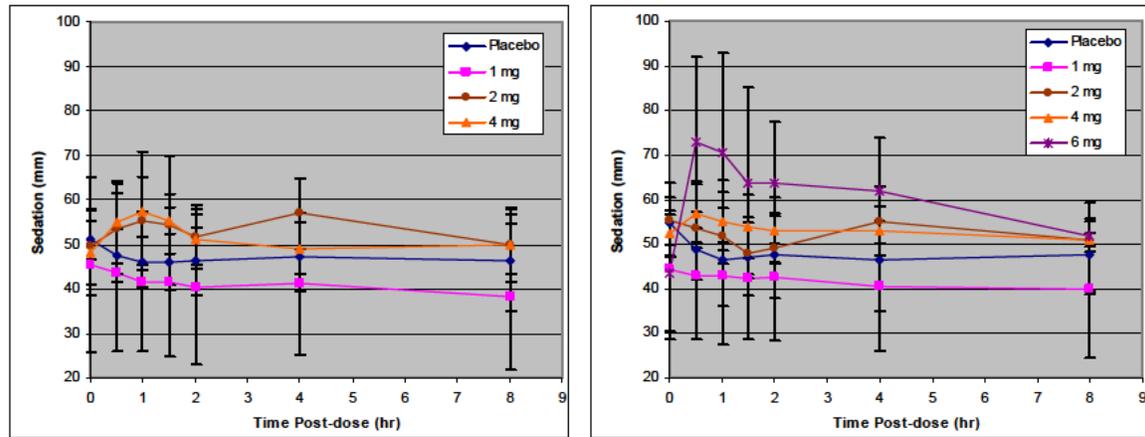
Figure 5. Day 14 Mean Plasma Concentration and Mean Saccadic Eye Movement Peak Saccadic Velocity Plots (Left panel: 2 mg; Right panel: 4 mg)



Bond and Lader Sedation Sub-score:

2mg E2007 appeared to induce an increase in feelings of sedation on Day 1 only. No clear sedation was noted on Days 7 and 14. Subjects receiving 4 mg E2007 reported slightly larger changes on Day 1 than seen with 2 mg, and there were small increases in sedation on the other dosing days, though these changes seemed to be smaller than those on Day 1. E2007 6mg induced marked changes in levels of sedation.

Figure 6. Mean (+SD) Bond and Lader Sub-score Sedation Following Once-daily Oral Administration of E2007 and Placebo (Left panel: Day 1; Right Panel: Day 14)



Safety Results

There appeared to be an incremental increase in the number of AEs with increasing dose. The most common AEs were somnolence, dizziness and postural dizziness, and headache, nasopharyngitis, fatigue and paraesthesia. The majority of AEs were mild or moderate in severity. Severe AEs occurred in two subjects (somnolence and/or vertigo), both of whom received 4 mg E2007 and withdraw from the study. All AEs resolved with no further sequelae.

Conclusions

- AUC and Cmax after multiple doses of E2007 (1 – 4 mg) increased in a dose-proportional manner.
- Steady state was approached at Day 14. AUC_{0-24hr} after 14-day once daily dosing was about 4.1-fold of AUC_{0-24hr} on Day 1. Fluctuation index at Day 14 was 59-82% after once daily dosing on mornings under fasted state.
- Elimination of E2007 by the renal route was minimal, with less than 0.2% of dose excreted unchanged into urine within 24 hrs of drug administration.
- Dose-dependent decreases in PSV were observed on Day 1 and more obviously on Day 7 and Day 14 after doses of 1 – 4 mg E2007. There seemed to be correlation between plasma concentrations of E2007 and PSV. E2007 6 mg induced marked sedation measured by Bond and Lader sedation subscore.

Study E2007-E044-003: A randomized, open label, single-dose, 2-way crossover, food effect study of E2007 in healthy male and female volunteers.

Objective	<p><i>Primary objective:</i> to evaluate the pharmacokinetics and pharmacological effects of single oral doses of E2007 in the fed, as compared to the fasted state, in healthy adult male and female volunteers</p> <p><i>Secondary objective:</i> to further evaluate safety and tolerability of E2007 in healthy volunteers and to compare the pharmacokinetics and pharmacodynamics of E2007 in female volunteers with those in males.</p>		
Study Design	This study was of a randomized, open-label, single-dose, 2-way crossover design, with a washout interval of at least three weeks.		
Study Population	12 healthy male and 14 healthy female subjects were randomized onto the study, of whom 12 males (age: 19-38 yr; weight: 56-91 kg; Race: 10 Caucasians) and 12 females (age: 19-41 yr; weight: 48-66 kg; Race: 10 Caucasians) completed the study successfully		
Dosage and Administration	<p>Treatment A: 1-mg single oral dose following a 10-hour overnight fast and no food allowed for at least 4 hours post-dose</p> <p>Treatment B: 1-mg single oral dose following high-fat breakfast</p> <p>For Treatment B, following an overnight fast of 10 hours, subjects were given the high-fat breakfast which should have been ingested within 30 minutes. E2007 was administered with 180mL water immediately (within 5 minutes) after completion of the meal. No food was allowed for at least 4 hours post-dose. The high fat breakfast was composed of the following:</p> <ul style="list-style-type: none"> • 2 slices of toast with butter • 2 strips of bacon • 2 eggs (fried in butter) • 4 ounces of hash brown potatoes • 8 ounces of whole milk <p>E2007 was provided as 1-mg tablet (<i>Formulation A</i>)</p>		
PK & PD Measurements	<p>PK: Blood samples for PK analysis were taken at pre-dose, and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120 and 168 hours post-dosing.</p> <p>Pharmacodynamic: Measurement of saccadic eye movements and Bond and Lader visual analogue mood scales (VAMS) were performed pre-dose on Day 1 and at 0.5, 1, 1.5, 2, 4 and 8 hours post-dose.</p>		
Bioanalytical Method	Analyze	E2007	
	Method	HPLC-Fluorescence	
	Internal Std.	E2007 associated substances	
	LOQ (ng/mL)	1	
	Calibration Range (ng/mL)	1, 2, 5, 10, 50, 101, 151, 202, 348, 504	
	QC (ng/mL)	3, 154, 300, 429	
	Accuracy	102.6 – 119.5%	
	Precision	1.54 – 2.30%	
PK & PD Assessments	<p>PK parameters C_{max}, t_{max}, λ_z, $t_{1/2z}$, AUC_{0-t} and $AUC_{0-\infty}$</p> <p>Peak saccadic velocity (PSV) and percentage of failed saccades were determined for saccadic eye movements. Sub-scores for anxiety, sedation and dysphoria were calculated from the VAMS.</p>		

Safety Assessment	12-lead ECG, vital signs, laboratory safety tests, adverse events, physical and neurological examinations
PK & PD Results	E2007

E2007 PK

Food Effect

High-fat meal reduced C_{max} of E2007 by 40%, delayed its T_{max} (median) by 2 hr, but did not alter AUC_{0-last}, AUC_{0-inf} and t_{1/2} of E2007. Food effect on C_{max} and AUC was similar among males and females.

Figure 1. Mean Plasma E2007 Concentration-time Profiles Following Single Oral Administration of 1-mg E2007 in the Fed and Fasted State (Left panel: 0-24 hr; Right panel: 0-168 hr)

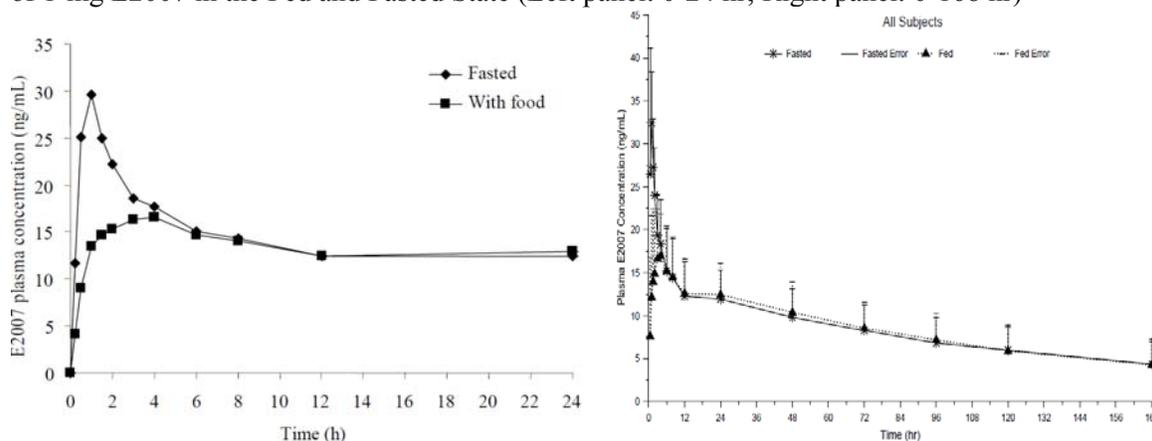


Table 1. Summary PK Parameters of E2007 (N=24)

Parameter	Summary statistic	E2007 1mg	
		Fasted	Fed
C _{max} (ng/mL)	Arithmetic mean	35.86	21.90
	SD	7.44	6.18
	Geometric mean	35.12	21.03
t _{max} (hr)	Median	1.00	3.00
	Range	0.25 – 1.52	0.50 – 8.00
AUC _{0-t} (ng·hr/mL)	Arithmetic mean	1397	1408
	SD	484	464
	Geometric mean	1318	1324
AUC _{0-∞} (ng·hr/mL)	Arithmetic mean	2280	2282
	SD	1435	1291
	Geometric mean	1950	1964
t _{1/2} (hr)	Arithmetic Mean	107.0	108.0
	SD	58.2	78.7
	Harmonic mean	83.4	74.1

Table 2. Results of the Statistical Comparisons

Parameter	N	Treatment Ratio (Fed/Fasted)			p-values from ANOVA of log-transformed data				
		Point Estimate	Lower 90% CI	Upper 90% CI	Treatment Effect	Period Effect	Sequence Effect	Gender by Period Interaction	Gender by Treatment Interaction
C _{max}	24	0.599	0.535	0.670	<0.0001	0.4701	0.0425	0.7412	0.7825
AUC _{0-∞}	24	1.007	0.905	1.122	0.9066	0.2607	0.1373	0.2551	0.3519
AUC _{0-t}	24	1.005	0.932	1.084	0.9094	0.7226	0.0740	0.8211	0.3863
t _{1/2}	24	0.945	0.844	1.058	0.3970	0.0593	0.8287	0.0916	0.3910

Gender Difference:

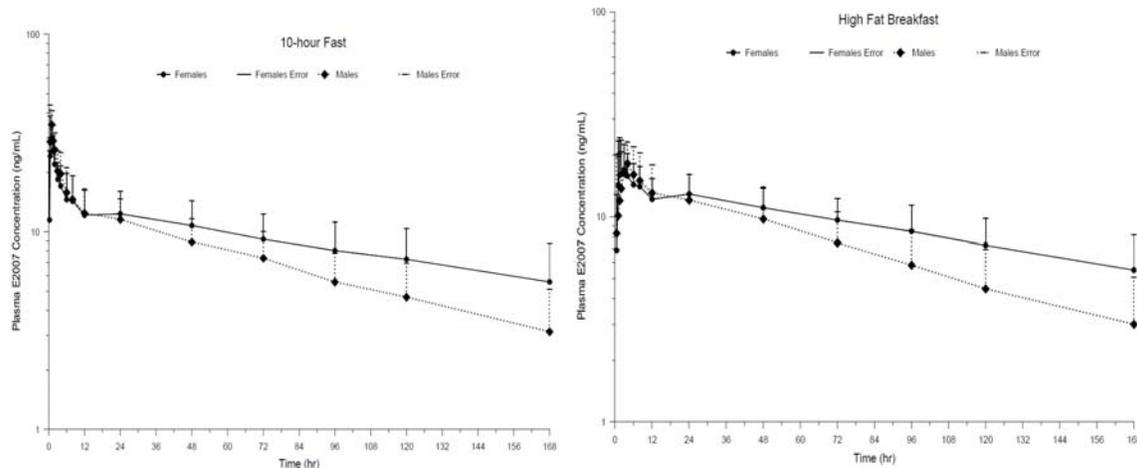
AUC_{0-t} and AUC_{0-∞} were approximately 20 - 30% and 50 - 70% greater, respectively, in females compared to males under fasted and fed states. Half-life was 45 - 65% longer in females compared to males. C_{max} was similar in males and females under both the fasted and fed states.

Table 3. Summary Pharmacokinetic Results: Male and Female Subjects

Parameter	Summary statistic	E2007 1mg Fasted		E2007 1mg Fed	
		Males	Females	Males	Females
C _{max} (ng/mL)	Arithmetic mean	37.73	33.99	22.51	21.29
	SD	7.95	6.70	6.14	6.43
	Geometric mean	36.93	33.39	21.71	20.36
t _{max} (hr)	Median	1.00	1.00	4.00	1.77
	Range	0.50 - 1.00	0.25 - 1.52	0.50 - 6.03	1.00 - 8.00
AUC _{0-t} (ng·hr/mL)	Arithmetic mean	1260	1533	1249	1567
	SD	400	539	478	410
	Geometric mean	1198	1450	1158	1515
AUC _{0-∞} (ng·hr/mL)	Arithmetic mean	1740	2819	1686	2878
	SD	791	1744	772	1453
	Geometric mean	1586	2397	1506	2563
t _{1/2} (hr)	Arithmetic mean	84.5	129.5	77.5	138.5
	SD	41.4	65.3	39.4	96.7
	Harmonic mean	70.1	102.8	59.8	97.3

N = 12 in all cases

Figure 2. Mean (+SD) Plasma E2007 Profiles: Males vs. Females in the Fasted State (left panel) and Fed condition (right panel)



Reviewer's Comment: The extent of gender difference in E2007 AUC_{0-inf} observed in this study was seen in another two studies (E2007-A001-039 and E2007-A001-040), but not in some other single- and multiple-dose studies which were also conducted in healthy subjects, i.e., E2007-A001-008, E2007-E044-009, E2007-A001-013 and E2007-E044-028. With a meta-analysis conducted by the reviewer based on all these studies, AUC_{0-inf} in females was estimated to be about 32% higher than that in males. This is consistent with the Phase 1 population PK analysis which was developed based on 19 Phase 1 studies. That analysis showed that females had 24% lower oral clearance than males, which translates into a 33% higher AUC_{0-inf} in females than males. These estimates in healthy subjects were also in line with that in patients. Based on a Phase 3 population PK analysis which utilized the PK data obtained from the three pivotal trials, females were estimated to have 16-21% lower oral clearance than males, which corresponds to 19-27% higher exposure (AUC_{0-inf}) in females.

The larger extent of gender difference observed in this study may be due to across-study

variability and also the uncertainty about AUC_{0-inf} estimation. It is noted that, in 18 out of 48 cases in this study, the extrapolated area of AUC_{0-inf} (beyond AUC_{0-last}) was larger than 35% of the whole AUC_{0-inf}. Therefore, AUC_{0-inf} values may not be well estimated. Majority of these cases (13 out of 18) were observed in females. The large extrapolation of AUC was due to the relatively short PK sample collection period (168 hr post-dosing) compared to the long terminal t_{1/2} of E2007, which was even longer in females than in males.

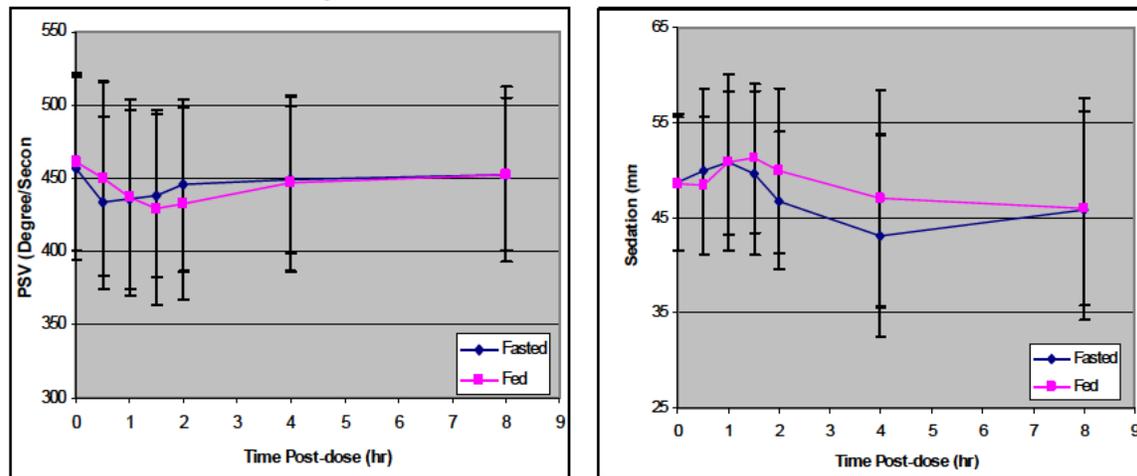
Pharmacodynamics:

Peak Saccadic Velocity (PSV): Though the peak decrease of PSV occurred later under fed condition (1.5 hr post-dosing) than fasted state (0.5 hr), the maximal extent of decrease was similar between fed and fasted states.

Bond and Lader Sedation Sub-score: No significant differences were noted between fasted state and fed condition in terms of the VAMS subjective measures of sedation employed in this study.

There were no clinically relevant gender differences in the measures of sedation.

Figure 3. Left Panel: Mean (± SD) Peak Saccadic Velocity (PSV, expressed as degree/second) by Treatment: Fasted vs. Fed; Right Panel: Mean (± SD) Absolute Value of Bond and Lader Sedation Sub-score (mm) by Treatment: Fasted vs. Fed.



Safety Result	No subjects were withdrawn from the study due to AEs related to E2007 administration. The most common AEs were fatigue, somnolence and headache. All the AEs were mild or moderate in severity.
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Conclusions	<ul style="list-style-type: none"> • High-fat meal decreased absorption rate of E2007, but not affected the extent of absorption. C_{max} of E2007 was reduced by 40% and T_{max} was delayed by 2 hrs with high-fat meal. • The maximal decrease of PSV post-dosing was similar between fed and fasted state. However, the time to reach the nadir was achieved earlier when E2007 was taken under fasted state. There was no significant difference (fasted state versus fed condition) in sedation measured as Bond & Lader sedation sub-score. • AUC_{0-inf} was 50 –70% greater in females compared to males in fasted and fed states. C_{max} was similar in males and females. The gender difference observed for AUC_{0-inf} in this study was larger than those estimated from
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	Phase 1 or Phase 3 population PK analyses. This may be due to across-study variability and also some uncertainty about $AUC_{0-\infty}$ estimation in this study due to the large extrapolation from $AUC_{0-\text{last}}$ to $AUC_{0-\infty}$.
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Study E2007-E044-004: A randomized, double-blind, single ascending dose study to evaluate the safety, tolerability and pharmacokinetic profile of E2007 in elderly subjects

Objective	<ul style="list-style-type: none"> • <i>Primary objective:</i> To evaluate the safety and tolerability of E2007 after single oral administration to generally healthy, elderly, male and female volunteers. • <i>Secondary objective:</i> To evaluate the PK profile of E2007 in this population. 		
Study Design	This was a randomized, double-blind, placebo-controlled, single ascending dose, parallel group study. Two groups of 12 healthy subjects (6 male and 6 female) were studied at dose levels of E2007 of 1 mg and 2 mg. The randomization was directed such that at each dose level, 8 subjects received E2007 (4 male and 4 female) and 4 subjects (2 male and 2 female) received placebo. Each subject participated in one treatment group only.		
Study Population	25 subjects (13 male and 12 female) were enrolled onto the study and 24 successfully completed. Age: 65 – 76 yr; Weight: 53 – 85 kg; Race: All Caucasians		
Dosage and Administration	E2007 was supplied as 1-mg tablet and was administered orally following an overnight fast.		
PK & PD Measurements	<p>PK: Blood samples were taken at pre-dose, and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36, 48, 72, 96, 120 and 168 hours post-dose.</p> <p>Pharmadynamic measurements: Bond and Lader visual analogue mood scales (VAMS) and saccadic eye movements were assessed pre-dose and at 1, 2, 4, 8 and 24 hours post-dose.</p>		
Bioanalytical Method		Analyze	E2007
		Method	HPLC-Fluorescence
		Internal Std.	E2007 associated substances
		LOQ (ng/mL)	1
		Calibration Range (ng/mL)	1, 2, 5, 10, 50, 100, 151, 201, 352, 502
		QC (ng/mL)	3, 151, 302, 423
		Accuracy	95.8 – 99.4%
		Precision	3.14 – 15.23%
PK & PD Assessments	<p>PK parameters: C_{max}, T_{max}, AUC_{0-t}, AUC_{0-∞}, λ_z, t_{1/2,z}, CL/F, V_z/F.</p> <p>PD parameters: Sub-scores for anxiety, sedation and dysphoria were calculated from the VAMS. Peak saccadic velocity (PSV) and percentage of failed saccades were determined for saccadic eye movements.</p>		
Safety Assessment	12-lead ECG, vital signs, laboratory safety tests and adverse events		
PK & PD Results	E2007		
<p>E2007 PK</p> <p>E2007 was rapidly absorbed with a median T_{max} of ~0.5 hours. E2007 was eliminated with an apparent terminal t_{1/2} around 105 hrs. Increases in C_{max} and AUC_{0-∞} were dose-proportional between 1 mg and 2 mg. There was no apparent gender effect on the PK of E2007.</p>			
<p>Figure 1. Geometric Mean Plasma E2007 Profiles</p>			

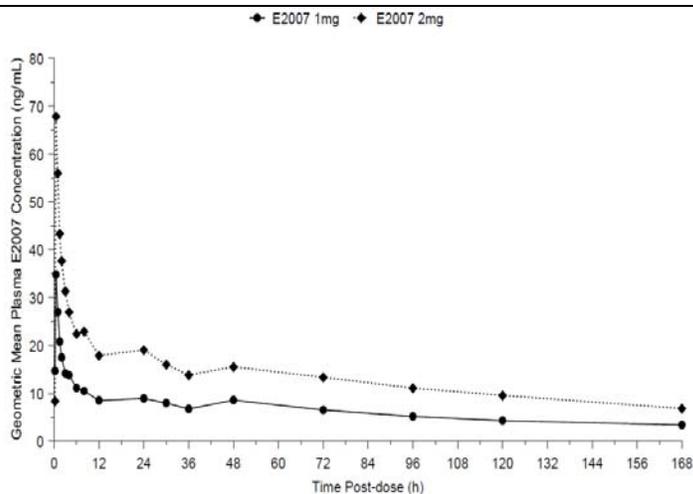


Table 1. Summary PK parameters of E2007

Parameter	Summary Statistic	E2007 1mg	E2007 2mg
C_{max} (ng/mL)	Arithmetic mean	36.7	73.6
	SD	8.9	17.4
	Geometric mean	35.7	71.6
t_{max} (h)	Median	0.50	0.51
	Range	0.42 – 1.02	0.50 – 1.00
AUC_{0-t} (ng·h/mL)	Arithmetic mean	1119	2273
	SD	198	499
	Geometric mean	1104	2225
$AUC_{0-\infty}$ (ng·h/mL)	Arithmetic mean	1754 ^a	3566
	SD	614 ^a	1436
	Geometric mean	1677 ^a	3360
$t_{1/2}$ (h)	Mean	105.8 ^a	109.9
	SD	43.3 ^a	38.3
	Harmonic mean	93.0 ^a	99.8
CL/F (mL/h)	Arithmetic mean	621 ^a	627
	SD	184 ^a	209
	Geometric mean	596 ^a	595
V_z/F (mL)	Arithmetic mean	86453 ^a	92471
	SD	15994 ^a	24806
	Geometric mean	85115 ^a	89773

N = 8 in all cases, except^a where N = 7 (the terminal phase could not be identified in Subject 15)

Table 2. Results of the Dose Proportionality Assessment

Dose-adjusted Parameter	N	Treatment Ratio (1mg/2mg)		
		Point Estimate	Lower 90% CI	Upper 90% CI
C_{max}	16	0.996	0.795	1.248
AUC_{0-t}	16	0.992	0.829	1.187
$AUC_{0-\infty}$	15	0.998	0.733	1.360

Table 3. Geometric Mean Pharmacokinetic Results: Males and Females

Parameter	E2007 1mg		E2007 2mg	
	Males	Females	Males	Females
C_{max} (ng/mL)	37.9	33.6	67.1	76.5
AUC_{0-t} (ng·h/mL)	1185	1028	2244	2206
$AUC_{0-\infty}$ (ng·h/mL)	1643	1724 ^a	3292	3429
$t_{1/2}$ (h) ^b	89.7	97.8 ^a	90.7	111
CL/F (mL/h)	609	580 ^a	607	583
V_z/F (mL)	80860	91137 ^a	83697	96289

N = 4 in all cases, except^a where N = 3

^b Harmonic mean

Table 4. Results of the Gender Effect assessment

Parameter	N	Treatment Ratio (Females/Males)		
		Point Estimate	Lower 90% CI	Upper 90% CI
$t_{1/2}$	15	1.195	0.868	1.645
CL/F	15	0.957	0.703	1.303
V_z/F	15	1.143	0.935	1.398

Pharmacodynamic:

Compared to placebo, there were no clinically relevant changes in reported feelings of anxiety, dysphoria, sedation or changes in peak saccadic velocity or percent failed saccades for doses up to 2mg of E2007 in this study.

Safety Result	There were no withdrawals due to AEs. AEs reported after E2007 1mg included somnolence (2/8 subjects), headache (1/8 subjects), myalgia (1/8 subjects), flatulence (1/8 subjects), anxiety (1/8 subjects) and psychiatric symptoms (1/8 subjects; “feeling of uncertainty” on one occasion whilst crossing the road). Adverse events reported after E2007 2mg included headache (1/8 subjects), diarrhoea (1/8 subjects), back pain (1/8 subjects), trigger finger (1/8 subjects) and nodule on extremity (1/8 subjects). AEs were mild or moderate in severity, except for severe diarrhoea, which occurred in Subject 17 who received placebo.
Conclusions	<ul style="list-style-type: none"> • In elderly subjects, E2007 (1 mg and 2 mg) was rapidly absorbed and was eliminated with an apparent terminal $t_{1/2}$ around 105 hours. • Increases in C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were dose proportional between 1 mg and 2 mg. • There was no apparent gender difference in PK of E2007.

Study E2007-E044-005: An open label, 2-way crossover study to evaluate the interaction between E2007 and ketoconazole

Objective	<ul style="list-style-type: none"> • <i>Primary objective:</i> To assess the effect of repeated oral doses of ketoconazole on the pharmacokinetics of single oral doses of E2007 in healthy men • <i>Secondary objective:</i> To assess the effect of repeated oral doses of ketoconazole on the safety and tolerability of single oral doses of E2007 in healthy men 																								
Study Design	<table border="1"> <tr> <td></td> <td></td> <td>Period 1</td> <td>Period 2</td> </tr> <tr> <td rowspan="2">Group A (n=13)</td> <td>Ketoconazole 400 mg</td> <td>Days 1–10</td> <td>–</td> </tr> <tr> <td>E2007 1 mg</td> <td>Day 3</td> <td>Day 1</td> </tr> <tr> <td></td> <td></td> <td>Period 1</td> <td>Period 2</td> </tr> <tr> <td rowspan="2">Group B (n=13)</td> <td>Ketoconazole 400 mg</td> <td>–</td> <td>Days 1–10</td> </tr> <tr> <td>E2007 1 mg</td> <td>Day 1</td> <td>Day 3</td> </tr> </table> <p>There was a washout of at least 10 days between successive periods.</p>					Period 1	Period 2	Group A (n=13)	Ketoconazole 400 mg	Days 1–10	–	E2007 1 mg	Day 3	Day 1			Period 1	Period 2	Group B (n=13)	Ketoconazole 400 mg	–	Days 1–10	E2007 1 mg	Day 1	Day 3
		Period 1	Period 2																						
Group A (n=13)	Ketoconazole 400 mg	Days 1–10	–																						
	E2007 1 mg	Day 3	Day 1																						
		Period 1	Period 2																						
Group B (n=13)	Ketoconazole 400 mg	–	Days 1–10																						
	E2007 1 mg	Day 1	Day 3																						
Study Population	<p>Healthy males (Age: 20 – 32, mean 24.3 yr; Weight: 59 – 103, 76.8 kg; White: 24, Afro-Caribbean: 2) Number of subjects planned, randomized, completed: 26</p>																								
Dosage and Administration	<p>All subjects received, by mouth, 10 once-daily doses of ketoconazole 400 mg (2 x 200 mg tablets, Nizoral®) and 2 single doses of E2007 1 mg. On Day 3 subjects were given a single 1-mg E2007 together with their dose of ketoconazole.</p> <p>All doses were given between 8:45-10:35 h with 250 mL of water. Subjects were dosed at the same time on each dosing day in each period.</p> <p>On the days when E2007 was administered, subjects were fasted overnight. Breakfast was given 2 h after dosing.</p> <p>On the days when only ketoconazole was administered subjects were dosed 15 minutes after the start of breakfast. Breakfast was consumed within the 15 min before dosing.</p>																								
PK Sampling	<p>Blood samples were collected to determine plasma concentrations of E2007: pre-dose, 15 min, 30 min, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 240, and 288 h after E2007 dosing.</p> <p>Ketoconazole: before dosing on Days 2, 3 and 4.</p>																								
Bioanalytical Method	Analyze	E2007	Ketoconazole																						
	Method	HPLC-Fluorescence	HPLC/MS																						
	Internal Std.	E2007 associated substances	(b) (4)																						
	LOQ (ng/mL)	1	50																						
	Calibration Range (ng/mL)	1, 2, 5, 10, 50, 100, 150, 200, 350, 500	50, 100, 250, 500, 750, 1000																						
	QC (ng/mL)	3, 155, 300, 430	201.3, 402.7, 805.3																						
	Accuracy	90.25 – 98.48%	93.3 – 98.8%																						
	Precision	2.13 – 3.98%	1.4 – 6.1%																						
PK Assessments	C_{max} , T_{max} , AUC_{0-last} , $AUC_{0-\infty}$, $t_{1/2}$ for E2007; C_{min} for ketoconazole																								

Safety Assessment	12-lead ECG, vital signs, laboratory safety tests and adverse events
PK Results	E2007 – Ketoconazole Interaction

E2007 PK

Figure 1. Mean E2007 plasma concentrations versus time in the presence (triangles) and absence (circles) of ketoconazole. The error bars show *standard errors* of the mean. (Upper panel: linear scale; Lower panel: semi-log scale)

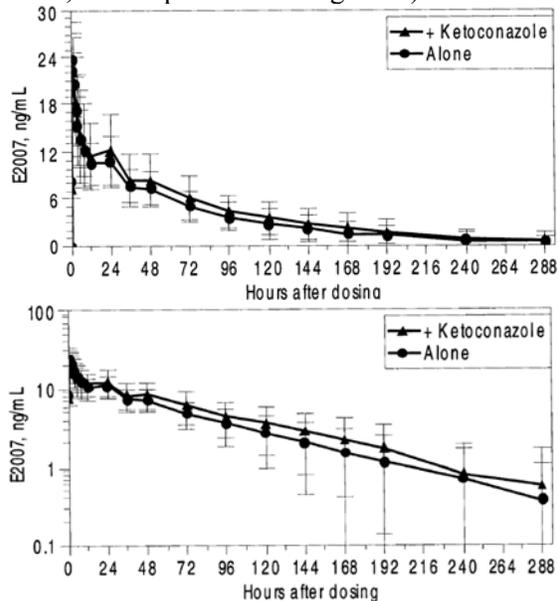


Table 1. PK parameters of E2007 after dosing with E2007 alone and with ketoconazole (n = 26)

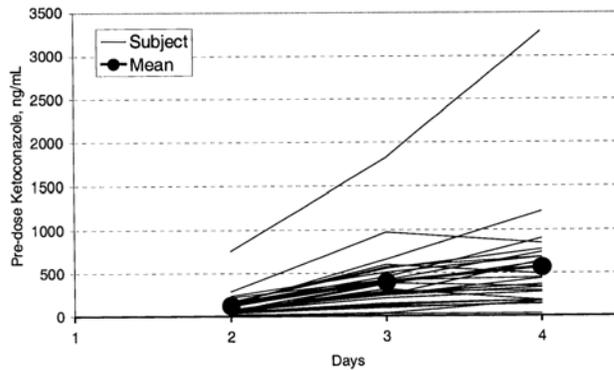
	After E2007	After E2007 and ketoconazole
t_{max} (h)		
Median	0.75	1.00
Mean (SD)	0.92 (0.62)	1.07 (0.64)
Range	0.25–3.00	0.25–2.00
C_{max} (ng/mL)		
Median	31.44	25.92
Geometric mean	29.49	26.66
Mean (SD)	30.44 (7.52)	27.92 (9.07)
Range	17.07–43.22	15.24–48.62
AUC_{0-t_n} (ng/mL.h)		
Median	1055.0	1092.6
Geometric mean	924.8	1082.7
Mean (SD)	1005.8 (393.7)	1200.2 (532.8)
Range	249.5–1880.4	251.5–2456.5
AUC_{0-∞} (ng/mL.h)		
Median	1169.0	1225.0
Geometric mean	1032.1	1234.3
Mean (SD)	1124.6 (458.2)	1373.6 (641.2)
Range	292.4–2241.1	317.5–3185.5
t_{1/2} (h)		
Median	53.4	61.3
Geometric mean	52.4	60.2
Mean (SD)	58.4 (27.8)	67.8 (33.6)
Range	17.1–136.7	22.0–150.9

Table 2. Bioequivalence ratios of E2007 with ketoconazole to E2007 alone, expressed as %

	-90% CI	Mean	+90% CI
C_{max}	80.8%	90.4%	101.2%
AUC_{0-t_n}	108.8%	117.1%	126.0%
$AUC_{0-\infty}$	111.3%	119.6%	128.5%
$t_{1/2}$	108.4%	115.0%	121.9%

Ketoconazole PK:

Figure 2. Individual and mean pre-dose (C_{min}) ketoconazole concentrations versus treatment day



The geometric mean C_{min} of ketoconazole on Day 2 was 87.9 ng/mL, rising to 284.3 ng/mL on Day 3, and to 391.3 ng/mL on Day 4. Statistical analysis of the log-transformed data showed that the mean values on Days 2, 3, and 4 were significantly different.

Reviewer's Comment: Trough concentrations tend to be more variable. The package insert for Nizoral[®] (source, <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=1332>, searched on Oct 21, 2012) states that, after reaching C_{max} , subsequent plasma elimination of ketoconazole is biphasic with a half-life of 2 hours during the first 10 hours and 8 hours thereafter. Based on this, steady-state of ketoconazole plasma concentrations should be achieved within 2 days, and no significant increase of ketoconazole concentrations is expected to occur between Day 3 and Day 4 after once-daily dosing.

Safety Result	Subjects in Group A reported 14 adverse events in Period 1 (E2007 + ketoconazole) and 6 in Period 2 (E2007 alone). Of the 14 events in Period 1, only 2 were considered possibly related to study treatment. 3 of the 6 adverse events in Period 2 were considered to be possibly related to study treatment. All adverse events were mild and short-lived, apart from tiredness and wheezing in Subject 5 that lasted for 4 d 4h and 3 d 8 h, respectively. Subjects in Group B reported 3 adverse events in Period 1 (E2007 alone), and 8 in Period 2 (E2007 + ketoconazole). Of the 8 events in Period 2, 5 were considered possibly related to study treatment. 2 of the 3 adverse events in Period 1 were considered to be possibly related to study treatment. All adverse events were mild and short-lived.
Conclusions	In healthy subjects, a strong CYP3A4 inhibitor, ketoconazole (400 mg once daily) co-administered with E2007 for 8 days (Day 3 – 10) increased E2007 AUC by 20% and slightly prolonged its half-life (67.8 h vs. 58.4 h), implying that CYP3A4/5 plays a limited role in E2007 metabolism in humans.

Study E2007-E044-006: An open label E2007 and carbamazepine interaction study in healthy male volunteers

Objective	<p>1. To compare the pharmacokinetics of a single dose of E2007 before and during treatment with carbamazepine (CBZ).</p> <p>2. To compare the safety and tolerability of a single dose of E2007 before and during treatment with CBZ.</p> <p>3. To compare the pharmacodynamics of a single dose of E2007 before and during treatment with CBZ.</p>
Study Design	<p>This was a three-treatment, fixed-sequence, crossover study in healthy male subjects. For each subject the study consisted of a screening visit (Days -21 to -2), a baseline assessment day (Day -1), a 42-day treatment period (Days 1 to 42) and a follow-up visit up to 10 days after the end of the treatment period (up to Day 52).</p> <p>The treatment period comprised of three phases: Days 1- 10: A <i>single</i> 2-mg dose (2 x 1-mg tablets) of E2007 ('E2007 alone') received on Day 1 Days 11 - 31: Repeated dosing with carbamazepine ('CBZ alone') 100 mg b.i.d. CBZ (Tegretol® tablets) for one week (Days 11-17) then the dose escalated to 200 mg b.i.d. for one week (Days 18-24) and 300 mg b.i.d. for one week (Days 25-31) Days 32-42: A <i>single</i> 2-mg dose of E2007 in the presence of steady-state CBZ ('E2007+CBZ') CBZ dosing was continued at 300 mg b.i.d. for 10 days with a single dose (2 x 1-mg tablets) of E2007 being co-administered on Day 32.</p> <p>The diagram illustrates the study timeline from Day -1 to Day 42. It shows the timing of E2007 dosing (single dots at Day 1 and Day 32), CBZ dosing (100mg bid, 200mg bid, and 300mg bid periods), PD assessments (double-headed arrows at Day 1 and Day 32), PK sampling (stars at Days 10, 17, 24, and 31), and Centre residency (horizontal bars at the bottom). The treatment phases are labeled as E2007 alone (Days 1-10), Carbamazepine alone (Days 11-31), and E2007 + carbamazepine (Days 32-42).</p>
Study Population	<p>20 healthy male subjects (Age: 18-51 yr; Weight: 56-98 kg; Race: 16 Caucasians, 2 Asians, 2 Afro-Caribbeans) were enrolled and received E2007 single dose on Day 1. 16 subjects received CBZ b.i.d. from Day 11 to at least Day 32, with a single dose of E2007 on Day 32. 14 subjects completed the CBZ dosing to Day 41. 6 subjects were withdrawn due to AEs.</p>
Dosage and Administration	<p>E2007 were administered on morning of Day 1 and 32 under fasted state. CBZ: During the ambulatory portion of this study (Days 3 – 29, see above scheme) subjects were asked to attend clinical site each morning to receive their morning dose of CBZ. At this time they were also provided with their evening dose which they were instructed to take 12 hours later.</p>
PK & PD Measurements	<p>E2007: Blood samples were taken at pre-dose of E2007 on Day 1 or Day 32 then at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 168 and 240 hr (Day 11 or Day 42) post-dose of E2007 on Day 1 or Day 32.</p>

	<p>Cortisol and 6-β-hydroxycortisol: Urine samples were obtained at pre-dose of E2007 on Day 1, then at 120h (Day 6) and 240h (Day 11) post-dose of E2007 on Day 1; pre-dose of CBZ on Days 18 and 25 and pre-dose of E2007 on Day 32; then at 240h (Day 42) post-dose of E2007 on Day 32 and at the post-study medical.</p> <p>CBZ: Blood samples before morning doses were collected twice a week in order to monitor the trough plasma level of CBZ, at the following timepoints; pre-dose of CBZ on Days 14, 18, 22, 25, 28 and 32; and at 48h (Day 34), 120h (Day 37) and 240h (Day 42) post-dose of E2007 on Day 32.</p> <p>Pharmacodynamic Measurements: On Day -1 at 0, 0.5, 1, 1.5, 2, 4 and 8 hr, 0 hr on Day 1 then at 0.5, 1, 1.5, 2, 4 and 8 hr and 24 hr (Day 2) post-dose of E2007 on Day 1. On Day 31 at 0, 0.5, 1, 1.5, 2, 4 and 8 hr, 0 hr on Day 32 then at 0.5, 1, 1.5, 2, 4 and 8 hr and 24 hr (Day 33) post-dose of E2007 on Day 32.</p>																																		
Bioanalytical Method		<table border="1"> <tr><td>Analyze</td><td>E2007</td></tr> <tr><td>Method</td><td>HPLC-Fluorescence</td></tr> <tr><td>Internal Std.</td><td>E2007 associated substances</td></tr> <tr><td>LOQ (ng/mL)</td><td>1</td></tr> <tr><td>Calibration Range (ng/mL)</td><td>1, 12, 34, 67.7, 112, 168, 234, 310, 401, 498</td></tr> <tr><td>QC (ng/mL)</td><td>3, 73.4, 213, 426</td></tr> <tr><td>Accuracy</td><td>89 – 103.5%</td></tr> <tr><td>Precision</td><td>2.88 – 6.96%</td></tr> </table>	Analyze	E2007	Method	HPLC-Fluorescence	Internal Std.	E2007 associated substances	LOQ (ng/mL)	1	Calibration Range (ng/mL)	1, 12, 34, 67.7, 112, 168, 234, 310, 401, 498	QC (ng/mL)	3, 73.4, 213, 426	Accuracy	89 – 103.5%	Precision	2.88 – 6.96%																	
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<p>PK & PD Assessments</p>	<p>E2007 PK parameters were determined on Days 1 and 32: C_{max}, t_{max}, λ_z, t_{1/2z}, AUC_{0-t}, AUC_{0-inf}, %AUC_{extra}, CL/F, V_z/F</p> <p>6-β-hydroxycortisol/cortisol ratio: Urine samples for cortisol and 6-β-hydroxycortisol were taken at screening, during the study period, and at the post-study medical to confirm that CYP3A4 was induced by CBZ.</p> <p>CBZ: Plasma carbamazepine concentrations were monitored at intervals throughout the treatment with carbamazepine.</p> <p>PD assessments: Potential sedative effects were evaluated by saccadic eye movement tests and Bond and Lader visual analogue mood scales</p>
<p>Safety Assessment</p>	<p>12-lead ECG, vital signs, laboratory safety tests and adverse events</p>
<p>PK & PD Results</p>	<p>E2007 – Carbamazepine Interaction</p>

E2007 PK

As shown in the Figures and Tables below, E2007 AUC was decreased by 67% with the presence of CBZ, and its t_{1/2} was shortened by half from 57 hrs to 25 hrs. C_{max} of E2007 was less affected and decreased by 25% with co-administration of CBZ. T_{max} of E2007 was not altered. These results suggested that CBZ induced E2007 clearance to 3-fold of that when E2007 was administered alone.

Figure 1. Mean+SD Plasma Concentration vs. Time Profiles of E2007 Following Administration of E2007 Alone and During Treatment with CBZ (linear and semi-log scales)

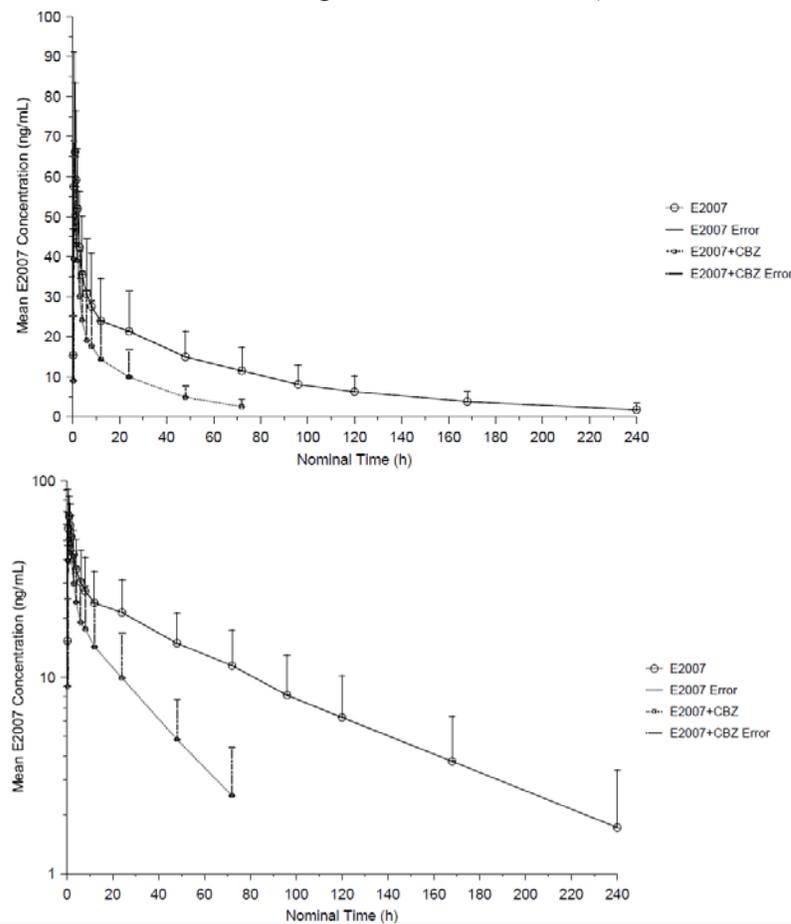


Table 1. PK parameters of E2007 after dosing with E2007 alone and with CBZ (n = 14)

Parameter	Summary Statistic	Treatment	
		E2007 Alone (Day 1) (n=14)	E2007 + Carbamazepine (Day 32) (n=14)
C_{max} (ng/mL)	Mean	74.183	54.684
	SD	23.0982	16.5637
	Geometric mean	70.717	52.527
t_{max} (h)	Median	1.000	1.000
	Range	0.32 - 1.50	0.50 - 1.00
AUC_{0-t} (ng-h/mL)	Mean	2262.48	760.11
	SD	972.897	412.061
	Geometric mean	2072.40	684.16
AUC_{0-inf} (ng-h/mL)	Mean	2484.82	822.09
	SD	1088.312	414.302
	Geometric mean	2267.67	748.61
$t_{1/2z}$ (h)	Mean	60.867	27.957
	SD	21.6588	12.6376
	Harmonic mean	52.207	22.563
	Geometric mean	56.798	25.272
CL/F (mL/min)	Mean	16.164	47.964
	SD	7.5708	17.1902
	Geometric mean	14.699	44.527
V_z/F (L)	Mean	80.270	111.000
	SD	36.9835	49.7288
	Geometric mean	72.270	97.409

Table 2. Statistical analysis of treatment differences between E2007 alone and E2007 + CBZ

Parameter	N	LSmean		Point Estimate (%) ¹ [Lower, Upper 90% CI]	p-values from ANOVA of log-transformed data
		Test (E2007+CBZ)	Reference (E2007 Alone)		
C_{max} (ng/mL)	14	52.527	70.717	74.28 [64.22, 85.92]	0.003
AUC_{0-inf} (ng-h/mL)	14	748.61	2267.66	33.01 [30.31, 35.95]	<0.001
AUC_{0-t} (ng-h/mL)	14	648.17	2072.39	33.01 [30.14, 36.17]	<0.001
$t_{1/2z}$ (h)	14	25.274	56.797	44.50 [39.81, 49.74]	<0.001
CL/F (mL/min)	14	44.528	14.698	302.95 [278.17, 329.93]	<0.001
V_z/F (L)	14	97.410	72.270	134.79 [115.94, 156.70]	0.004

CBZ PK: On average, trough CBZ concentrations were in the therapeutic range (4 to 12 µg/mL) at the time of the administration of E2007 on Day 32 and subsequent post-dose period. Steady-state plasma levels of CBZ appeared to have been attained by Day 28.

Table 3. Summary Trough Plasma Carbamazepine and Metabolite Concentrations

Visit	Carbamazepine (µg/mL)			Carbamazepine 10, 11-epoxide (µg/mL)		
	n	Mean	SD	n	Mean	SD
Day 14	14	3.785	0.6696		NQ	
Day 18	14	3.681	0.8976	2	0.525	0.0212
Day 22	14	5.927	1.0728	13	0.924	0.2316
Day 25	14	5.469	1.6256	11	0.832	0.2550
Day 28	14	6.991	1.1846	14	1.331	0.3153
Day 32	14	7.036	1.3091	14	1.282	0.3354
Day 34	14	6.643	1.2908	14	1.170	0.2731
Day 37	14	7.039	1.3897	14	1.098	0.2361
Day 42	14	6.576	1.4668	13	1.060	0.2415

NQ = Not quantifiable

Cortisol and 6-β-hydroxycortisol:

The average urinary 6-β-hydroxycortisol/cortisol ratio increased over the course of the study, consistent with induction of CYP3A4 metabolism by CBZ and indicating that administration of E2007 on Day 32 took place under conditions of increased CYP450 activity.

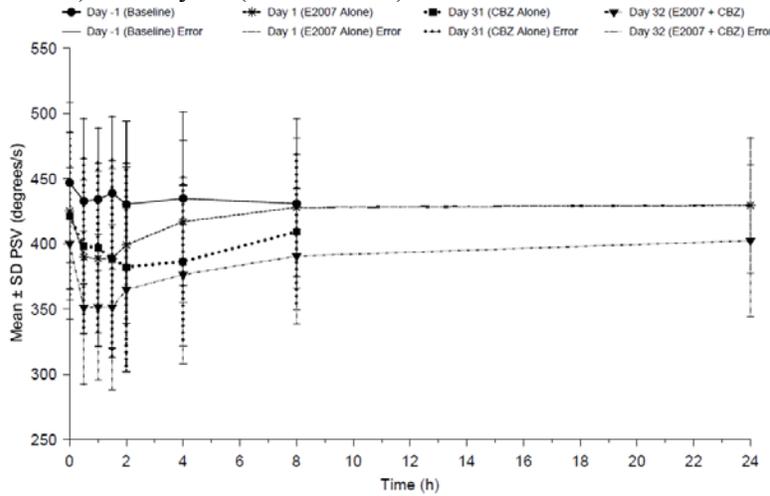
Table 4. Summary 6-β-hydroxycortisol / Cortisol Ratios

Visit	n	6- β -hydroxycortisol / cortisol Ratio	
		Mean	SD
Day 1	13	0.731	0.3752
Day 6	14	0.964	0.4220
Day 11	14	0.942	0.5966
Day 18	14	1.370	0.9820
Day 25	11	1.390	0.8644
Day 32	9	1.484	1.4035
Day 42	7	1.774	1.2328
Post-study	14	2.571	2.1689

Pharmacodynamics:

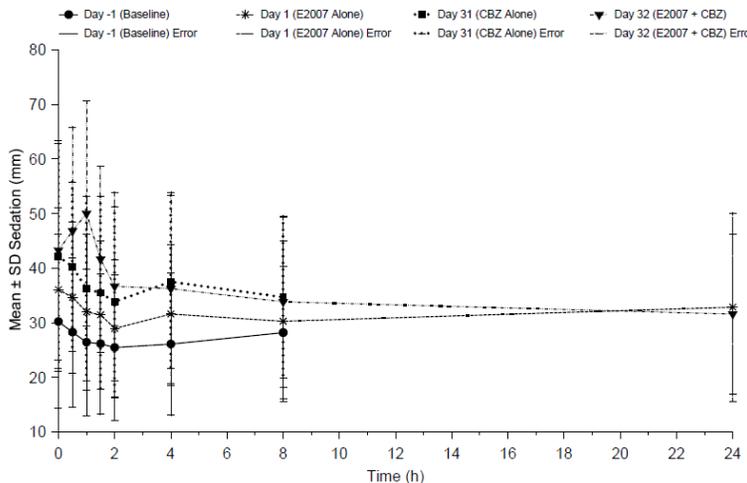
- Peak saccadic velocity: PSV was reduced compared with baseline after administration of either E2007 alone or CBZ alone but the effect when E2007 was co-administered with CBZ was greater than that from either treatment alone.

Figure 2. Mean \pm SD Absolute PSV versus Time Profiles on Day 1 (E2007 Alone), Day 31 (CBZ Alone) and Day 32 (E2007+CBZ)



- Bond and Lader sedation sub-score: sedation effect was observed when E2007 was co-administered with CBZ.

Figure 3. Mean \pm SD Absolute Value of Bond and Lader Subscore Sedation versus Time Profiles on Day 1 (E2007 Alone), Day 31 (CBZ Alone) and Day 32 (E2007+CBZ)



<p>Safety Results</p>	<p>After administration of E2007 alone, AEs occurred predominantly in the general disorder with fatigue and lethargy being the most frequently reported individual events. In contrast, dizziness, headache, somnolence, and the skin and subcutaneous tissue disorders including pruritic rash were the most frequently reported events following co-administration of E2007 with carbamazepine.</p> <table border="1" data-bbox="516 401 1393 569"> <thead> <tr> <th></th> <th>E2007 alone (Days 1–10) (N=20)</th> <th>CBZ alone (Days 11–31) (N=20)</th> <th>E2007+CBZ (Days 32–End) (N=16)</th> </tr> </thead> <tbody> <tr> <td>AEs of all causality</td> <td>13 [0]</td> <td>19 [4]</td> <td>13 [2]</td> </tr> <tr> <td>Treatment-related AEs</td> <td>11 [0]</td> <td>18 [3]</td> <td>8 [2]</td> </tr> <tr> <td>SAEs of all causality</td> <td>0 [0]</td> <td>0 [0]</td> <td>0 [0]</td> </tr> <tr> <td>Out-of range laboratory tests</td> <td>19 [0]</td> <td>19 [0]</td> <td>16 [2]</td> </tr> </tbody> </table> <p>[]: resulting in discontinuation of treatment</p> <p>After E2007 only treatment, out-of-range laboratory values were sporadic and there were no trends in mean values suggesting a relationship between laboratory parameter and E2007 treatment. In contrast, 5 subjects presented ALT, AST and/or gamma GT values above the normal range after co-administration of E2007 with CBZ and this was accompanied by an elevation in mean gamma GT. Two subjects discontinued from the study because of elevated liver enzymes (ALT, AST and gamma GT) which were reported as AEs related to study treatment and which resolved after CBZ dosing was stopped.</p>		E2007 alone (Days 1–10) (N=20)	CBZ alone (Days 11–31) (N=20)	E2007+CBZ (Days 32–End) (N=16)	AEs of all causality	13 [0]	19 [4]	13 [2]	Treatment-related AEs	11 [0]	18 [3]	8 [2]	SAEs of all causality	0 [0]	0 [0]	0 [0]	Out-of range laboratory tests	19 [0]	19 [0]	16 [2]
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<p>Conclusions</p>	<ul style="list-style-type: none"> • Carbamazepine (300 mg, b.i.d, i.e, 600 mg/day) induced oral clearance of E2007 to 3-fold of control group, and thus reduced E2007 AUC by 67%. E2007 t_{1/2} was shortened by about half with the presence of CBZ. • Measures of sedation showed a pharmacodynamic interaction between E2007 and CBZ in healthy volunteers. Both a single 2-mg dose of E2007 and CBZ 300 mg b.i.d. dosing reduced peak saccadic velocity but co-administration of CBZ with E2007 caused greater effects than either drug administered alone. When assessed by Bond and Lader sedation subscore, sedation effect was only observed when E2007 was co-administered with CBZ but not for either treatment alone. 																				

Study E2007-E044-007: A Single Radio-labeled Dose Absorption, Metabolism and Elimination Study of 14C-E2007 in Healthy Elderly Volunteers

Objective	<ul style="list-style-type: none"> • <i>Primary objective:</i> to gain information on the absorption, metabolism and elimination of 14C-E2007 after a single radiolabeled dose in healthy elderly volunteers. Mass balance was investigated along with the pharmacokinetics of E2007, the radiokinetics of administered 14C-E2007 and the nature of the E2007 metabolites in plasma, urine and faeces. • <i>Secondary objective:</i> to assess the safety and tolerability of a single oral dose of 2 mg 14C-E2007
Study Design	<p>Treatment: Eight healthy elderly volunteers (4 males and 4 females) received single dose of 2 mg E2007 containing 7.4 kBq (200 nCi) of radiochemically pure 14C-E2007 in the morning under fasted state.</p> <p>Observation period: in clinic from Day -1 prior to drug administration (i.e. Day 1) up to Day 8 post-dose; ambulatory visits on Days 10, 12, 15, 22, 29, and 36 after drug administration; follow-up on Day 43 post-dose</p>
Study Population	<p>Age: 65 – 79 yr; Weight: 53.6 – 88.6 kg; Caucasians 21 subjects screened, 8 received medication and completed.</p>
PK Sampling	<p>1. Blood sampling:</p> <p>1.1. for plasma radiokinetics (14C-radioactivity) and plasma E2007 pharmacokinetics: at screening, pre-dose, and at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36, 48, 72, 96, 120, and 168 h (i.e. Day 8) after drug administration and at ambulatory visits (last sampling time was 1008 hr);</p> <p>1.2. for whole blood radiokinetics (14C-radioactivity): at screening, pre-dose, and at 1, 8, 24 and 96 h after drug administration, and at ambulatory visits Day 22 (504 h) and 29 (672 h)</p> <p>1.3. for metabolic profiling: plasma samples at 0.5 hr post-dosing.</p> <p>2. Urine sampling:</p> <p>2.1. for radiokinetics (14C-radioactivity) and mass balance: pre-dose, and during following intervals: 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168h (i.e. Day 8), and between the ambulatory visits, i.e. during following intervals: 168-216, 216-264, 264-336, 336-504, 504-672, 672-840, and 840-1008 h</p> <p>2.2. for metabolic profiling: urine samples collected between 4 and 8 hr post-dosing.</p> <p>3. Faeces sampling:</p> <p>3.1. for mass balance: pre-dose, and in 24 h intervals from 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168 h (i.e. Day 8), and between the ambulatory visits, i.e. during following intervals: 168-216, 216-264, 264-336, 336-504, 504-672, 672-840, and 840-1008 h</p> <p>3.2. for metabolic profiling: feces samples collected between 144 and 168 hr</p>
Bioanalytical Method	<p>1. Determination of 14C in plasma, whole blood, urine and faeces</p> <p>This study utilized accelerator mass spectrometry (AMS) to measure radioactivity of samples rather than liquid scintillation counting (LSC) method. AMS is a nuclear physics technique that permits the measurement of isotopes in a sample on the basis of their mass/charge ratio and is more sensitive than decay counting methods. The high sensitivity of AMS enables use of lower doses of radioactivity in clinical studies than would be required</p>

using conventional LSC. This study employed AMS for sample analysis in order to allow use of small amounts of radiolabelled E2007 to minimize the exposure of subjects to radioactivity.

The AMS results were expressed as Percent Modern Carbon (pMC) values, which were converted to dpm/mL or dpm/g. LSC was used to measure the total radioactivity (dpm) of the dosing tablet (mg) [Specific activity of dosing tablet was determined to be 233363 dpm/mg (4.67×10^5 dpm / 2 mg)]. Thus, AMS results were further converted to ng/mL for plasma samples. The Lower Limit of Quantitation was 0.17 ng eq/mL.

2. Metabolic profiling in plasma, urine and feces

The pooled plasma and feces samples were extracted and the extracts were analyzed by HPLC and AMS to determine the extraction efficiencies and to generate metabolic profiles. The pooled urine samples were injected directly on a HPLC system and then underwent AMS analysis.

Plasma extraction

One volume of 0.01% v/v hydrochloric acid (HCl) in acetonitrile was added to one volume of the plasma sample. After vortexing, the mixture was sonicated for 45 min in iced water and centrifuged at 9600 rpm for 20 min at room temperature. The supernatant was removed into a separate vial and retained. One volume of 0.01% HCl in acetonitrile/water (1:1 v/v) was added to the residue. The residue was manually disrupted, the mixture was vortexed, sonicated and centrifuged as previously. The supernatants were combined and analyzed by AMS.

Feces extraction

Prior to extraction, the feces sample was diluted approximately 4 fold with water. Two volumes of acetonitrile were added to one volume of the feces sample. After vortexing, the mixture was sonicated for 30 min and centrifuged at 9600 rpm for 15 min at room temperature. The residue was manually disrupted, the mixture was vortexed, sonicated and centrifuged as previously. The supernatant was removed into a separate vial and retained. One volume of acetonitrile was added to the residue. The residue was manually disrupted, the mixture was vortexed, sonicated and centrifuged as previously. The supernatant was removed. This process was repeated two additional times. The supernatants were combined and analyzed by AMS.

The extraction efficiencies for plasma and feces pools were 59.7% - 68.8% and 83.2% - 83.5%, respectively.

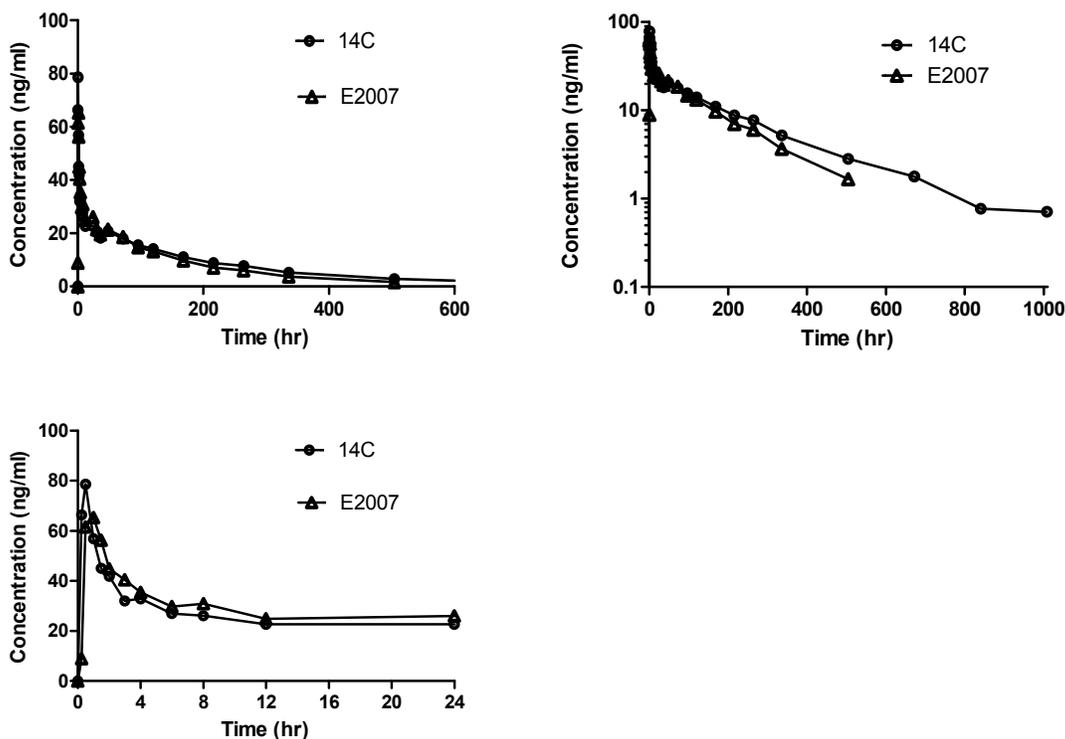
HPLC fractionate and AMS analysis

Urine samples and extracted plasma and feces samples were fractionated by HPLC first. The eluent was collected as a series of fractions every 30 seconds from 1 to 15.5 min. Each fraction (a total of 29 per HPLC run) was analyzed by AMS to determine the radioactivity. A radio-chromatogram was created based on the radioactivity in each fraction. The percentage contribution to the total radioactivity for each peak in the radio-chromatograms was determined as the ratio of ^{14}C in each peak to the total ^{14}C recovered from the HPLC column.

	3. Measurement of parent drug in plasma																
	<table border="1"> <tr> <td>Analyze</td> <td>E2007</td> </tr> <tr> <td>Method</td> <td>HPLC-Fluorescence</td> </tr> <tr> <td>Internal Std.</td> <td>E2007 associated substance</td> </tr> <tr> <td>LOQ (ng/mL)</td> <td>1</td> </tr> <tr> <td>Calibration Range (ng/mL)</td> <td>1, 12, 34, 68, 113, 167, 231, 312, 398, 500</td> </tr> <tr> <td>QC (ng/mL)</td> <td>3, 73.4, 217, 424</td> </tr> <tr> <td>Accuracy</td> <td>93.5 – 100.54%</td> </tr> <tr> <td>Precision</td> <td>2.53 – 5.67%</td> </tr> </table>	Analyze	E2007	Method	HPLC-Fluorescence	Internal Std.	E2007 associated substance	LOQ (ng/mL)	1	Calibration Range (ng/mL)	1, 12, 34, 68, 113, 167, 231, 312, 398, 500	QC (ng/mL)	3, 73.4, 217, 424	Accuracy	93.5 – 100.54%	Precision	2.53 – 5.67%
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PK Assessments	Radiokinetics: ¹⁴ C-radioactivity in plasma, whole blood, urine, and faeces; C _{max} , T _{max} , k _{el} , t _{1/2} , AUC _{last} , AUC _{inf} , %AUC _{extra} , CL/F, V _z /F, A _e urine, A _e faeces, A _e total																
Safety Assessment	Adverse events, vital signs, ECG, clinical laboratory, neurological and physical examination.																
Pharmacokinetic Results	¹⁴ C (E2007 + metabolites) and Unlabeled Perampanel (E2007) Metabolic Profiling in Plasma, Urine and Feces																

1. ¹⁴C (E2007 + metabolites) and Parent E2007 in Plasma

Figure 1. Mean Plasma Concentration vs. Time Profiles of Parent E2007 and Total Radioactivity Following Oral Administration of a Single 2 mg (200 nCi) Perampanel Dose (geometric mean data presented in linear and semi-log scales)



The PK profile of ¹⁴C (E2007 + metabolites) was largely comparable to that of the unlabelled parent compound. The terminal half-life of ¹⁴C (E2007 + metabolites) was longer, i.e. 199.4 h (geometric mean, compared to 130.7 hrs for unchanged drug), and ¹⁴C-radioactivity could still be measured in plasma up to 1008h post-dose.

Table 1. Plasma PK and Radiokinetic Parameters Following Oral Administration of a Single 2 mg (200 nCi) Perampanel Dose

	Males (N=4)	Females (N=4)	All Subjects (N=8)
Pharmacokinetic Profile of Perampanel			
C_{max} (ng/mL)			
Mean	79.8	84.9	82.4
SD	25.8	22.2	22.5
t_{max} (h)			
Median	1.00	0.50	0.75
Min – Max	(0.50 – 1.00)	(0.50 – 1.00)	(0.50 – 1.00)
$t_{1/2}$ (h)			
Mean	109	163	136
SD	31.5	16.5	37.1
$AUC_{(0-t)}$ (ng-h/mL)			
Mean	4165	5778	4972
SD	1377	1576	1619
$AUC_{(0-inf)}$ (ng-h/mL)			
Mean	4382	6103	5243
SD	1411	1575	1662
Radiokinetic Profile of ^{14}C			
C_{max} (ng.eq/mL)			
Mean	83.5	84.8	84.1
SD	12.3	22.3	16.7
t_{max} (h)			
Median	0.50	0.38	0.50
Min – Max	(0.5 – 0.5)	(0.25 – 1.00)	(0.25 – 1.00)
$t_{1/2}$ (h)			
Mean	205	201	203
SD	52.2	36.1	41.6
$AUC_{(0-t)}$ (ng.eq.h/mL)			
Mean	5439	6895	6167
SD	1854	1811	1866
$AUC_{(0-inf)}$ (ng.eq.h/mL)			
Mean	5577	7135	6356
SD	1887	1933	1955

Reviewer's Comment: As shown in the above Table, parent drug accounted for 80% of the total radioactivity in plasma (77% in males, 84% in females). Based on metabolic profiling results of plasma samples, the sponsor claimed that no circulating metabolites of perampanel were detected in plasma. However, only plasma sample collected at 0.5 hr post-dosing was analyzed. For a drug with low clearance like E2007, first-pass metabolism is negligible. Thus, it is not expected to see much formation of metabolites at a time point around T_{max} for a rapidly absorbed drug. The metabolic profiling result obtained for this early timepoint can not be generalized to the whole profile of plasma concentrations. More informative results for metabolic profiling in plasma were obtained from the absolute bioavailability study (E2007-E044-017) where plasma samples collected at multiple timepoints post-dosing were analyzed by AMS and LC/MS-MS. Please refer to that study review for details.

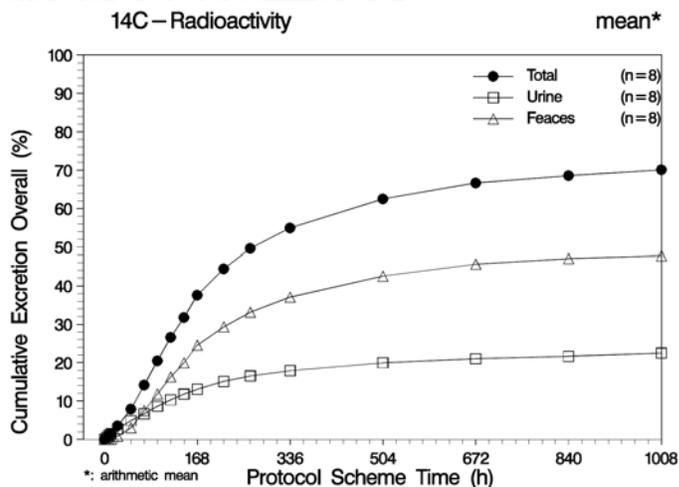
2. Radiokinetics in urine and feces

Table 2. Mean cumulative excretion of ^{14}C -radioactivity in urine and faeces; overall (mean (min-max)) and per gender (mean)

	Ae_{urine} %	Ae_{faeces} %	Ae_{total} (%)
Overall	22.3	47.8	70.1
n = 8	(19.7-27.5)	(39.8-58.2)	(61.6-79.3)
Male	23.8	50.1	74.0
n = 4			
Female	20.8	45.4	66.2
n = 4			

% = percentage of dose administered

Figure 2. Mean cumulative ¹⁴C-radioactivity excretion versus time for urine, faeces and total excretion after oral administration



Over a collection period of 42 days, 70% of administered radiolabeled dose was recovered, with 48% of dose found in feces and 22% of dose recovered in urine. Only 3% (mean value, range: 0.07% – 9.53%, median value: 1.5%) of total radioactivity was recovered from feces during the first 48 hr post-dosing, indicating that most of dose administered has been absorbed from GI tract.

3. Metabolic profiling

Reviewer's Comment: It should be aware that in this study metabolic profiling was only conducted for very limited sample collection periods for urine and feces (Table 3). Thus, the results can not represent the whole profiles of E2007 and its metabolites in excreta.

For the samples analyzed, most of the drug-related material was present as metabolites and unchanged E2007 was only a minor component. The major metabolite species in excreta were tentatively identified as hydroxylated E2007 and glucuronide conjugates.

Table 3. Relative abundance of metabolites of E2007 in pooled urine and faeces samples (mean for all subjects)

Urine (4-8 h)		Faeces (144-168 h)		Identity
Retention time (min)	% of chromatogram	Retention time (min)	% of chromatogram	
4.0	60.4	3.0	23.4	Unknown*
		4.5-5	14.1	Glucuronide conjugates**
6.5	17.7	7.0	40.0	ER-179392-00
8.5	11.1	8.5	6.5	Unknown
-	-	10.5	9.4	Parent E2007
13.0	7.9	-	-	ER-260862-00

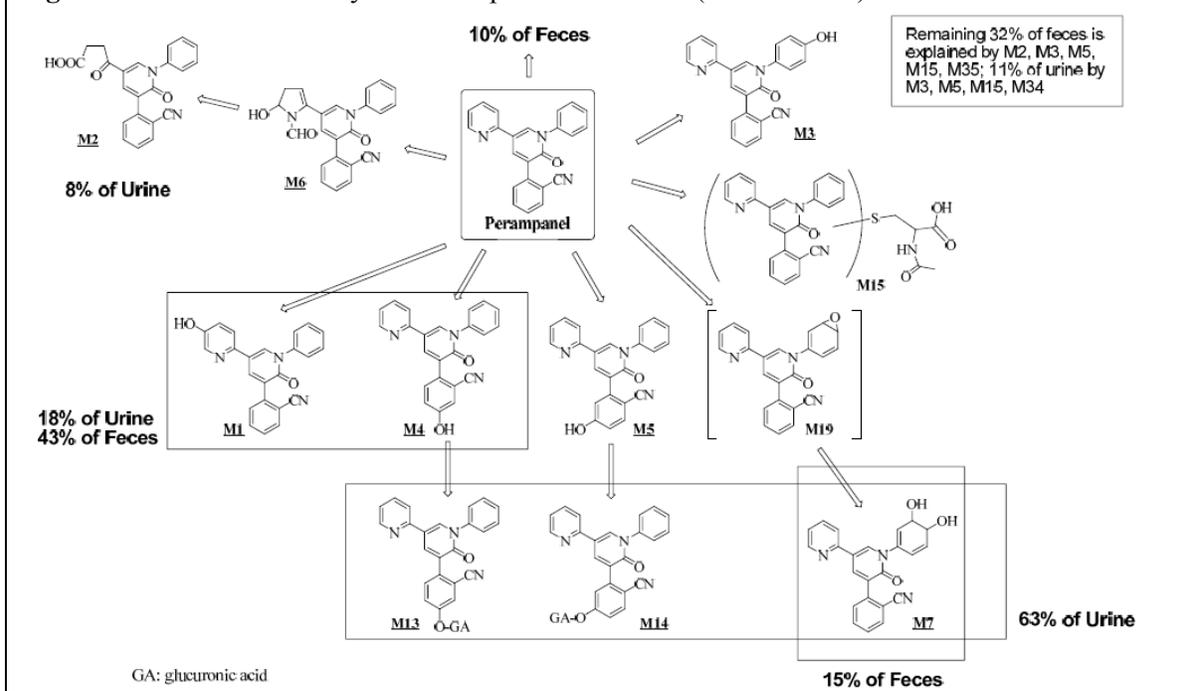
* considered to be extraneous material eluting through the column unretained.

** Two glucuronide conjugates but position of conjugation not determined.

ER-179392 was eventually named as M1. ER-260862 is finally named as M2.

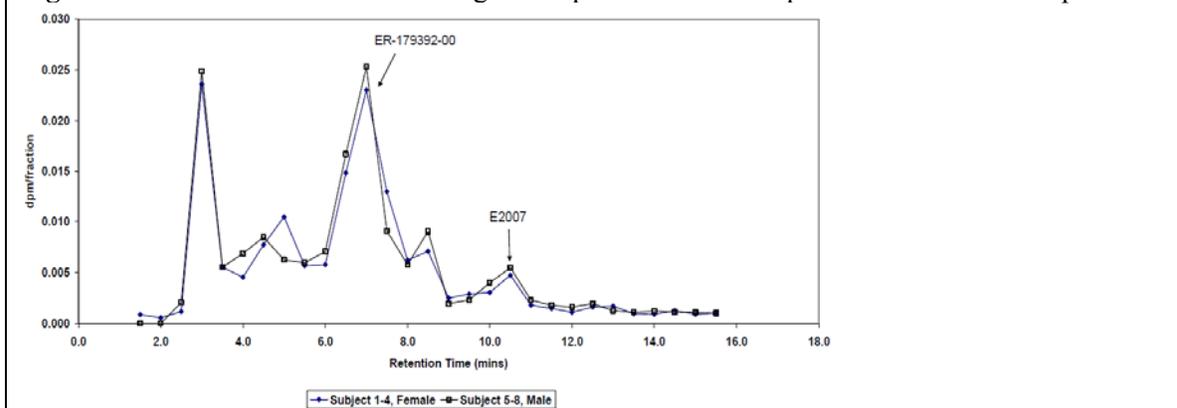
Reviewer's Comment: In the Summary of Clinical Pharmacology provided by the sponsor, a scheme of metabolic pathways of perampanel in humans was proposed with percentages of parent drug and metabolites in urine and feces (Figure 3). The sources of these percentage numbers remain unclear. It appears that some of the numbers came from this study (Table 3).

Figure 3. Metabolic Pathways of Perampanel in Humans (In Vivo Data)



The numbers in the graph are not reliable for several reasons: First, as mentioned above, metabolic profiling results were obtained only for 4-8 hr urine sample and 144-168 hr feces sample, which may not reflect the profiles for samples collected at other periods; Secondly, the extraction efficiency for feces samples in this study was claimed as 83%, much higher than those (20-30%) reported in the absolute bioavailability study (E2007-E044-017). Metabolic profiling for both studies was conducted by the same company and the extraction procedures for feces samples were similar (refer to study 017 review for details about extraction procedure). The large discrepancy of extraction efficiency is unexplainable. If the extraction efficiency of feces sample analysis in this study was essentially similar to those (i.e., 20-30%) in the other study, the results from this study would be only qualitative due to low extraction efficiency. Lastly, the % of chromatogram (9.4%) reported for parent drug in feces sample may be an over-estimation, as there was interference from other peaks as shown in the following figure. Overall, the information provided by this study in terms of metabolic profiling in excreta is very limited and more useful results were obtained from the absolute bioavailability study E2007-E044-017.

Figure 4. HPLC-AMS radio-chromatogram of pooled faeces samples for the 144-168 hr period



4. Blood/Plasma ratio for ¹⁴C (E2007 + metabolites)

The ratio of ¹⁴C in whole blood to plasma was between 0.73 to 0.81 during the first 96 hours post-dosing.

Table 4. Mean ratio ¹⁴C-Radioactivity Whole Blood/Plasma (n = 8)

Time* h	n	mean	SD
1	8	0.73	0.16
8	8	0.77	0.15
24	8	0.78	0.12
96	8	0.81	0.10
504	7	1.24	0.44
672	7	1.27	0.69

* = post-dose

Safety Results	There were few adverse events during the study and none was considered by the investigator to be treatment-related. There were no clinically important changes in clinical laboratory values, vital signs, ECG parameters, or physical and neurological examination data during the study.
Conclusions	<p>1. During a period of 42 days after dosing, 70% of total radioactivity administered was recovered, with 22% of dose given found in urine and 48% of dose recovered in feces. Only 3% of the total radioactivity was recovered in feces within the first 48 hrs post-dosing.</p> <p>2. Unchanged perampanel accounted for about 80% of total drug-related material in plasma.</p>

Study E2007-A001-008: An Open-Label, Randomized, Single Oral Dose Bioequivalence Assessment of Two Formulations of E2007 in Healthy Subjects

Objective	<p><i>Primary objective:</i> To evaluate the bioequivalence of a new formulation of E2007 (test formulation) compared to a reference formulation after a single oral dose in healthy subjects.</p> <p><i>Secondary objective:</i> to determine the safety and tolerability of E2007 and to study the pharmacokinetic (PK) profile of E2007.</p>																																
Study Design	<p>This was an open-label, randomized, two-period. Two-sequence crossover study to compare two formulations of E2007, the test (T, Formulation B) and the reference (R, Formulation A) formulations for bioequivalence. Each dose of E2007 was separated by a washout period of at least 6 weeks.</p>																																
Study Population	<p>All 34 subjects enrolled were analyzed for safety. Demographic features: age: 18 – 45, mean 29.7 yr; weight: mean 75 kg; race: white (82.4%); gender: male (67.6%).</p>																																
Dosage and Administration	<p>A single oral dose (2 x 1 mg tablets) of E2007 in either the test (T) or reference (R) formulation was administered after overnight fast.</p>																																
PK Sampling	<p>Blood samples were collected at pre-dose, and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 168, 216, 264 and 312 hours after each dose</p>																																
Bioanalytical Method	Analyze	E2007																															
	Method	LC-MS/MS																															
	Internal Std.	E2007 associated substances																															
	LOQ (ng/mL)	0.25																															
	Calibration Range (ng/mL)	0.25, 0.5, 1, 3, 10																															
	QC (ng/mL)	0.75, 15, 90																															
	Accuracy	93.5 – 106.3%																															
	Precision	7 – 13.3%																															
PK Assessments	C_{max} , T_{max} , AUC_{0-last} , $AUC_{0-\infty}$, $t_{1/2}$																																
Safety Assessment	<p>12-lead ECG, vital signs, laboratory safety tests and adverse events</p>																																
PK Results	<p>E2007</p>																																
<p>E2007 PK: Formulation B was bioequivalent to Formulation A as assessed by AUC and Cmax. Tmax was similar between the two formulations.</p>																																	
<p>Figure 1. Arithmetic Mean Plasma Concentration vs. Time Profiles of E2007 (0-8 hr, linear scale)</p>																																	
<table border="1"> <caption>Approximate data points from Figure 1</caption> <thead> <tr> <th>Scheduled Collection Time (hours)</th> <th>Reference Formulation (ng/mL)</th> <th>Test Formulation (ng/mL)</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>~5</td> <td>~5</td> </tr> <tr> <td>0.25</td> <td>~45</td> <td>~45</td> </tr> <tr> <td>0.5</td> <td>~55</td> <td>~55</td> </tr> <tr> <td>1</td> <td>~65</td> <td>~65</td> </tr> <tr> <td>2</td> <td>~50</td> <td>~50</td> </tr> <tr> <td>3</td> <td>~45</td> <td>~45</td> </tr> <tr> <td>4</td> <td>~40</td> <td>~40</td> </tr> <tr> <td>6</td> <td>~30</td> <td>~30</td> </tr> <tr> <td>8</td> <td>~28</td> <td>~28</td> </tr> </tbody> </table>				Scheduled Collection Time (hours)	Reference Formulation (ng/mL)	Test Formulation (ng/mL)	0	~5	~5	0.25	~45	~45	0.5	~55	~55	1	~65	~65	2	~50	~50	3	~45	~45	4	~40	~40	6	~30	~30	8	~28	~28
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0	~5	~5																															
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6	~30	~30																															
8	~28	~28																															

Figure 2. Arithmetic Mean Plasma Concentration vs. Time Profiles of E2007 (0-120 hr, linear scale)

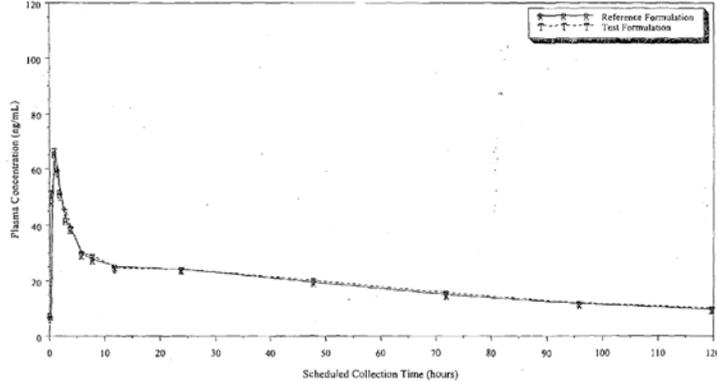


Table 1. Summary PK parameters of E2007

PK Parameter		T Formulation (n=32)	R Formulation (n=32)
AUC ₀₋₁ (ng*hr/mL)	Mean ¹ (SE)	3264 (198)	3116 (177)
	Min-max	1600-5325	1669-5853
	CV	34.32%	32.13%
	Lsmean (SE)	3252 (70.86)	3106 (70.86)
AUC _{0-inf} (ng*hr/mL)	Mean ¹ (SE)	3846 (347)	3683 (390)
	Min-max	1628-10582	1702-13944
	CV	51.04%	59.93%
	Lsmean (SE)	3836 (237.9)	3651 (237.9)
C _{max} (ng/mL)	Mean ¹ (SE)	75.59 (3.15)	72.56 (3.17)
	Min-max	39.92-111.2	39.36-113.5
	CV	23.54%	24.71%
	Lsmean (SE)	75.71 (1.573)	72.97 (1.573)
t _{max} (hr)	Mean ¹ (SE)	1.000 (0.081)	1.047 (0.069)
	Min-max	0.500-3.000	0.500-1.500
	CV	45.79%	37.11%
	Lsmean (SE)	1.002 (0.067)	1.046 (0.067)
t _{1/2} (hr)	Mean ¹ (SE)	97.45 (12.8)	97.98 (17.3)
	Min-max	35.37-429.7	30.24-592.8
	CV	74.17%	99.62%
	Lsmean (SE)	97.23 (13.52)	96.22 (13.52)

hr = hour SE = standard error CV = coefficient of variation

¹ Arithmetic mean.

Table 2. Results of Bioequivalence Evaluation

Pharmacokinetic Parameter	Geometric Least-Square Mean		Ratio of Geometric Means (%) (B:A)	90% Confidence Interval
	Formulation B Test (N=32)	Formulation A Reference (N=32)		
C _{max} (ng/mL)	73.5	70.8	104	98.8, 109
AUC _(0-312h) (ng·h/mL)	3063	2966	103	97.7, 109
AUC _(0-inf) (ng·h/mL)	3439	3303	104	95.4, 114

Safety Result	Approximately half of the subjects experienced at least one TESS while taking Formulation B (53.1 %) and Formulation A (50.0%). A total of 84 TESS were reported during the study. No subjects discontinued from the study because of a TESS. The most common TESS were dizziness and headache. The majority of TESS (65 of 84 events) were mild in severity, with the rest being moderate. A total of 11 TESS were considered to be probably related to study treatment. A total of 7 subjects reported at least one TESS that was considered probably related to study treatment. All of these TESS were single occurrences except for dizziness.
Conclusions	Formulation B is bioequivalent to Formulation A.

Study E2007-E044-009: A two part, randomized study to identify an E2007 dosing regimen suitable to achieve supratherapeutic plasma concentrations in healthy young volunteers.

Objective

Primary objective: To identify an E2007 dosing regimen suitable to achieve supratherapeutic plasma concentrations in healthy young volunteers.

Secondary objective:

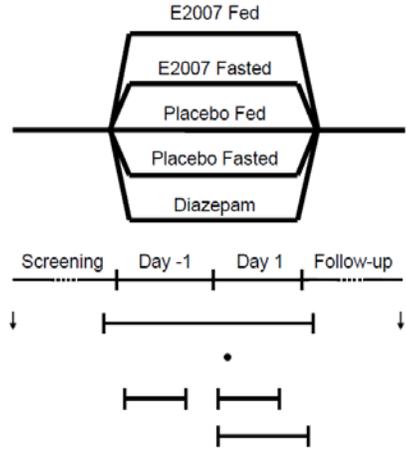
- To quantify the effects of E2007 on sedation and cognitive function pharmacodynamic (PD) parameters.
- To explore the effects of E2007 on quantitative EEGs.
- To investigate the impact of food on the PD effects of E2007.
- To investigate the impact of time of dosing on the PD of E2007.
- To investigate the development of tolerance to the PD effects of E2007 over time.
- To explore the relationship between E2007 plasma concentrations and QT interval duration.

Study Design

The study consisted of two separate parts: a single dose phase and a repeated dosing phase.

Part 1: Single dose Phase

A randomized, active- and placebo-controlled, five treatment, *parallel* group study to investigate the impact of food on the PD effects of E2007. Subjects were randomized to receive a single 6 mg dose (3 x 2-mg tablets, Formulation B) of E2007 (n=8 for each group) or placebo (n=4 for each group) administered either after food or while fasted, or a single 5 mg dose of the active comparator diazepam while fasted (n=8). E2007 treatment was blinded by the use of matching placebo but diazepam treatment was open label.



Dietary Composition of Breakfasts Provided During Single Dose Phase

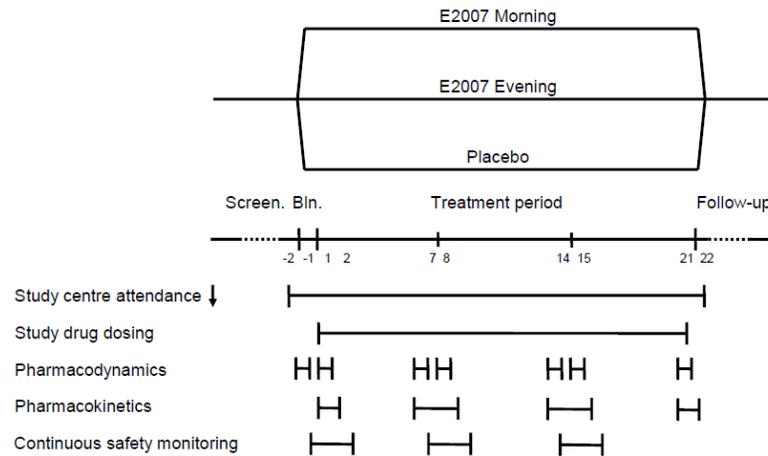
	Weight (g)	Fat [#]	Calories (Kcal)	Protein [#]
High fat breakfast*	331	41	610	30
Wholemeal toast and Flora x 2	-	16.2	297	29
Total		57.2	907	59

Grams per portion

*High fat breakfast contains: 1 slice of bacon, 2 sausages, scrambled eggs, chopped tomatoes, potato roasties (56 % of total calories are from fat).

Part 2: Repeated Dosing Phase

A randomized, double-blind, placebo-controlled, three treatment, parallel group study to investigate the impact of time of dosing and the development of tolerance on the pharmacodynamic effects of E2007 after repeated dosing. Subjects were randomized to receive either E2007 once daily in the morning (n=8) or evening (n=8), or placebo twice daily (b.i.d, n=4) for 21 days.



E2007 treatment was started from 6 mg E2007 q.d. and escalated to a maximum 10 mg q.d. in 2 mg increments at seven day intervals. Morning and evening dosing times were separated by 12 hr and in all treatment groups study drug dosing was administered *immediately* before breakfast and dinner.

AM dosing: 6 mg Day 1-7, 8 mg Day 8-14, 10 mg Day 15-21

PM dosing: 6 mg Day -1 – 6, 8 mg Day 7 – 13, 10 mg Day 14 – 20

Day	Time	E2007 Morning	E2007 Evening	Placebo Morning	Placebo Evening
-1	AM	-	-	-	-
	PM	3 x placebo	3 x 2 mg E2007	3 x placebo	3 x placebo
1 to 6	AM	3 x 2 mg E2007	3 x placebo	3 x placebo	3 x placebo
	PM	3 x placebo	3 x 2 mg E2007	3 x placebo	3 x placebo
7	AM	3 x 2 mg E2007	3 x placebo	3 x placebo	3 x placebo
	PM	4 x placebo	4 x 2 mg E2007	4 x placebo	4 x placebo
8 to 13	AM	4 x 2 mg E2007	4 x placebo	4 x placebo	4 x placebo
	PM	4 x placebo	4 x 2 mg E2007	4 x placebo	4 x placebo
14	AM	4 x 2 mg E2007	4 x placebo	4 x placebo	4 x placebo
	PM	5 x placebo	5 x 2 mg E2007	5 x placebo	5 x placebo
15 to 20	AM	5 x 2 mg E2007	5 x placebo	5 x placebo	5 x placebo
	PM	5 x placebo	5 x 2 mg E2007	5 x placebo	5 x placebo
21	AM	5 x 2 mg E2007	5 x placebo	5 x placebo	5 x placebo
	PM	-	-	-	-

	<p align="center">Content of Meals and Snacks Provided During the Study</p> <table border="1"> <thead> <tr> <th>Study Part</th> <th>Breakfast</th> <th>Lunch</th> <th>Tea</th> <th>Evening Meal</th> </tr> </thead> <tbody> <tr> <td>Part 1 and Part 2</td> <td>A selection of cereal.* Two pieces of toast with flora + jam, marmalade or marmite.*</td> <td>A hot meal, e.g. lasagne, chips and salad</td> <td>Biscuits and a piece of fruit</td> <td>A filled baguette - fillings were ham, cheese, turkey, chicken tikka and salad (optional). A packet of crisp. Yoghurt. A piece of fruit.</td> </tr> </tbody> </table> <p>*Part 2 Breakfast only: See Table 5 for breakfasts provided during Part 1 of the study. (note: Table 5 refers to the table above with the title of “Dietary Composition of Breakfasts Provided During Single Dose Phase”.</p>	Study Part	Breakfast	Lunch	Tea	Evening Meal	Part 1 and Part 2	A selection of cereal.* Two pieces of toast with flora + jam, marmalade or marmite.*	A hot meal, e.g. lasagne, chips and salad	Biscuits and a piece of fruit	A filled baguette - fillings were ham, cheese, turkey, chicken tikka and salad (optional). A packet of crisp. Yoghurt. A piece of fruit.
Study Part	Breakfast	Lunch	Tea	Evening Meal							
Part 1 and Part 2	A selection of cereal.* Two pieces of toast with flora + jam, marmalade or marmite.*	A hot meal, e.g. lasagne, chips and salad	Biscuits and a piece of fruit	A filled baguette - fillings were ham, cheese, turkey, chicken tikka and salad (optional). A packet of crisp. Yoghurt. A piece of fruit.							
Study Population	<p><i>Part 1:</i> 32 subjects were randomized and 31 subjects completed the study (one subject in diazepam group discontinued the study) The following demographic information represented placebo, 6 mg fasted, 6 mg fed and diazepam treatment groups, respectively. Age: 24.1 ± 6.3 yr, 30.1 ± 8.1 yr, 29.6 ± 9.7 yr, 28.6 ± 8.6 yr Weight: 80.5 ± 11.3 kg, 78.6 ± 11.8 kg, 75.3 ± 8.7 kg, 78.1 ± 15 kg. Gender: Male – 75%, 87.5%, 87.5% and 85.7%. Race: Most of subjects were Caucasians</p> <p><i>Part 2:</i> 20 subjects were randomized and 19 completed the study. One subject receiving 6 mg in evening dosing group discontinued form the study. The following demographic features represented placebo, morning dosing and evening dosing groups, respectively. Age: 23.8 ± 4.9 yr, 23.6 ± 4.1 yr, 27.5 ± 11.5 ye Weight: 69.3 ± 5.9 kg, 75 ± 11.6 kg, 73.4 ± 11.7 kg Gender: Male – 50%; Race: most of the subjects were Caucasians</p>										
PK & PD Measurements	<p>E2007 PK: Part 1: Blood samples were taken at pre-dose (-0.5 hr) and at 0.5, 1, 2, 3, 4, 6, 12 and 24 hr post-dosing. Part 2: Blood samples were taken at pre-dose (-0.5 hr) and 1, 2, 3, 4, 6, and 12 hr after <u>morning dosing</u> on Days 1, 7, 8, 14, 15 and 21. Samples were also taken before (-0.5 hr) morning dosing on Days 2, 9, and 16, and on the morning of Day 22.</p> <p>PD: <i>Part 1:</i> Peak saccadic velocity were measured before (-0.5 hr) and 0.5, 1, 2, 3, 4, 6 and 12 hr after drug administration on Day 1 and <i>corresponding</i> timepoints on Day -1. Quantitative EEGs and the cognitive function test battery were recorded 1 hr (fasted groups) or 3 hr (fed groups) after drug administration on Day 1 and corresponding timepoints on Day -1.</p> <p><i>Part 2:</i> Peak saccadic velocity were measured before (-0.5 hr) and 1, 2, 3, 4, 6 and 12 hr after study drug administration on Days 1, 7, 8, 14, 15 and 21 and <i>corresponding</i> timepoints on Day -1.</p> <p>Bond and Lader visual analogue scale (VAS) subjective mood scales and the cognitive function test battery were recorded before (-0.5 hr) and 3 hr after morning drug dosing on Days 1, 7, 8, 14, 15 and 21 and corresponding timepoints on Day -1.</p>										

Bioanalytical Method	Analyze	E2007
	Method	HPLC-Fluorescence
	Internal Std.	E2007 associated substances
	LOQ (ng/mL)	1
	Calibration Range (ng/mL)	1, 12, 34, 68, 110, 165, 235, 310, 400, 500
	QC (ng/mL)	2.95, 73.3, 212.6, 425
	Accuracy	92.3 – 101.4%
Precision	3.43 – 8.34%	

PK & PD Assessments	<p>PK: AUC0-24, Cmax, and Tmax on Day 1, AUC0-24, Cmax, Tmax, Cav, PTF ratio (Fluctuation Index) and Rac (Accumulation ratio) on Days 7, 8, 14, 15 and 21 for AM dosing group. Ctrough on Days 1, 2, 7, 8, 9, 14, 15, 16, 21 and 22 (AM dosing group) Or 1, 7, 8, 14, 15 and 21 (PM dosing group).</p> <p>PD: Peak saccadic velocity: Change from baseline in Emax and AUEC0-12 parameters on Days 1, 7, 8, 14, 15 and 21. Baseline-adjusted PSV at each on-treatment timepoint was calculated by subtracting the corresponding Day -1 values. The maximum effect on baseline-adjusted PSV (Emax) was obtained directly from baseline-adjusted data while area under the baseline-adjusted PSV effect vs. time curve (AUEC0-12) parameters were calculated using a linear trapezoidal method.</p> <p>Cognitive function and B&L VAS mood scale: Change from baseline in cognition factor scores and B&L VAS mood sub-scores before (-0.5 hr) and 3 hr after dosing on Days 1, 7, 8, 14, 15 and 21.</p> <p>QT interval: 12-lead ECG traces were centrally read to generate QT interval data.</p>
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Safety Assessment	Physical examination, ECG, vital signs, laboratory safety tests and AEs
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PK & PD Results	E2007
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E2007 PK

Food Effect:

High-fat meal reduced Cmax of E2007 by 28% and delayed its (median) Tmax by 3 hr, but only reduced AUC0-24hr of E2007 by 6%.

Figure 1. Profile of E2007 Plasma Concentrations under Fasted (black) and Fed states (red)

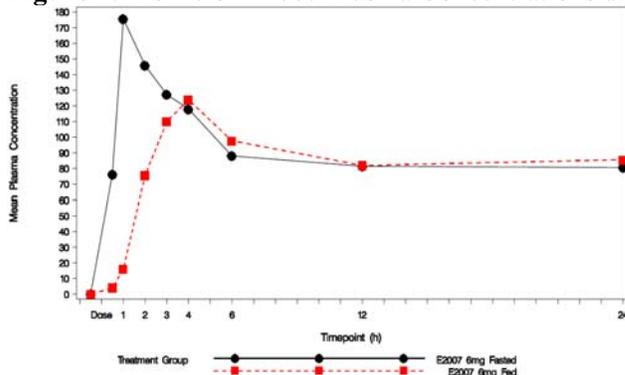


Table 1. Summary of the Effect of a High Fat Meal on E2007 PK Parameters from a Single 6 mg Dose

Parameter	Unadjusted Means*		Ratio between GLS means (90% CI)
	E2007 fasted (n=8)	E2007 fed (n=8)	
AUC ₀₋₂₄ (ng.hr/mL)	2071.2	1938.6	0.94 (0.69, 1.28)
C _{max} (ng/mL)	174.4	125.4	0.72 (0.53, 0.97)
T _{max} (hr)	1.0	4.0	-

*Geometric mean for AUC₀₋₂₄ and C_{max}. Median for T_{max}.

Parameter		E2007 6mg Fasted (N=8)	E2007 6mg Fed (N=8)
AUC0-24	N	8	8
	Mean	2183.0	2042.7
	Geometric Mean	2071.2	1938.6
	Standard Deviation	793.03	635.93
	Coefficient of Variation(%)	34.9	38.0
	Median	1885	2191
	Minimum	1421	907
	Maximum	3557	2980
C _{MAX}	N	8	8
	Mean	183.0	131.1
	Geometric Mean	174.4	125.4
	Standard Deviation	60.33	37.55
	Coefficient of Variation(%)	34.3	34.7
	Median	168	139
	Minimum	113	65
	Maximum	273	167
T _{MAX}	N	8	8
	Median	1.0	4.0
	Minimum	0.5	2.0
	Maximum	3.0	4.0

Time of Dosing (Evening vs. Morning Dosing):

Ctrough concentrations of E2007 after evening dosing were 41% higher than those after morning dosing for the first 6-mg dose (i.e Day -1 for PM dosing and Day 1 for AM dosing, Ctrough 76.9 ± 28.7 ng/mL and 51.5 ± 4.1 ng/mL, respectively). Such difference gradually decreased along with multiple dosing as illustrated by the Ctrough values in the Table below. At Day 7 (6 mg) and Day 14 (8 mg), Ctrough concentrations after evening dosing were 27% and 23% higher than those after morning dosing, respectively. Finally, at Day 21 (10 mg), Ctrough after evening dosing was almost the same as that after morning dosing.

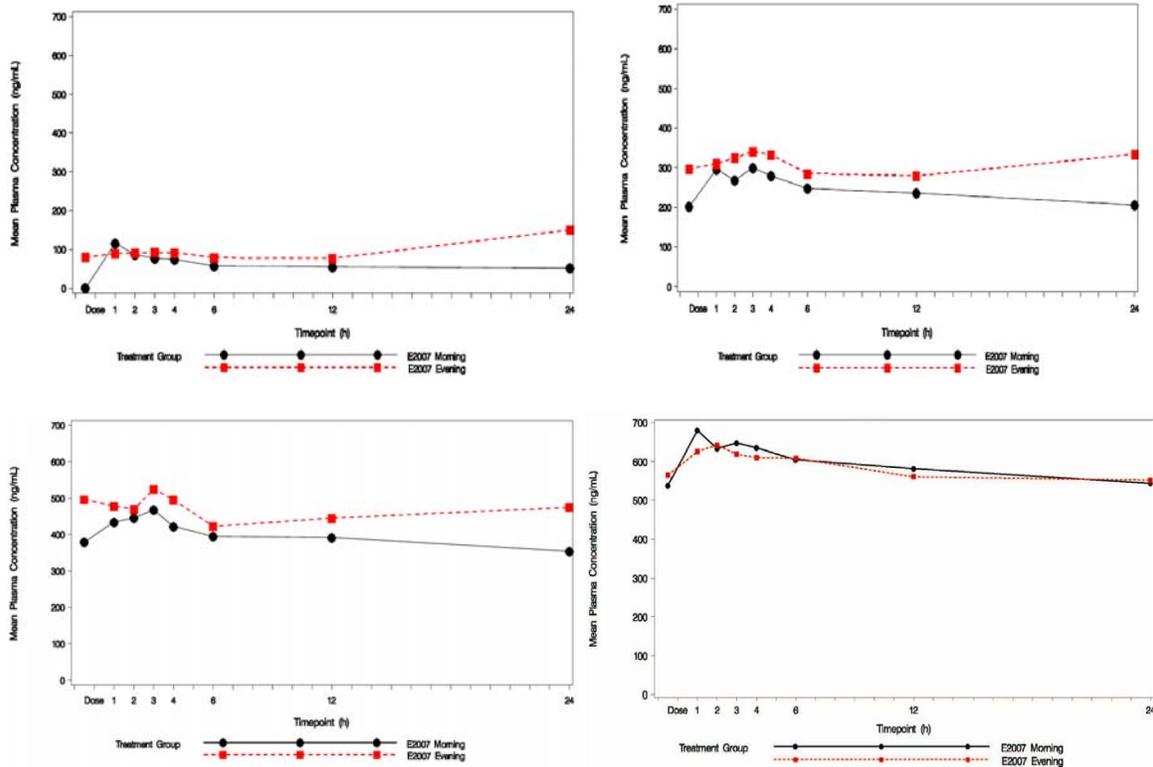
Table 2. Summary of E2007 PK Parameters after Repeated Dosing (Days 7, 14 and 21)

Parameter	E2007 Morning			E2007 Evening		
	6 mg (n=8)	8 mg (n=8)	10 mg (n=8)	6 mg (n=8)	8 mg (n=7)	10 mg (n=8) or (n=15)*
AUC ₀₋₂₄ (ng.hr/mL)	5566.8	9037.0	13516.9	ND	ND	ND
C _{max} (ng/mL)	300.7	492.1	684.1	ND	ND	ND
T _{max} (hr)	1.0	2.5	1.0	ND	ND	ND
C _{av} (ng/mL)	231.5	376.1	562.6	ND	ND	ND
C _{trough} (ng/mL)	202.5	345.0	529.1	256.6	423.8	519.0
PTF ratio	0.38	0.36	0.22	ND	ND	ND
R _{ac}	4.0	ND	ND	ND	ND	ND

Geometric mean for AUC₀₋₂₄, C_{max}, C_{av}, PTF ratio and R_{ac}. Median for T_{max}. ND = not done

* Geometric mean for C_{trough}.

Figure 2. Summary of E2007 PK Plasma Concentration after Repeated Dosing (Left upper panel: Day 1; Right upper panel: Day 7; Left lower panel: Day 14; Right lower panel: Day 21)



(Note: The ‘pre-dose’ concentrations of E2007 after evening dosing on Day 1 were not zero because the timepoints of x-axis represented the time relative to morning dosing. Since evening dosing started from Day -1, the “pre-dose” concentrations in the figures actually reflected concentrations at 12-hr post-dosing for evening dosing group. In addition, the concentrations at 24-hr in the above figures for evening dosing group represented the concentrations at 12-hr after another evening dose except in the figure for Day 21.)

Multiple-Dose PK:

Accumulation Ratio: Rac can only be calculated for morning dose group at 6-mg dose level in this study. The accumulation ratio for AUC_{0-24hr} was 4.0. As steady state has not been reached for 6 mg dose level, the accumulation ratio is expected to be further higher. This is consistent with the results from multiple dose escalation studies E2007-E044-002 (Western population) and E2007-J081-026 (Japanese population) which showed an accumulation ratio of 4.3 on average (3.41 - 4.93).

Fluctuation Index (FI%): Mean fluctuation index values (i.e, PTF ratio in Table 2, calculated as (C_{max,ss} – C_{min,ss})/C_{avg,ss} x 100%) were 43%, 40% and 28%, respectively, for morning dosing groups at 6, 8, and 10 mg dose levels. The gradual decrease of FI% may reflect that steady state has been approached.

Reviewer’s Comment: The FI% was considerably lower than those observed in studies E2007-E044-002 (59%, 68% and 82%) and E2007-J081-026 (67% and 74%). The exact mechanism underlying such difference is unclear. It is speculated that the difference may be related to timing of dosing relative to food intake. In study E2007-E044-002, E2007 was administered under fasted state. In study E2007-J081-026, though E2007 was administered under fed conditions for most of

the doses, subjects were instructed to take E2007 under fasted state on days when blood samples for PK analysis were collected, i.e, Day 1, 7, 14, 21 and 28. Thus, the PK data obtained for these days more reflected those under fasted state. In contrast, morning doses of E2007 were administered immediately before breakfast in the current study. The compositions of breakfast served were a selection of cereal, two pieces of toast with flora + jam, marmalade or marmite. Since effect of low-fat meal on E2007 PK, especially Cmax, has not been evaluated, a definitive conclusion about the reason causing the difference in FI% among these studies can not be made at this moment.

Pharmacodynamic of E2007:

Food Effect:

Peak Saccadic Velocity (PSV): Dosing with either E2007 6 mg Fed, E2007 6 mg Fasted or Diazepam resulted in a decrease in PSV parameters (Emax and AUEC0-12) compared with Placebo. E2007 6 mg Fed group had similar Emax and slightly higher AUC0-12hr (not statistically significant) compared to E2007 6 mg Fasted, while the time to reach Emax was delayed in E2007 Fed group. These observations were similar to those seen in study E2007-E044-003, though the effects of 6 mg E2007 on PSV were more pronounced than those of 1 mg E2007 under either fasted or fed state.

Figure 3. Change from Baseline to Day 1 of Peak Saccadic Velocity by Treatment Group

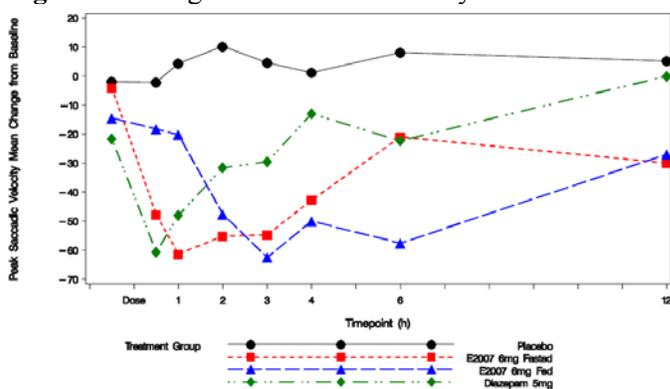


Table 3. Summary Statistics of PSV Parameter Emax

	Placebo (n=8)	E2007 6 mg fasted (n=8)	E2007 6 mg fed (n=8)	Diazepam 5 mg (n=8)
Mean (SD)	-23.9 (18.80)	-80.4 (10.88)	-71.9 (29.64)	-67.0 (9.80)
Median (min to max)	-24 (-50 to 6)	-81 (-96 to -64)	-73 (-115 to -25)	-63 (-83 to -54)

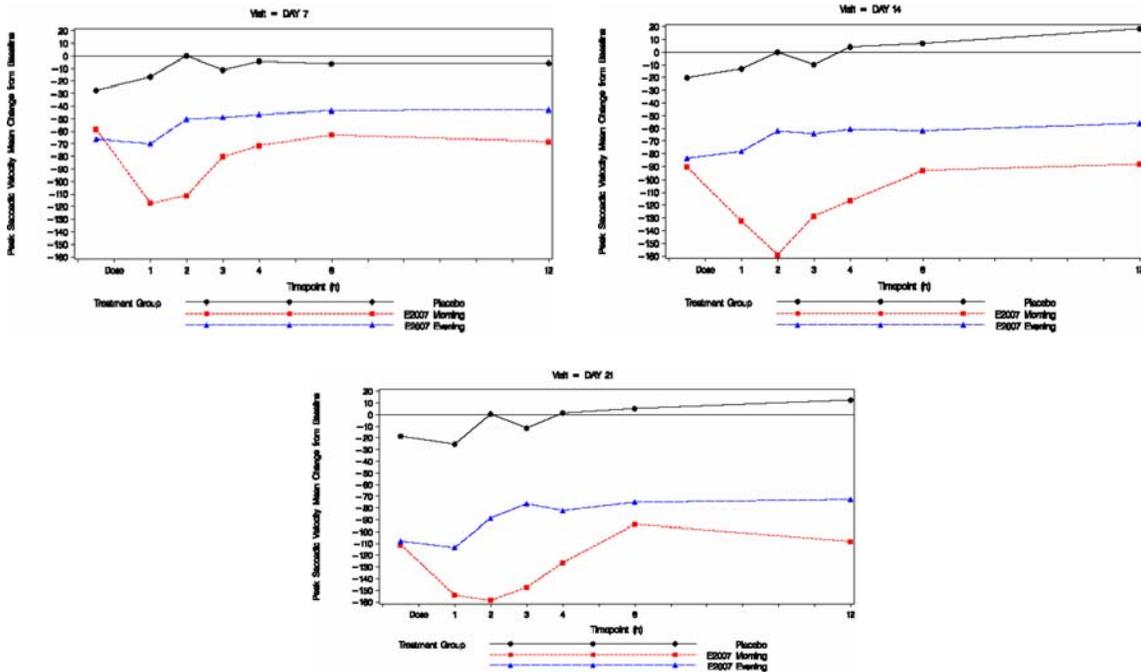
Table 4. Summary of Change from Baseline of Peak Saccadic Velocity Parameter AUEC0-12

	Placebo (n=8)	E2007 6 mg fasted (n=8)	E2007 6 mg fed (n=8)	Diazepam 5 mg (n=7)
Mean (SD)	69.3 (127.57)	-431.2 (142.61)	-499.8 (251.98)	-275.9 (124.11)
Median (min to max)	102 (-171 to 212)	-398 (-710 to -305)	-509 (-797 to -75)	-290 (-461 to -120)

Time of Dosing (Evening vs. Morning Dosing):

The decrease in Emax, AUEC0-12 and E12hr was larger for each parameter in the morning dosing group than the evening dosing group, suggesting that evening dosing may produce less daytime sedation than morning dosing. In contrast, there was no clear difference between evening dosing and morning dosing in terms of Bond and Lader sedation sub-scores measured at 0.5 hr pre-dose and 3-hr post-dose.

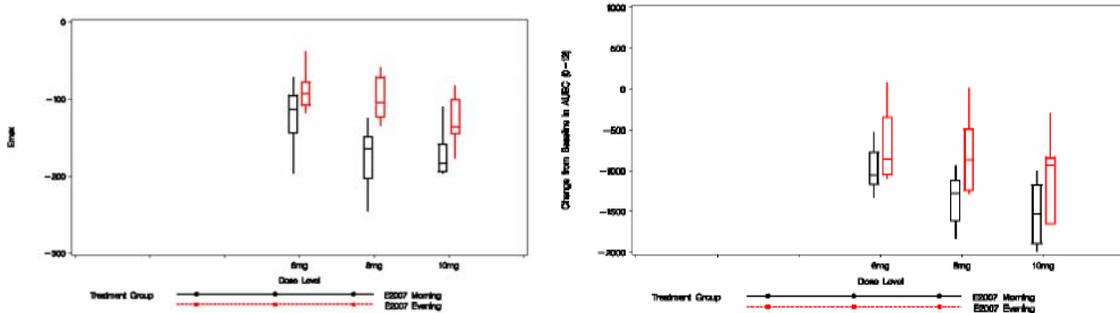
Figure 4. Summary of Peak Saccadic Velocity Changes from Baseline (Left upper panel: Day 7, E2007 6 mg; Right upper panel: Day 14, E2007 8 mg; Lower panel: Day 21, E2007 10 mg)



Multiple-Dosing:

There was evidence of a decrease in the PSV parameters as E2007 dose increased.

Figure 6. Summary of Peak Saccadic Eye Velocity Parameter (Left panel: Emax; Right panel: AUC0-12hr)



Safety Result

Part 1: Tolerability of E2007 appeared comparable with the Placebo dosing groups. Reported AEs were: diarrhoea, nasopharyngitis, contusion, myalgia, dizziness and headache. None were considered by the investigator to be related to study medication.

Part 2: Compared with the 10 mg E2007 dose, fewer subjects assigned 6 mg E2007 or 8 mg E2007 reported an AE. The most common AEs were dizziness, headache and nausea. The majority of AEs were mild in nature with no AEs of severe intensity reported.

Conclusions

- High-fat meal decreased C_{max} of E2007 by 28% and delayed its (median) T_{max} by 3 hrs (from 1 hr to 4 hrs), but did not affect E2007 AUC_{0-24hr} (only reduced by 6%).

	<ul style="list-style-type: none">• Dosing under fed state did not alter the extent of sedation caused by E2007 but delayed the onset of the effects. Maximum changes from baseline in peak saccadic velocity (PSV) from a single 6-mg dose were similar in both fed and fasted states, but dosing after food delayed occurrence of peak effects by ~2 hrs (3 hrs vs. 1 hr). The maximum sedative effects measured as PSV from a single 6 mg dose of E2007 were comparable to those from a 5 mg dose of diazepam.• Evening dosing appeared to results in a higher C_{trough} concentration than that after morning dosing after a single dose (Day 1). However, such difference gradually disappeared after multiple dosing.• There is evidence that PSV parameters measured in the morning after evening dosing are less affected by E2007 than after morning dosing, suggesting that evening dosing of E2007 may result in less daytime sedation.
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Study E2007-J081-010: Phase I Ascending Single dose Study of E2007 in Healthy Japanese Male Volunteers

Objective	<p><i>Primary objective:</i> To evaluate safety, tolerability and pharmacokinetics of a single dose of E2007 when given orally at dose levels of 0.25, 0.5, 1, 2, 4, 6 and 8 mg to healthy Japanese male subjects</p> <p><i>Secondary objective:</i> To evaluate the pharmacodynamic effects of E2007 on healthy Japanese male subject</p>		
Study Design	This was a randomized, double-blind, placebo-controlled, ascending single dose study. Study drug was administered following an overnight fast.		
	Step	Dose level	Formulation and the number of tablets taken
	1	0.25 mg	E2007 0.25 mg tablet × 1
	2	0.5 mg	E2007 0.5mg tablet × 1
	3	1 mg	E2007 1 mg tablet × 1
	4	2 mg	E2007 2 mg tablet × 1
	5	4 mg	E2007 2 mg tablet × 2
	6	6 mg	E2007 2 mg tablet × 3
7	8 mg	E2007 2 mg tablet × 4	
Study Population	56 subjects (8 per dose level, consisting of 6 for active drug and 2 for placebo) were enrolled and completed the study. Age: 20 – 43yr, mean: 26.2 yr; Weight: 50.3 – 78.4 kg, mean: 62.8 kg		
PK & PD measurements	<p><i>PK:</i> blood samples were collected at pre-dose, and at 15, 30 and 45 minutes, and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 168, 240 and 336 hours after drug administration.</p> <p><i>PD:</i> Saccadic eye movements - within 1 hour before drug administration, and at 1, 2, 4, 8, 12, 24 and 48 hours post-dosing</p> <p>Visual Analogue Mood Scale (VAMS) – within 1 hour before drug administration, and at 1, 2, 4, 8, 12, 24 and 48 hours post-dosing</p>		
Bioanalytical Method	Analyze	E2007	
	Method	LC/MS-MS	
	Internal Std.	(b) (4)	
	LOQ (ng/mL)	0.25	
	Calibration Range (ng/mL)	0.25, 1, 3, 10, 30	
	QC (ng/mL)	60, 120, 200	
	Accuracy	1, 30, 160	
	Precision	89 – 113.6 %	
PK & PD Assessments	<p><i>PK:</i> C_{max}, T_{max}, AUC, λ_z, t_{1/2}, V_z/F, MRT, CL/F were determined using model independent methods.</p> <p><i>PD:</i> peak saccadic velocity (PSV), Bond & Lader Sub-scores (anxiety, dysphoria and sedation)</p>		
Safety Assessment	12-lead ECG, vital signs, laboratory safety tests and adverse events		
PK & PD Results	E2007		
PK	<p>E2007 was rapidly absorbed with median T_{max} of 0.75 to 1.0 hour and then decreased bi-exponentially with a long half-life of 60.6 to 94.8 hours (mean). Mean CL/F and V_z/F values in the evaluated dose range were 480 to 796 mL/hr and 63.3 to 83.2 L. AUC and C_{max} of E2007 increased in a dose-proportional manner in the dose range from 0.25 to 8 mg.</p>		

Figure 1. Geometric mean plasma concentrations after single oral administration of E2007 (0-24hr, linear scale)

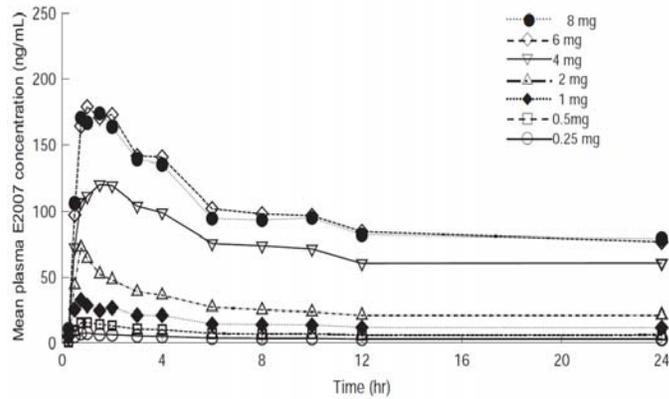


Figure 2. Geometric mean plasma concentrations after single oral administration of E2007 (0-336 hr, semi-log scale)

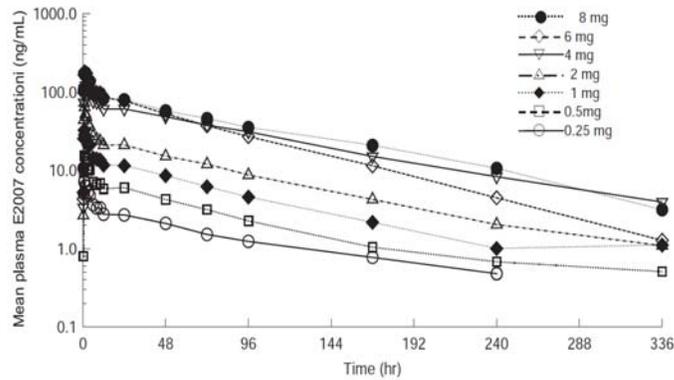


Table 1. Summary table of model independent pharmacokinetic parameters

Dose (mg)	Pharmacokinetic parameter					
	C_{max} (ng/mL)	t_{max} (hr)	$AUC_{(0-inf)}$ (ng·hr/mL)	$t_{1/2}$ (hr)	CL/F (mL/hr)	V_z/F (L)
0.25 n=6	9.0 ±3.7	0.750 0.50-1.00	382 ±87	81.5 ±31.1	699.9 ±243.1	77.4 ±22.3
0.5 n=6	17.5 ±2.6	1.000 0.75-2.00	753 ±277	76.8 ±33.1	730.2 ±231.1	73.0 ±19.9
1 n=6	39.8 ±14.0	0.750 0.50-2.00	1464 ±442	74.8 ±27.4	733.2 ±208.1	73.8 ±18.1
2 n=6	80.8 ±18.4	0.750 0.50-1.00	2816 ±1204	78.9 ±28.3	792.2 ±239.0	83.2 ±16.8
4 n=6	150.1 ±50.3	0.875 0.50-2.00	8746 ±2003	94.8 ±36.6	480.0 ±121.8	65.9 ±30.6
6 n=6	202.6 ±28.9	1.000 0.75-2.00	8795 ±3117	60.6 ±23.2	775.5 ±334.2	63.3 ±22.0
8 n=6	199.6 ±35.1	0.750 0.50-2.00	11107 ±4510	75.8 ±28.7	796.1 ±234.7	81.3 ±22.6

Each value in the table indicates mean ±standard deviation. In case of t_{max} , the upper column and the lower column indicate median and minimum-maximum, respectively.

A cross-study comparison of PK parameters (C_{max} , T_{max} , AUC_{0-inf} and $t_{1/2}$) between this study and study E2007-E044-001 (single-dose escalation study in Western Population) did not reveal significant difference between Japanese and Western (majority Caucasians) populations.

Figure 3. Relationship between Dose and Cmax (Left panel) or AUC0-inf (Right panel)

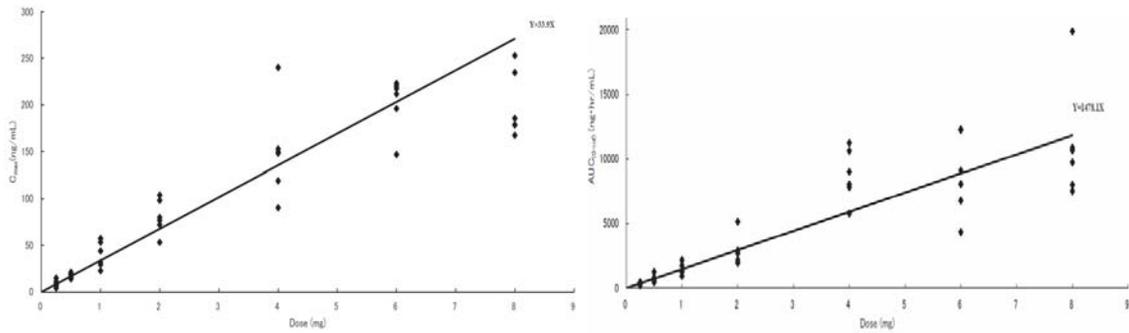


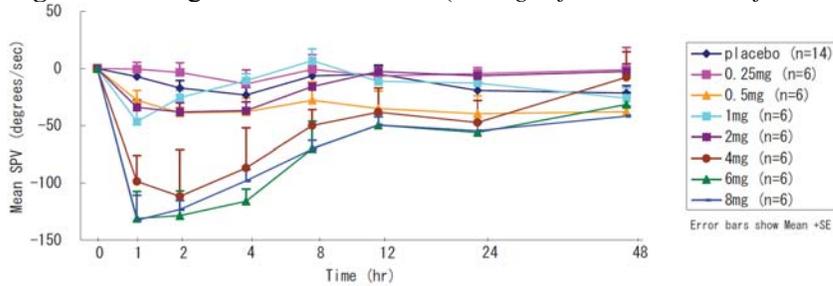
Table 2. Point estimate of β and its 95% confidence interval in an equation of $Y=\alpha X^\beta$ when dose was defined as X and Cmax or AUC0-inf was defined as Y

Parameter	point estimate	β 95% confidence interval
C_{max}	0.9518	0.8756-1.028
$AUC_{(0-inf)}$	1.008	0.9191-1.097

Pharmacodynamics:

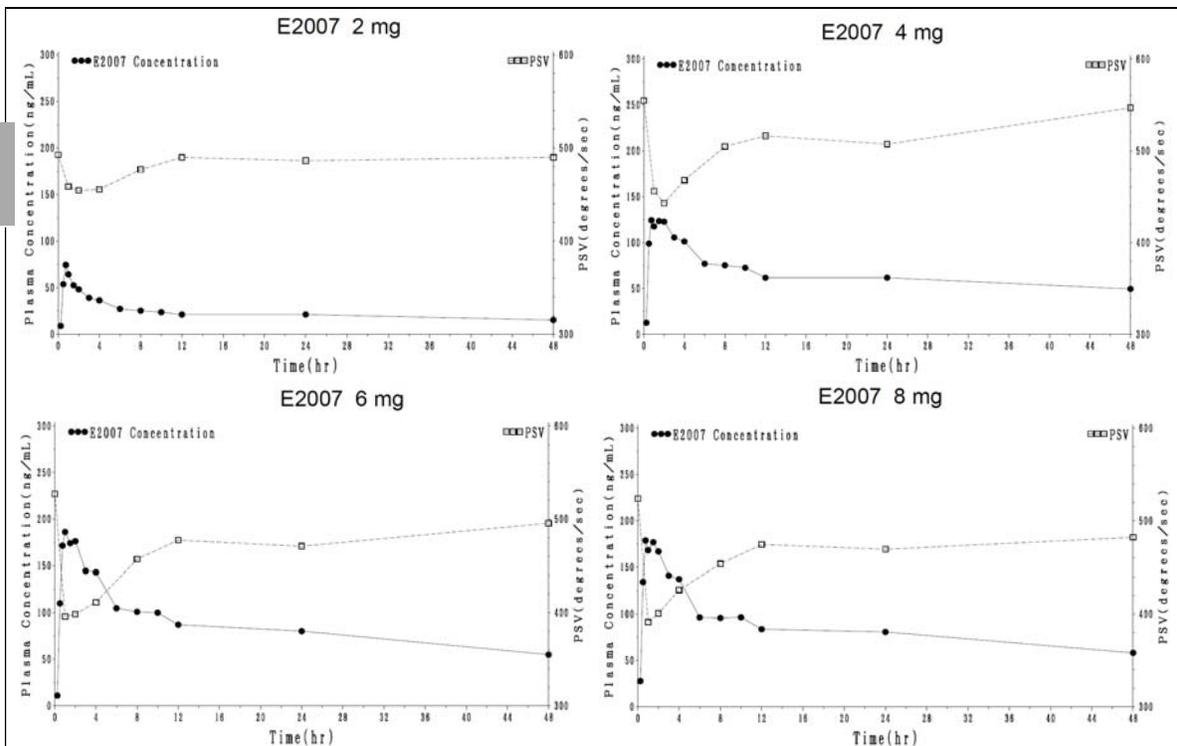
Peak saccadic velocity (PSV): Compared to the placebo group, the 0.25, 0.5, 1 and 2 mg groups of E2007 did not have statistically significant visual changes over time in PSV measurements. Decreases in the PSV measurements were apparent at higher doses of E2007 groups. The maximum decreases occurred at 1 or 2 hours after administration and there was a tendency to recover to the pre-dose levels by 48 hours after administration.

Figure 4. Changes over time in PSV (*Changes from the level before administration*)



A correlation was observed between changes over time of PSV measurements and plasma E2007 concentrations in these dose groups.

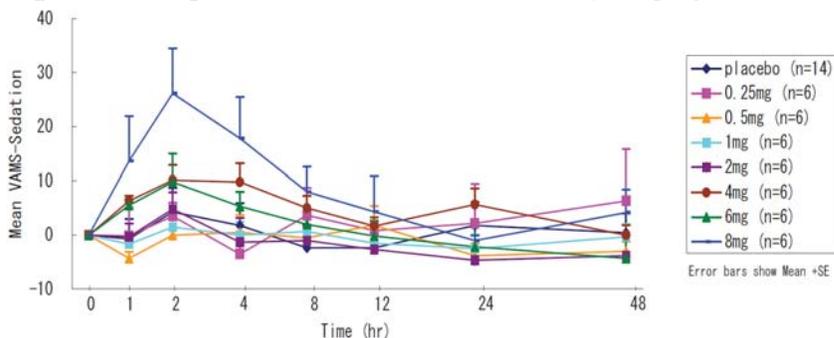
Figure 5. Superimposed plots of mean plasma concentration and mean PSV after administration of E2007



Bond & Lader Sedation Sub-Score:

There were no apparent changes over time in the total sedation score in the 0.25, 0.5, 1 and 2 mg groups of E2007, compared to the placebo group. Increases in the total sedation score were noted at higher doses of E2007. The maximum sedation levels were observed at 2 hours post-dosing, and recovered to the baseline by 24 hours after administration.

Figure 6. Changes over time in VAMS-Sedation (*changes from baseline*)



Safety Result

During the study, 39 and 3 AEs of which the causal relationship with drug cannot be denied were reported, respectively, from the subjects in the E2007 group (62%, 26/42) and the placebo group (14%, 2/14). The most common AEs in the E2007 group was somnolence (40.5%, 17/42), followed by dizziness (14.3%, 6/42), abnormal feces (11.9%, 5/42), hypoaesthesia (7.1%, 3/42) and malaise (4.8%, 2/42). The AEs occurring in the placebo group included headaches, somnolence and nausea (7.1%, 1/14, respectively). The incidences of AEs increased dose-dependently. All these AEs were mild or moderate in severity, with full resolution during the study period or the follow-up period.

Conclusions	<ul style="list-style-type: none">• In Japanese healthy males, E2007 was rapidly absorbed with (median) T_{max} observed at 0.75 to 1.0 hour post-dose and then the concentrations declined slowly with a t_{1/2} of 60.6 to 94.8 hours.• The C_{max} and AUC_{0-inf} of E2007 appeared to increase in a dose-proportional manner, suggesting linear PK of E2007 from 0.25 to 8 mg.• PSV tended to decrease in a dose-dependent manner, and a correlation was observed between PSV change and E2007 plasma concentrations.• Bond & Lader Sedation sub-score increased at dose levels of 4 mg or above.
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Study E2007-A001-013: A Randomized, Double-blind, Active- and Placebo-controlled, Combined Fixed-sequence, Parallel Group Study to Investigate the Effect of E2007 on the QT Interval Duration in Healthy Volunteers

Objective	<p><i>Primary objective:</i> To quantify the effect of perampanel on the QT interval duration in healthy subjects</p> <p><i>Secondary objective:</i> To explore the relationship between perampanel plasma concentrations and QT interval duration in healthy subjects and to explore the safety and tolerability of perampanel in healthy subjects.</p>																																																									
Study Design	<p>Perampanel dosing was started at 6 mg once daily and subsequently escalated to 12 mg once daily as shown below,</p> <table border="1" data-bbox="488 575 1393 974"> <thead> <tr> <th>Day</th> <th>Perampanel Group</th> <th>Placebo Group</th> <th>Moxifloxacin Group</th> </tr> </thead> <tbody> <tr> <td>1 to 6</td> <td>3 x 2-mg perampanel tablets once daily PM</td> <td>3 x placebo tablets once daily PM</td> <td>3 x placebo tablets once daily PM</td> </tr> <tr> <td>7</td> <td>3 x 2-mg perampanel tablets AM</td> <td>3 x placebo tablets AM</td> <td>3 x placebo tablets AM</td> </tr> <tr> <td>8</td> <td>4 x 2 mg perampanel tablets PM</td> <td>4 x placebo tablets PM</td> <td>4 x placebo tablets PM</td> </tr> <tr> <td>9</td> <td>5 x 2-mg perampanel tablets PM</td> <td>5 x placebo tablets PM</td> <td>5 x placebo tablets PM</td> </tr> <tr> <td>10 to 15</td> <td>6 x 2-mg perampanel tablets once daily PM</td> <td>6 x placebo tablets once daily PM</td> <td>6 x placebo tablets once daily PM</td> </tr> <tr> <td>16</td> <td>6 x 2-mg perampanel tablets AM</td> <td>6 x placebo tablets AM</td> <td>6 x placebo tablets AM</td> </tr> <tr> <td>16</td> <td>1 x moxifloxacin placebo capsule AM</td> <td>1 x moxifloxacin placebo capsule AM</td> <td>1 x 400 mg moxifloxacin tablet (overencapsulated) AM</td> </tr> </tbody> </table> <p>On on-treatment QT assessment days (Days 7 and 16), study drug administration was in the morning while fasted.</p> <p>On days on which QT assessments were not being performed, study drug was administered in the evening. Either the main meal of the day was eaten in the 2 hours before dosing or an additional snack was to be given at the same time as dosing.</p> <p>(Thus, on QT assessment days perampanel were administered the evening before with a meal as well as in the morning of the assessment.)</p>	Day	Perampanel Group	Placebo Group	Moxifloxacin Group	1 to 6	3 x 2-mg perampanel tablets once daily PM	3 x placebo tablets once daily PM	3 x placebo tablets once daily PM	7	3 x 2-mg perampanel tablets AM	3 x placebo tablets AM	3 x placebo tablets AM	8	4 x 2 mg perampanel tablets PM	4 x placebo tablets PM	4 x placebo tablets PM	9	5 x 2-mg perampanel tablets PM	5 x placebo tablets PM	5 x placebo tablets PM	10 to 15	6 x 2-mg perampanel tablets once daily PM	6 x placebo tablets once daily PM	6 x placebo tablets once daily PM	16	6 x 2-mg perampanel tablets AM	6 x placebo tablets AM	6 x placebo tablets AM	16	1 x moxifloxacin placebo capsule AM	1 x moxifloxacin placebo capsule AM	1 x 400 mg moxifloxacin tablet (overencapsulated) AM																									
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PK & PD measurements	<p><i>PK:</i> blood samples were collected on Days 7 and 16 before (-0.5 hours) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after study drug dosing.</p> <p><i>QT:</i> Serial 12-lead ECGs (3 standard ECGs per time point, approximately 2 minutes apart) to measure QT interval duration were recorded (just prior to PK sample collection) before (-0.5 hours) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12</p>																																																									

hours after study drug dosing on Days 7 and 16. Baseline ECGs, collected on Day -1, were time-matched to post-dose ECGs on Days 7 and 16 with additional measurements corresponding to 2.5, 5, 7, 9, 10, 11, and 14 hours to be collected on Day -1. On Days -1, 7, and 16, subjects received identical meals and observed identical food/fast schedules.

Bioanalytical Method	Analyze	E2007
	Method	LC/MS-MS
	Internal Std.	E2007 associated substance
	LOQ (ng/mL)	2.5
	Calibration Range (ng/mL)	2.5, 5, 10, 30, 100 300, 800 and 1,000
	QC (ng/mL)	2.5, 7.5, 150 and 750
	Accuracy	97.5 – 101.4 %
	Precision	4.9 to 6.2 %

PK & PD Assessments
PK: C_{max}, T_{max}, AUC_{0-12hr} were determined for Day 7 (i.e., 6 mg once daily) and Day 16 (i.e., 12 mg once daily)
QT: The primary analysis was performed with QTcF. On each QT assessment day, the mean difference at each time point in change from baseline between perampanel and placebo at the doses of 6 mg or 12 mg were compared using a repeated measures mixed effects analysis of variance (ANOVA).

Safety Assessment 12-lead ECG, vital signs, laboratory safety tests and adverse events

PK Results E2007

PK: E2007 was rapidly absorbed with median T_{max} of 1.5 to 2.0 hours. Following multiple-dose regimens, mean C_{max} and AUC₀₋₁₂ at the perampanel 12-mg dose were approximately twice those of the perampanel 6-mg dose.

Figure 1. E2007 Pharmacokinetic Plasma Concentrations

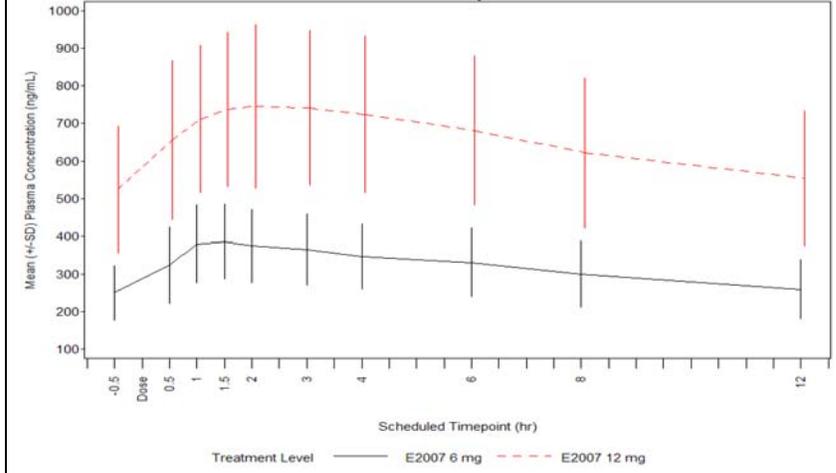


Table 1. Perampanel Pharmacokinetic Parameters Mean (±SD)

Parameters	Perampanel Day 7 (6 mg) n=79	Perampanel Day 16 (12 mg) n=69
C _{max} (ng/mL)	412.31 (97.251)	799.31 (221.756)
t _{max} (hr) ^b	1.5 (0.5-6.0)	2.0 (0.5-6.0)
AUC ₀₋₁₂ (ng*hr/mL)	3828.40 (1016.650) ^c	7899.14 (2313.023)

SD = standard deviation.

^a Included only subjects who had PK data.

^b Median (min-max) reported for t_{max}

^c For AUC₀₋₁₂, n=77.

Reviewers' Comment: As 6 mg and 12 mg E2007 were only administered for 7 days at each level, steady state of E2007 may not have been achieved considering the long $t_{1/2}$ of E2007.

QT: At all time points, the upper one-sided 95% CI of $\Delta\Delta QTcF$ in perampanel 6 mg and 12 mg treatment groups were less than 10 msec. Exploratory graphical evaluation showed no relationship between perampanel concentrations and baseline-adjusted QTc. Please refer to the review documented by Dr. Joanne Zhang for details about this thorough QT study.

Safety Result	<p>One subject discontinued the study while taking perampanel 12 mg due to an SAE of severe concussion, with associated fall and head injury, considered probably related to study drug and requiring overnight hospitalization. The SAE resolved. Sixteen additional subjects were withdrawn from the study due to TEAEs (14 subjects while receiving perampanel and 2 subjects while receiving placebo).</p> <p>There was a higher incidence of treatment-emergent adverse events in the perampanel-treated subjects (especially at the 12-mg dose) compared to placebo and moxifloxacin, with the most frequently reported events being dizziness, dysarthria, headache, nausea, gait disturbance, ataxia, feeling drunk, somnolence, and fatigue. Eleven of the perampanel-treated subjects experienced a fall, compared to 1 subject in the placebo group. One subject experienced loss of consciousness and 1 subject experienced syncope while taking perampanel 12 mg. Nine of the TEAEs in the perampanel-treated subjects were considered to be severe compared with none in the placebo group and 1 in the moxifloxacin-treated group. Many of the TEAEs experienced by subjects at the 12-mg perampanel dose resembled intoxication (slowed or slurred speech, dizziness, clumsiness, ataxia, falls, numbness, visual impairment, drowsiness, sleepiness, impaired mental status, sedation, poor judgment, decreased memory, or change in mood, inappropriate euphoria, anger, or abnormal behavior).</p>
Conclusions	<ul style="list-style-type: none">• E2007 was rapidly absorbed with median T_{max} of 1.5 to 2.0 hours. Exposure of E2007 appeared to increase proportionally from 6 mg to 12 mg daily doses. However, it should be noted that steady state may not be reached for either 6 mg or 12 mg dose levels in this study.• No significant QTc prolongation effect of perampanel (6 mg and 12 mg) was detected in this TQT study.

Study E2007-A001-014: An open label, fixed sequence, crossover study to investigate the pharmacokinetic interaction between E2007 and midazolam

Objective	<p><i>Primary objective:</i> To determine the effect of E2007 on the PK of the CYP3A4/5 substrate midazolam.</p> <p><i>Secondary objective:</i> To collect urine samples for metabolite identification and to explore the safety and tolerability of E2007 in combination with midazolam in healthy subjects.</p>																																						
Study Design	<p>This was a three-treatment, three-period, fixed-sequence crossover study.</p> <table border="1"> <thead> <tr> <th>Treatment period</th> <th>Day</th> <th>Treatment</th> </tr> </thead> <tbody> <tr> <td>Midazolam alone</td> <td>1</td> <td>2 mL midazolam syrup (2 mg/mL)</td> </tr> <tr> <td>E2007 alone</td> <td>2-21</td> <td>3 x 2 mg E2007 tablets</td> </tr> <tr> <td>E2007 plus midazolam</td> <td>22</td> <td>3 x 2 mg E2007 tablets plus 2 mL midazolam syrup (2 mg/mL)</td> </tr> </tbody> </table>			Treatment period	Day	Treatment	Midazolam alone	1	2 mL midazolam syrup (2 mg/mL)	E2007 alone	2-21	3 x 2 mg E2007 tablets	E2007 plus midazolam	22	3 x 2 mg E2007 tablets plus 2 mL midazolam syrup (2 mg/mL)																								
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Dosage and Administration	<p>On Days 1 and 22, study drug dosing was in the morning while fasted. On all other days, E2007 was taken at bedtime, preferably after a substantial evening meal. E2007 and midazolam administration on Day 22 was simultaneous.</p>																																						
PK Sampling	<p><i>Midazolam:</i> On Days 1 and 22, blood samples were collected at pre-dose 0.5 hr, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 hr post-dosing</p> <p><i>E2007:</i> plasma concentrations were assessed at the same time as laboratory safety test sampling (i.e, at any convenient time) on Days 8 and 15 and before (-0.5 hours) E2007 administration on Day 22.</p> <p><i>Urine:</i> samples of the first morning urination were collected on Days 1, 8, 15, and 22 for measurement of 6-β-hydroxycortisol and cortisol concentrations, and also to provide material for metabolite identification.</p>																																						
Bioanalytical Method	<table border="1"> <thead> <tr> <th>Analyze</th> <th>Midazolam</th> <th>E2007</th> </tr> </thead> <tbody> <tr> <td>Method</td> <td>LC/MS-MS</td> <td>LC/MS-MS</td> </tr> <tr> <td>Internal Std.</td> <td>Midazolam-d4</td> <td>E2007 associated substances</td> </tr> <tr> <td>LOQ (ng/mL)</td> <td>0.1</td> <td>2.5</td> </tr> <tr> <td>Calibration Range (ng/mL)</td> <td>0.1, 0.2, 0.4, 1.6, 6.4, 25.6, 76.8, 100</td> <td>2.5, 5, 10, 30, 100, 300, 800, 1000</td> </tr> <tr> <td>QC (ng/mL)</td> <td>0.3, 0.75, 3, 12, 75</td> <td>7.5, 150, 750</td> </tr> <tr> <td>Accuracy</td> <td>93.1 – 95.3%</td> <td>80.8 – 113.9%</td> </tr> <tr> <td>Precision</td> <td>5.25 – 9.53%</td> <td>1.6 – 17.2%</td> </tr> </tbody> </table> <table border="1"> <thead> <tr> <th>Analyze</th> <th>6β-hydroxycortisol</th> <th>Cortisol</th> </tr> </thead> <tbody> <tr> <td>Method</td> <td>LC/MS-MS</td> <td>LC/MS-MS</td> </tr> <tr> <td>Internal Std.</td> <td>cortisol-d4</td> <td>cortisol-d4</td> </tr> <tr> <td>LOQ (ng/mL)</td> <td>6</td> <td>1</td> </tr> </tbody> </table>			Analyze	Midazolam	E2007	Method	LC/MS-MS	LC/MS-MS	Internal Std.	Midazolam-d4	E2007 associated substances	LOQ (ng/mL)	0.1	2.5	Calibration Range (ng/mL)	0.1, 0.2, 0.4, 1.6, 6.4, 25.6, 76.8, 100	2.5, 5, 10, 30, 100, 300, 800, 1000	QC (ng/mL)	0.3, 0.75, 3, 12, 75	7.5, 150, 750	Accuracy	93.1 – 95.3%	80.8 – 113.9%	Precision	5.25 – 9.53%	1.6 – 17.2%	Analyze	6β-hydroxycortisol	Cortisol	Method	LC/MS-MS	LC/MS-MS	Internal Std.	cortisol-d4	cortisol-d4	LOQ (ng/mL)	6	1
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	Calibration Range (ng/mL)	6, 10.5, 18, 45, 150 450, 1050, 1200	1, 1.75, 3, 7.5, 25 75, 175, 200
	QC (ng/mL)	12, 30, 90, 240, 960	2, 5, 15, 40, 160
	Accuracy	95 – 99.7%	91 – 100.7%
	Precision	1.25 – 3.26%	1.47 – 3.95%
PK Assessments	Midazolam: AUC _{0-inf} , AUC _{0-t} , C _{max} , T _{max} , t _{1/2} , CL/F, and V/F on Days 1 and 22 6-β-hydroxycortisol : cortisol ratios: on Days 1, 8, 15, and 22		
Safety Assessment	Physical examination, 12-lead ECG, vital signs, laboratory safety tests and adverse events		
Pharmacokinetic Results	E2007 – Midazolam Interaction		

Midazolam PK

Co-administration of multiple doses of 6-mg E2007 decreased C_{max} and AUC of midazolam by 15% and 13%, respectively. E2007 did not affect T_{max} and t_{1/2} of midazolam.

Figure 1. Midazolam Plasma Concentration vs. Time Profile (Mean ± SD)

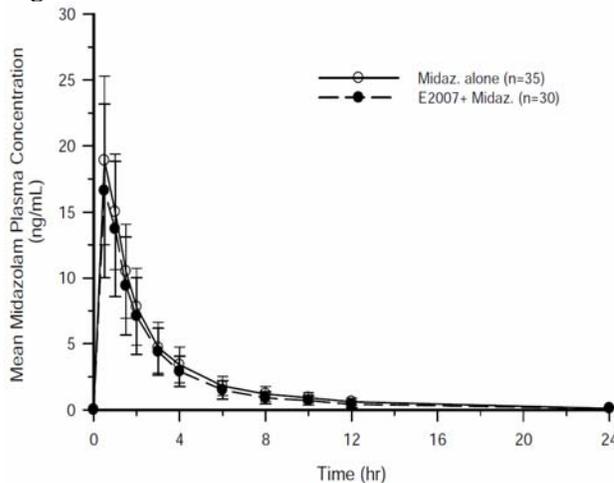


Table 1. Oral Midazolam Pharmacokinetic Parameters - Mean (SD)

Parameters	Midazolam Alone Treatment N=35	E2007 plus Midazolam Treatment N=30
Primary Endpoints		
AUC _{0-inf} (h*ng/mL)	50.40 (16.227)	43.59 (17.214)
C _{max} (ng/mL)	20.27 (5.400)	17.41 (6.524)
Secondary Endpoints		
AUC _{0-t} (h *ng/mL)	48.74 (15.937)	42.08 (16.812)
CL/F (L/h)	134.20 (52.349)	159.10 (64.529)
V/F (L)	908.43 (307.808)	1012.13 (376.175)
t _{1/2} (h)	5.06 (1.766)	4.86 (2.021)
t _{max} (h) ^a	0.5 (0.5-1.0)	0.5 (0.5-1.0)

^a median (min-max) reported for t_{max}

Table 2. Summary Statistics of Midazolam Pharmacokinetic Parameters

Parameters	LS Mean		E2007 plus Midazolam/ Midazolam Alone
	Midazolam Alone N=35	E2007 plus Midazolam N=30	Ratio (90% CI)
Primary Endpoints			
AUC _{0-inf} (h*ng/mL)	47.65	41.43	0.87 (0.81, 0.93)
C _{max} (ng/mL)	19.57	16.65	0.85 (0.78, 0.92)
Secondary Endpoints			
AUC ₀₋₄ (h*ng/mL)	45.99	39.94	0.87 (0.81, 0.93)
CL/F (L/h)	125.89	144.81	1.15 (1.07, 1.23)
V/F (L)	860.65	931.06	1.08 (0.98, 1.20)
t _{1/2} (h)	5.06	4.88	-0.18 (-0.64, 0.28) ^a
Median t _{max} (h)	0.5	0.5	NS ^b

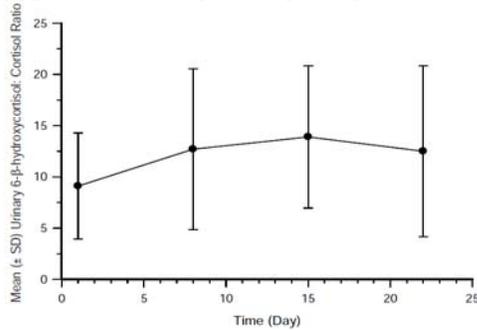
^a t_{1/2} was untransformed, mean difference (90% CI) was reported.

^b Wilcoxon signed-rank test, p value = 0.7709.

Urinary 6-β-hydroxycortisol: cortisol Ratio:

The 6-β-hydroxycortisol: cortisol ratio on Day 22 (12.5 ± 8.33 , n=30) was 37.4% higher than that observed on Day 1 (9.1 ± 5.19 , n=35). The difference in least square mean (3.52) was statistically significant with a 95% CI of 1.01-6.03. This higher ratio was maintained at a stable level since Day 8.

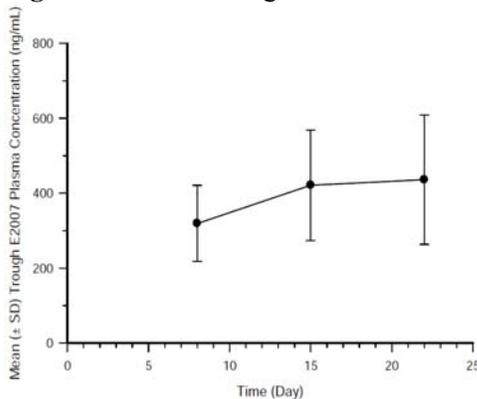
Figure 2. Urinary 6-β-hydroxycortisol: Cortisol Ratio (Mean ± SD)



E2007 PK:

Similar mean (± SD) E2007 trough plasma concentrations were observed on Day 15 and Day 22 ($421.4 \text{ ng/mL} \pm 147.73$ vs. $436.1 \pm 172.86 \text{ ng/mL}$, respectively), suggesting that steady-state of E2007 may be reached after 14-day once daily dosing.

Figure 3. E2007 Trough Plasma Concentration vs. Time Profile (Mean ± SD)



Reviewer's Comment:

In vitro induction study conducted in human hepatocytes (GE-0045) showed that E2007 increased mRNA level of CYP3A4/5 at concentrations of 3 µM and higher. In this study, the mean trough concentrations of E2007 were 436.1 ng/mL, corresponding to 1.25 µM. The urinary 6-β-hydroxycortisol:cortisol ratio, a marker of CYP3A4 activity in vivo, was increased after multiple treatments of E2007. Thus, the observed effects of 6-mg E2007 on midazolam AUC and Cmax may be due to induction of CYP3A4/5 by E2007.

However, the extent of reduction of midazolam exposure (decreased by 13-15%) was small and is not considered clinically significant. This is also supported by the findings from the in vitro study, which showed that at 3 µM, the induction effect of E2007 on CYP3A4 enzyme activity was less than 20% of the positive control (rifampicin). Also, in the current study, the urinary 6-β-hydroxycortisol: cortisol ratio was increased by 37% at Day 22 compared to Day 1. The increase was much less than that observed after carbamazepine treatment (an increase by 100-142%, study E2007-E044-006), suggesting that E2007 is only a weak CYP3A4 inducer.

The effect of higher doses of E2007 on midazolam has not been evaluated. In study E2007-E044-029, multiple doses of 12 mg E2007 decreased Cmax of ethinylestradiol by 18%, but did not affect its AUC. Ethinylestradiol is partially metabolized by CYP3A4 and its clearance is known to be increased by some CYP3A4 inducers (e.g, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, topiramate, rifampicin, etc.). The results from study 029 indicated that at 12 mg dose level E2007 was likely to also be a weak CYP3A4 inducer.

Safety Result	A total of 27 of 35 (77%) subjects exposed to study medication reported a total of 137 treatment-emergent AEs (TEAEs) throughout the course of this study. Three subjects discontinued due to AEs. Two subjects experienced 3 TEAEs during treatment with midazolam alone, 26 subjects experienced TEAEs during treatment with E2007 alone, and 9 subjects experienced TEAEs during treatment with E2007 plus midazolam. There were no SAEs reported. The majority of TEAEs reported were mild in severity (87%), with the rest reported as moderate. The treatment-related TEAE most frequently reported was dizziness (57%), followed by abnormal gait (14%); nausea (14%) and headache (17%).
Conclusions	<ul style="list-style-type: none">• Cmax and AUC of midazolam were decreased by 15% and 13%, respectively, after multiple treatments with E2007 (6 mg, q.d., 21 days). The reduction of midazolam exposure is not clinically significant.• Based on the trough concentrations, E2007 appeared to reach or approach steady state after 14 days of once-daily administration.• The urinary 6-β-hydroxycortisol:cortisol ratio was approximately 37% higher on Day 22 compared to Day 1, suggesting that effect of 6-mg E2007 on midazolam exposure may be due to induction of CYP3A4/5.

Study E2007-E044-015: An open-label, parallel group study to explore the pharmacokinetics of E2007 in subjects with reduced hepatic function.

Objective	<p><i>Primary:</i> To determine the effect of impaired hepatic function on the pharmacokinetics of E2007. <i>Secondary:</i> To explore the safety and toleration of E2007 among subjects with reduced hepatic function.</p>																																					
Study Design	<p>This was an open-label, one-treatment, parallel, four group study. Each subject received a single 1 mg dose of E2007 after food on Day 1.</p>																																					
Study Population	<p>A total of 24 subjects in total. 6 Child-Pugh A subjects were matched for age, weight, and sex with 6 healthy subjects with normal hepatic function ('Normal A'), and 6 Child-Pugh B subjects were matched for age, weight, and sex with 6 healthy subjects with normal hepatic function ('Normal B'). All subjects completed the study as per protocol.</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Normal A (n=6)</th> <th>Child-Pugh A (n=6)</th> <th>Normal B (n=6)</th> <th>Child-Pugh B (n=6)</th> </tr> </thead> <tbody> <tr> <td>Age in years mean (SD) min-max</td> <td>52.2 (7.8) 40-62</td> <td>50.3 (6.6) 40-57</td> <td>48.0 (13.5) 33-69</td> <td>49.2 (11.5) 36-68</td> </tr> <tr> <td>Gender n (%) Male Female</td> <td>4 (66.7) 2 (33.3)</td> <td>4 (66.7) 2 (33.3)</td> <td>5 (83.3) 1 (16.7)</td> <td>5 (83.3) 1 (16.7)</td> </tr> <tr> <td>Race n (%) Caucasian Asian</td> <td>5 (83.3) 1 (16.7)</td> <td>6 (100.0)</td> <td>6 (100.0)</td> <td>5 (83.3) 1 (16.7)</td> </tr> <tr> <td>Height in cm mean (SD)</td> <td>172.0 (9.5)</td> <td>173.2 (9.9)</td> <td>178.7 (7.0)</td> <td>177.0 (8.8)</td> </tr> <tr> <td>Weight in kg mean (SD)</td> <td>84.9 (12.7)</td> <td>82.5 (13.2)</td> <td>84.1 (15.1)</td> <td>84.0 (19.6)</td> </tr> <tr> <td>BMI in kg/m² mean (SD)</td> <td>28.8 (4.4)</td> <td>27.5 (3.4)</td> <td>26.2 (3.8)</td> <td>26.7 (5.6)</td> </tr> </tbody> </table>			Parameter	Normal A (n=6)	Child-Pugh A (n=6)	Normal B (n=6)	Child-Pugh B (n=6)	Age in years mean (SD) min-max	52.2 (7.8) 40-62	50.3 (6.6) 40-57	48.0 (13.5) 33-69	49.2 (11.5) 36-68	Gender n (%) Male Female	4 (66.7) 2 (33.3)	4 (66.7) 2 (33.3)	5 (83.3) 1 (16.7)	5 (83.3) 1 (16.7)	Race n (%) Caucasian Asian	5 (83.3) 1 (16.7)	6 (100.0)	6 (100.0)	5 (83.3) 1 (16.7)	Height in cm mean (SD)	172.0 (9.5)	173.2 (9.9)	178.7 (7.0)	177.0 (8.8)	Weight in kg mean (SD)	84.9 (12.7)	82.5 (13.2)	84.1 (15.1)	84.0 (19.6)	BMI in kg/m ² mean (SD)	28.8 (4.4)	27.5 (3.4)	26.2 (3.8)	26.7 (5.6)
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PK Sampling	<p>Blood samples were taken before (-0.5 hrs) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 120, 168, 216, 264, and 312 hrs after study drug administration, and also at follow-up. A blood sample for measurement of E2007 plasma protein binding was taken at 2 hrs post-dose.</p>																																					
Bioanalytical Method	Analyze	E2007	Unbound E2007																																			
	Method	HPLC-Fluorescence	LC/MS-MS																																			
	Internal Std.	E2007 associated substances	E2007 associated substances																																			
	LOQ (ng/mL)	1	0.1																																			
	Calibration Range (ng/mL)	1, 3.2, 7.7, 14, 23, 34, 47, 62, 80, 100	0.1, 0.14, 0.23, 0.36, 0.51, 0.72, 0.98, 1.29, 1.59, 2.01																																			
	QC (ng/mL)	3, 16.6, 44, 85	0.29, 0.52, 1.0, 1.71																																			
	Accuracy	81.9 – 104.3%	96.1 – 118.5%																																			
	Precision	1.24 – 8.6%	0.37 – 10.6%																																			
PK Assessments	<p>AUC_{0-∞}, AUC_{0-t}, C_{max}, T_{max}, t_{1/2}, CL/F and V/F were derived by non-compartmental methods. The fraction of E2007 unbound in plasma (f_u) was determined by an ex vivo protein binding assay (equilibrium dialysis) and used to calculate unbound AUC_{0-∞}, unbound AUC_{0-t}, unbound C_{max}, unbound CL/F and unbound V/F.</p>																																					
Safety Assessment	<p>Physical examination, 12-lead ECG, vital signs, laboratory safety tests and adverse events</p>																																					
PK Results	<p>E2007</p>																																					

E2007 PK

1. Plasma Protein Binding

The unbound fraction (f_u) of E2007 was calculated from the estimation of unbound plasma concentration at 2 hrs post dose. f_u was increased by 27.3% in Child-Pugh A, and 73.5% in Child-Pugh B, compared with Normal A and Normal B respectively.

Table 1. Mean (SD) Unbound Fraction of E2007 (n=6 in each group)

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)

2. PK Profiles and Parameters

Total AUC $_{0-\infty}$ was increased by 49% in Child-Pugh A compared with Normal A and by 155% in Child-Pugh B compared with Normal B. Unbound AUC $_{0-\infty}$ was increased by 81% and 228% in Child Pugh A and B, respectively, compared with Normal A and B. The half-life of E2007 was increased to 2.5-fold in Child-Pugh A (306.3 hrs vs. 125.2 hrs), and to 2-fold in Child-Pugh B (295.3 hrs vs. 138.6 hrs), compared with Normal A and Normal B, respectively.

Figure 1. Mean \pm SD E2007 Plasma Concentrations Profiles for Normal A (n=6) and Child-Pugh A (n=6) subjects (left panel: linear scale; right panel: semi-log scale)

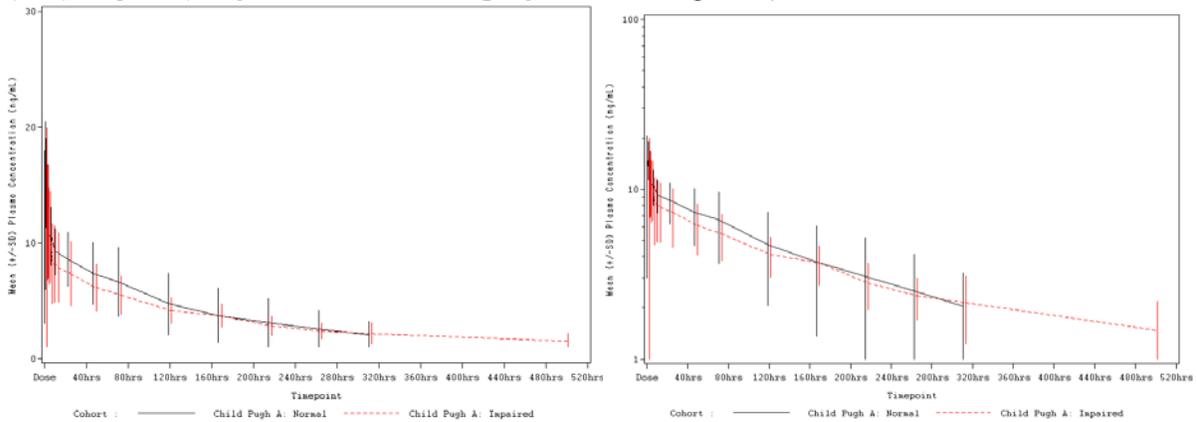


Figure 2. Mean \pm SD E2007 Plasma Concentrations Profiles Normal B (n=6) and Child-Pugh B (n=6) (left panel: linear scale; right panel: semi-log scale)

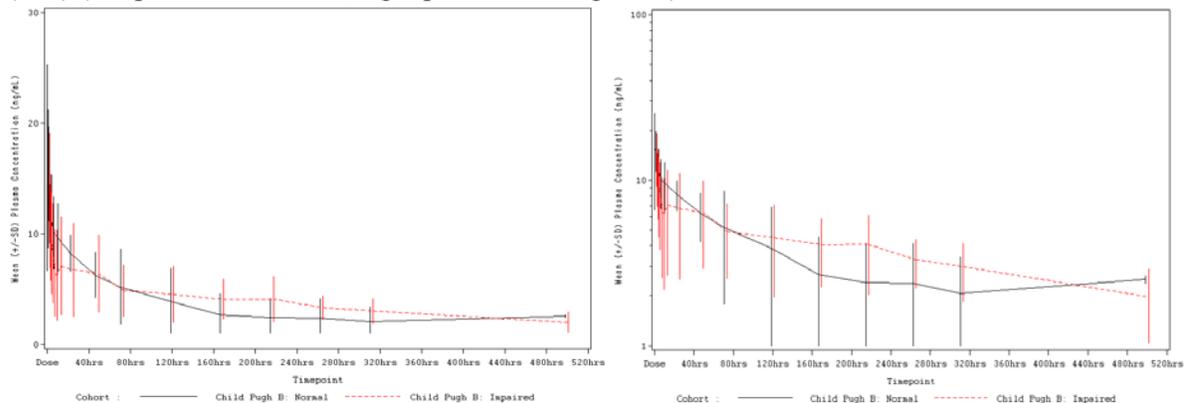


Figure 3. Mean Unbound E2007 Plasma Concentrations Profiles for Child-Pugh A or Child-Pugh B Subjects and Their Respective Control Groups (Normal A and Normal B, respectively)

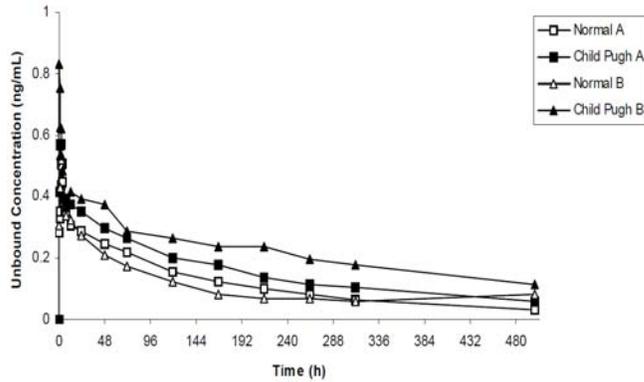


Table 1. Summary geometric mean (%CV) PK parameters for E2007 in Normal A, Child-Pugh A, Normal B, and Child-Pugh B

Parameter	Normal A (n=6)	n	Child-Pugh A (n=6)	n*	Normal B (n=6)	n	Child-Pugh B (n=6)	n*
T_{max} (hr) ¹	2.5 (0.5–3.0)	6	1.3 (0.5–4.0)	6	1.3 (0.5–3.0)	6	0.5 (0.5–2.0)	6
C_{max} (ng/mL)	19.5 (26.7)	6	13.6 (53.8)	6	20.3 (29.2)	6	16.0 (20.8)	6
C_u at 2 hr (ng/mL)	0.34 (0.12)	6	0.43 (0.13)	6	0.44 (0.14)	6	0.52 (0.25)	6
Total AUC _{0-t} (ng.hr/mL)	1374.3 (76.9)	6	1450.7 (39.3)	6	1074.4 (84.9)	6	1640.8 (61.6)	6
Unbound AUC _{0-t} (ng.hr/mL)	42.1 (53.9)	6	57.3 (36.7)	6	34.5 (70.0)	6	88.7 (31.9)	6
Total AUC _{0-∞} (ng.hr/mL)	1603.6 (74.7)	6	2471.3 (44.6)	5	1324.2 (103.6)	6	3126.6 (32.0)	4
Unbound AUC _{0-∞} (ng.hr/mL)	49.2 (57.5)	6	88.8 (80.0)	5	42.5 (85.2)	6	139.4 (14.9)	4
Total V/F (L)	100.0 (34.4)	6	136.5 (42.4)	5	91.8 (46.5)	6	129.5 (32.0)	4
Unbound V/F (L)	3262.1 (16.0)	6	3798.0 (23.4)	5	2860.1 (54.8)	6	2904.7 (43.9)	4
Total CL/F (L/hr)	0.62 (74.8)	6	0.40 (44.7)	5	0.76 (103.7)	6	0.32 (32.0)	4
Unbound CL/F (L/hr)	20.3 (57.5)	6	11.3 (79.9)	5	23.5 (85.3)	6	7.2 (14.9)	4
$t_{1/2}$ (hr) ²	125.2 (56.2)	6	306.3 (275.0)	5	138.6 (145.5)	6	295.3 (116.3)	4

¹Median (min–max); ²Mean (SD)

* Reduction in n reflects impossibility of calculating $t_{1/2}$.

Table 2. Statistical analysis of E2007 PK parameters for Child-Pugh A compared with Normal A

Parameter	Least Square Means		Least Square Mean Ratio ¹ (Impaired:Normal)	90% Confidence Interval
	Normal	Impaired		
C_{max} (ng/mL)	19.5	13.6	0.70	0.51, 0.95
Total AUC _{0-t} (ng.hr/mL)	1374	1451	1.06	0.57, 1.95
Unbound AUC _{0-t} (ng.hr/mL)	42.1	57.3	1.36	0.85, 2.17
Total AUC _{0-∞} (ng.hr/mL)	1604	2392	1.49	0.79, 2.81
Unbound AUC _{0-∞} (ng.hr/mL)	49.2	88.8	1.81	0.96, 3.41
Total V/F (L)	100.0	133.7	1.34	0.93, 1.91
Unbound V/F (L)	3262	3837	1.18	0.91, 1.53
Total CL/F (L/hr)	0.62	0.42	0.67	0.36, 1.27
Unbound CL/F (L/hr)	20.3	11.3	0.55	0.29, 1.05
$t_{1/2}$ (hr)	125.2	304.8	179.7	–0.40, 359.7

¹ $t_{1/2}$ is untransformed and therefore presented as the difference between the 2 groups rather than the ratio

Table 3. Statistical analysis of E2007 PK parameters for Child-Pugh B compared with Normal B

Parameter	Least Square Means		Least Square Mean Ratio ¹ (Impaired:Normal)	90% Confidence Interval
	Normal	Impaired		
C _{max} (ng/mL)	20.3	16.0	0.79	0.58, 1.07
Total AUC _{0-t} (ng.hr/mL)	1074	1641	1.53	0.82, 2.83
Unbound AUC _{0-t} (ng.hr/mL)	34.5	88.7	2.57	1.61, 4.10
Total AUC _{0-∞} (ng.hr/mL)	1324	3378	2.55	1.28, 5.09
Unbound AUC _{0-∞} (ng.hr/mL)	42.5	139.4	3.28	1.67, 6.47
Total V/F (L)	91.8	137.4	1.50	1.01, 2.21
Unbound V/F (L)	2860	3523	1.23	0.92, 1.64
Total CL/F (L/hr)	0.76	0.30	0.39	0.20, 0.78
Unbound CL/F (L/hr)	23.5	7.2	0.30	0.15, 0.60
t _{1/2} (hr)	138.6	300.5	162.0	-31.4, 355.3

¹t_{1/2} is untransformed and therefore presented as the difference between the 2 groups rather than the ratio

Safety Result	Four AEs were reported: one event of nausea in a subject in Normal A, one event of fatigue in a subject in Normal B, one event of headache in a subject in Normal B, and one event of headache in a subject in Child-Pugh B. All the AEs were mild. The onset of the AEs was within 12 hrs of dosing, and all resolved on the same day. No subject was withdrawn from the study due to an AE.
Conclusions	<ul style="list-style-type: none"> • The fraction of E2007 unbound in plasma (fu) at 2 hrs was increased by 27.3% and 73.5% in hepatically impaired Child-Pugh A and Child-Pugh B subjects, respectively, compared with demographically matched normal subjects. • Compared with their respective Normals A and B, t_{1/2} of E2007 was prolonged by 2-3 fold in Child-Pugh A and B subjects (306.3 hrs vs. 125.2 hrs, and 295.3 hrs vs. 138.6 hrs, respectively). AUC was increased to 1.49- and 2.55-fold in Child-Pugh A and B subjects, respectively, of those in the matched healthy subjects. Unbound AUC of E2007 was further increased in Child-Pugh A (to 1.81-fold) and B subjects (to 3.28-fold) compared to controls. • Maximum dose of E2007 should be reduced in mild and moderate hepatically impaired subjects. Up-titration of E2007 should be conducted slowly in these patients. Dose of E2007 should be increased no more frequently than every two weeks, rather than weekly increase in patients with normal hepatic functions.

Study E2007-E044-016: A randomized, open label, crossover study to demonstrate dose strength equivalence between 2 mg and 4 mg E2007 tablet strengths in healthy young volunteers

Objective	<p><i>Primary objective:</i> To demonstrate dose strength equivalence between two 2 mg E2007 tablets and a single 4 mg E2007 tablet.</p> <p><i>Secondary objective:</i> To explore the safety and toleration of E2007 among healthy subjects</p>		
Study Design	<p>This was a randomized, open label, two treatment, two-period, two-sequence, two-way crossover study. In each treatment period, subjects received a single 4 mg dose of E2007 administered either as two 2 mg E2007 tablets (Formulation C, reference) or a single 4 mg E2007 tablet (Formulation C, test) while fasting on the morning of Day 1 . There was a four week wash-out between treatments.</p>		
Study Population	<p>A total of 24 healthy adults (age: 39.3 ± 10.3 yr, 37.9 ± 11.8 yr; Weight: 67 ± 11.1 kg, 75.8 ± 14.2 kg; Gender: Male (50%); Race: All Caucasians) were enrolled and completed the study.</p>		
PK Sampling	<p>Blood samples were taken before dose (-0.5 hr) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hr post-dosing.</p>		
Bioanalytical Method	Analyze	E2007	
	Method	HPLC-Fluorescence	
	Internal Std.	E2007 associated substances	
	LOQ (ng/mL)	1	
	Calibration Range (ng/mL)	1, 5, 14, 27, 44, 66, 93, 124, 159, 199	
	QC (ng/mL)	3, 31, 87.5, 172	
	Accuracy	95.8 – 103.5%	
	Precision	6.26 – 6.92%	
PK Assessments	<p>E2007 PK parameters (AUC₀₋₇₂, C_{max}, and T_{max}) were derived from plasma concentrations by non-compartmental methods. ANOVA was used to estimate the ratio of treatment means and associated 90% CIs for log transformed AUC₀₋₇₂ and C_{max}. The model included terms for treatment, period and subject. T_{max} was not subject to formal statistical analysis.</p>		
Safety Assessment	<p>Physical examination, 12-lead ECG, vital signs, laboratory safety tests and adverse events</p>		
PK Results	E2007		
<p>E2007 PK 4 mg tablet was bioequivalent to 2 x 2 mg tablets as assessed by AUC_{0-72hr} and C_{max}. T_{max} was similar between the two strengths.</p>			

Figure 1. E2007 Mean (\pm SD) Plasma Concentrations

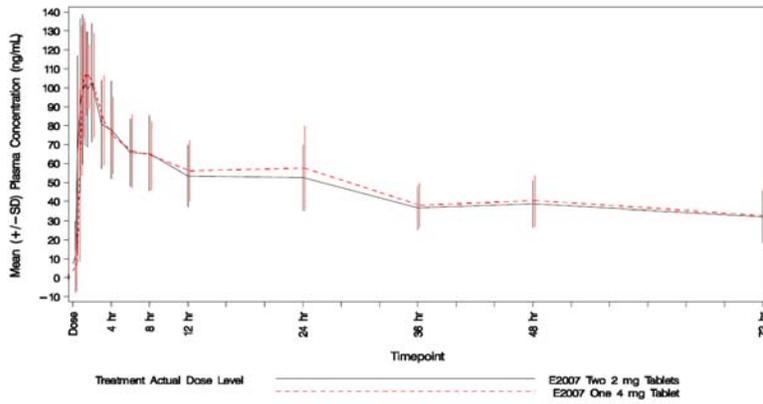


Table 1. E2007 Pharmacokinetic Parameters

Pharmacokinetic Parameter	One Perampanel 4-mg Tablet (N=24)	Two Perampanel 2-mg Tablets (N=24)
C_{max} (ng/mL)		
Mean	130	134
SD	24.7	28.3
$AUC_{(0-72h)}$ (ng-h/mL)		
Mean	3426	3295
SD	949	939
t_{max} (h)		
Median	1.1	1.3
Min - Max	0.5 - 3.0	0.5 - 4.0

Table 2. Statistical Analysis of Pharmacokinetic Parameters

Pharmacokinetic Parameter	Geometric Means		Ratio of Geometric Means (%) (4 mg : 2 × 2 mg)	90% Confidence Interval
	One Perampanel 4-mg tablet (N=24)	Two Perampanel 2-mg tablets (N=24)		
C_{max} (ng/mL)	127	131	98	92, 103
$AUC_{(0-72h)}$ (ng-h/mL)	3307	3169	104	99, 110

Safety Result	<p>In total, 20 subjects reported treatment emergent AEs in at least one of the treatment periods. Fourteen subjects reported AEs after receiving one 4 mg tablet of E2007 and 18 subjects reported AEs after taking two 2 mg tablets of E2007. The onset of the majority of AEs was within 12 hours of dosing and the duration of the majority of AEs was no longer than 12 hours. All AEs were resolved during the course of the study. No subjects were withdrawn from the study due to adverse events.</p> <p>The most common TEAEs were dizziness, headache, somnolence and muscle cramp. Dizziness, headache and somnolence were reported by more than 25% of subjects. All AEs were mild or moderate in severity, with the majority considered mild. Twenty subjects (83% of all subjects) had mild TEAEs and eight subjects (33%) had moderate TEAEs. There were 18 subjects with AEs that were related (probably or possibly) to study treatment.</p>
Conclusion	<p>Dose strength equivalence was demonstrated between two 2 mg E2007 tablets and a single 4 mg E2007 tablet as measured by AUC_{0-72} and C_{max}. T_{max} was similar between the two strengths.</p>

Study E2007-E044-017: An Open-label, Single-center Study to Determine the Absolute Oral Bioavailability and to Investigate the Metabolite Profile of Perampanel Following Administration of an Intravenous Microdose of 14C-Perampanel Solution and a Single Oral Dose of Perampanel in Healthy Male Subjects

Objective	<p><i>Primary objective:</i></p> <ul style="list-style-type: none"> • To evaluate the absolute oral bioavailability of perampanel following concomitant administration of an intravenous (IV) microdose of 14C-perampanel solution and a single oral dose of perampanel. • To investigate the metabolite profile of perampanel in plasma, urine and feces, and characterize metabolites where appropriate. <p><i>Secondary objective:</i></p> <ul style="list-style-type: none"> • To investigate the PK of perampanel in plasma following administration of a single IV microdose of 14C-perampanel solution and a single oral dose of perampanel.
Study Design	Healthy male subjects received a single oral 8-mg dose (2 × 4-mg tablets) of perampanel in the morning under fasted condition followed by a single 10- μ g (2 μ g/mL) IV micro-dose of 14C-perampanel (200 nCi). 14C-perampanel was intravenously administered as a 15 minute infusion starting 45 minutes after administration of oral perampanel in order to coincide with t _{max} of the oral dose.
Study Population	Age: 35.5 ± 10.5 yr; Weight: 80.4 ± 11.6 kg; Race: White 10 healthy male subjects were enrolled and completed the study.
PK Sampling	<p>1. Blood sampling: All sample times were relative to p.o. administration.</p> <p>1.1. for PK of total 14C, 14C-perampanel, unlabeled perampanel and metabolites (where appropriate): pre-dose (60 minutes) and at 30, 45, 50, 55 minutes, and 1 (end of infusion), 1.25, 1.5, 2, 3, 4, 6, 8, 12, 24 (Day 2), 48 (Day 3), 72 (Day 4) 96 (Day 5), 132 (Day 6), 144 (Day 7), 192 (Day 9), 216 (Day 10), 312 (Day 14), and 480 hours (Day 21) post-dose. At 50 minutes and 55 min post-dose, samples were taken for analysis of total 14C and 14C-perampanel from IV perampanel only.</p> <p>1.2. for whole blood 14C-radioactivity: pre-dose and 1 (Day 1), 132 (Day 6), and 312 hours (Day 14) post-dose only.</p> <p>1.3. for protein binding: pre-dose (60 minutes), and 1 and 312 hours (Day 14) post-dose.</p> <p>1.4. for metabolic profiling: at 1, 132 (Day 6), 216 (Day 10), 312 (Day 14), and 480 hours (Day 21) post-dose.</p> <p>2. Urine sampling (for metabolic profiling): prior to dosing (morning of Day 1), 0–24 (Day 1–2), 132–156 (Days 6–7), and 300–324 hours (Days 13–14) post-dose</p> <p>3. Feces sampling for metabolic profiling: collected over Days –1 to 14. Samples from 0–96, 120–168 (Days 6–8), and 264–312 hours (Days 12–14) post-dose periods were originally planned to be analyzed. Eventually, metabolic profiling was performed for the 0-24, 48-72, and 120-168 hr time-points only.</p>
Bioanalytical Method	1. Determination of 14C (i.e., parent plus metabolites) and 14C-perampanel (radiolabeled parent drug) in plasma

Plasma concentrations of total ¹⁴C were quantified by AMS. The AMS results were expressed as Percent Modern Carbon (pMC) values, which were converted to dpm/mL, and then to pg/mL with the information about the specific radioactivity of the administered dose (19.1 μCi/mg or 4.24 x 10⁻² dpm/pg). The LLOQ for total ¹⁴C was 2.12 pg eq/mL. Plasma concentrations of ¹⁴C-perampanel for the IV dose were quantified by AMS following HPLC fractionation. LLOQ for ¹⁴C-perampanel in plasma was 0.24 pg/mL.

2. Analysis of Total ¹⁴C (i.e, parent plus metabolites) in Whole Blood
 Blood concentrations of total ¹⁴C for the IV dose were quantified by AMS to determine the blood : plasma ratio. The LLOQ for total ¹⁴C in whole blood was 7.08 pg eq/mL.

3. Measurement of Unlabeled Parent drug and Metabolites in plasma
 Concentrations of perampanel and metabolites (M1, M2, M3, M4, M5, M7) in plasma samples with or without β-glucuronidase incubation were quantified by LC/MS/MS for the oral dose for all time points (pre-dose to 480 hr post-dose) except 50 and 55 minutes.

Analyze	E2007	Metabolites
Method	LC-MS/MS	LC-MS/MS
Internal Std.	Perampanel-d5	M4 – d5
LOQ (ng/mL)	1	1
Calibration Range (ng/mL)	1, 2, 8.4, 20, 80, 140, 210, 250	Same as those for parent
QC (ng/mL)	3, 80, 200	Same as those for parent
Accuracy	92 – 107%	87.5 – 113.7%
Precision	1.9 – 4.8%	1.5 – 13.3%

4. Metabolic Profiling in Plasma, Urine and Feces
 Pooled plasma samples and pooled faeces homogenates were extracted first and then fractionated by HPLC followed by AMS analyses to generate metabolite profiles. The urine pool samples were injected directly onto the HPLC system and then underwent AMS analysis. The eluant from HPLC was collected as a series of fractions every 30 seconds from 0 to 75 minutes.

Extraction of Plasma Samples
 An aliquot (200 μL) of the plasma sample spiked with the non-radiolabeled perampanel was added to 600 μL acetonitrile. After shaking for 10 min at 600 rpm, a vacuum was applied to the plate for 30 min. The eluent was collected and evaporated to dryness under a gentle stream of nitrogen. The residue was reconstituted in 200 μL of starting conditions mobile phase. The extraction efficiencies ranged from 73.3% to 107.3%.

Extraction of Feces Samples
 The sponsor tested four extraction methods. All of them had low extraction efficiencies (20%-30%). Finally, method 3 was chosen for formal analyses. The procedures are briefly described here. Prior to extraction, the pooled feces homogenate samples were diluted with water. Two volumes of

	<p>acetonitrile was added to one volume of the diluted pooled feces homogenates. After vortex mixing, the mixture was sonicated for 30 min and centrifuged at 9600 rpm for 15 min at room temperature. The residue was manually disrupted, vortex mixed thoroughly, sonicated and centrifuged as previously. The supernatant was removed into a separate vial and retained. One volume of acetonitrile was added to the residue and the residue manually disrupted. The mixture was vortex mixed thoroughly, sonicated and centrifuged as previously. The supernatant was removed. The process was repeated two additional times. The supernatants were combined and analyzed by AMS.</p> <p>An aliquot of the pooled plasma sample at 1 hour post-dose, urine sample at 0-24hr, and feces samples at different collection periods was further analyzed by LC/MS/MS in order to characterize selected metabolites.</p> <p>5. Ultracentrifuged plasma supernatant was analyzed by LC/MS/MS to determine plasma protein binding of perampanel.</p>
PK Assessments	<p>Plasma concentrations of total ¹⁴C, ¹⁴C-perampanel, and perampanel were analyzed by non-compartmental methods to determine the following PK parameters:</p> <ul style="list-style-type: none"> • AUC_{0-inf}, CL, and, V_{ss} of IV dosed perampanel • AUC_{0-inf} of orally dosed perampanel • Absolute bioavailability of orally dosed perampanel = $\text{Dose}_{iv} \times \text{AUC}_{oral} / (\text{Dose}_{oral} \times \text{AUC}_{iv}) \times 100$ • C_{max}, AUC_{last}, T_{max}, t_{1/2}, and MRT of orally dosed perampanel • C_{max}, AUC_{last}, T_{max}, and t_{1/2} of total ¹⁴C • C_{max}, AUC_{last}, T_{max}, t_{1/2}, and MRT of IV dosed perampanel <p>Blood and plasma were analyzed at specific time points to determine:</p> <ul style="list-style-type: none"> • Plasma protein binding • Blood : plasma ratio <p>Plasma, urine, and feces samples were analyzed at specific time points for metabolite profiling and identification.</p>
Safety Assessment	Adverse events, vital signs, ECG, clinical laboratory, physical examination.
Pharmacokinetic Results	<p style="text-align: center;"> ¹⁴C (total: E2007 + metabolites), ¹⁴C-Perampanel (unchanged radiolabeled E2007), Unlabeled Perampanel (E2007), and Metabolic Profiling in Plasma, Urine and Feces </p>
	<p>1. Absolute Bioavailability: Absolute Bioavailability (F_{po}) was estimated as 116 ± 9.42% (ranged from 105% to 129%, N=5) based on ¹⁴C-E2007 concentrations (derived from i.v. administration) measured by AMS and unlabeled E2007 concentrations (from p.o. administration) determined by LC-MS/MS. For 5 of the 10 subjects, quality control (QC) samples for the fractionated AMS assay failed the acceptance criteria and reliable plasma concentrations of ¹⁴C-perampanel could not be provided. Therefore, absolute bioavailability was only calculable for 5 subjects. Nevertheless, this estimated F_{po}, along with result from mass-balance study (i.e, 3% of total radioactivity recovered from feces during the first 48 hr post-dosing), suggested that perampanel has almost complete absorption.</p> <p><i>Reviewer's Note:</i> The acceptance criterion is that at least 6 out of 9 QC samples (low, middle,</p>

high; triplicates for each) should fall within 80-120% of the actual values. For 5 subjects, 7 out of 9 QC samples were acceptable and thus plasma concentrations of ¹⁴C-perampanel were available for calculation of absolute F_{po}. However, for the other 5 subjects whose samples were analyzed at different time, only 5 out of 9 QC samples fell within the acceptable range. Remaining samples for these subjects were analyzed again. The QC samples used last time passed the criteria (6 out of 9) this time. However, for another set of freshly prepared QC samples, only 5 out of 9 fell within 80-120% range. Thus, it was determined that reliable concentrations of ¹⁴C-perampanel can not be obtained for these 5 subjects whom were excluded from the calculation of absolute F_{po}.

2. Comparison between Total radioactivity (¹⁴C) and unchanged perampanel (¹⁴C-perampanel) in plasma after IV dosing

For the 5 subjects who had measurable concentrations of ¹⁴C-perampanel after IV dosing, the AUC of ¹⁴C-perampanel was about 74% of the AUC of total radioactivity. This result is similar to that after oral dosing as shown from the mass-balance study (E2007-E044-007).

Figure 1. Mean total radioactivity concentration and unchanged [¹⁴C]-Perampanel concentration in plasma (left: linear scale; right: semi-log scale)

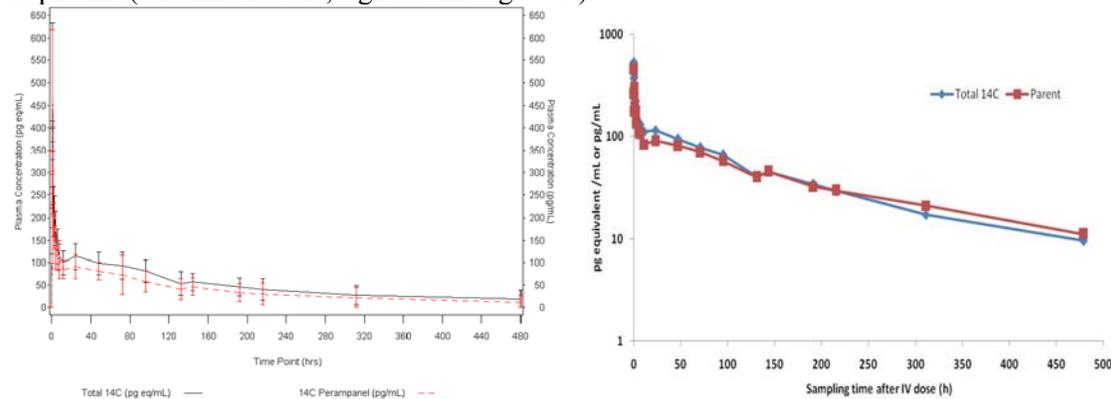


Table 1. Summary of ¹⁴C-Perampanel and Total ¹⁴C PK Parameters in Plasma Following IV Administration of 10- μ g Perampanel (mean \pm SD, except for T_{max}, median (min – max))

N = 5	¹⁴ C-Perampanel	¹⁴ C-Total
C _{max} (pg/mL)	456 \pm 161	520 \pm 112
AUC _{0-inf} (hr·pg/mL)	21600 \pm 16200	27860 \pm 17022
t _{max} (hours)	0.25 (0.25-0.25)	0.25 (0.25-0.5)
AUC _{last} (hr·pg/mL)	17900 \pm 10000	22866 \pm 9769
t _{1/2} (hours)	148 \pm 83.9	148.6 \pm 79

For total ¹⁴C, units are pg eq.

3. PK Profile and Parameters of Unlabeled Perampanel after Oral Dosing

Figure 2. Mean \pm SD Plasma Concentrations of Perampanel over 24-hr (Left) or 480-hr (Right) Following Oral Administration of 8-mg Perampanel (PK Evaluable Population)

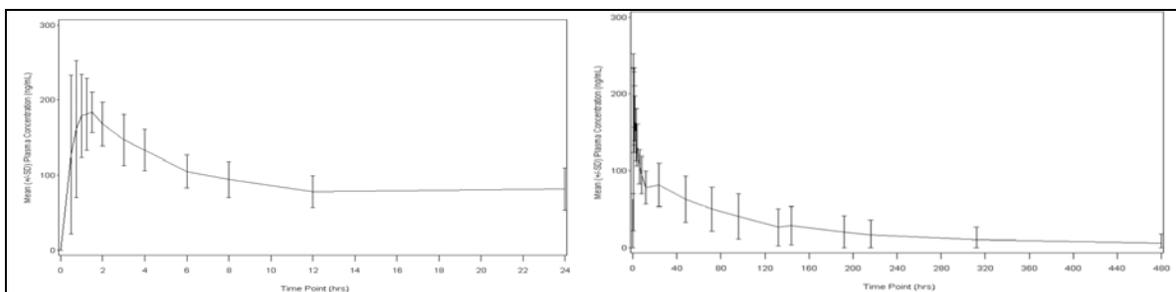


Table 2. Summary of Perampanel PK Parameters in Plasma Following Oral Administration of 8-mg Perampanel (PK Evaluable Population)

Parameter	8-mg Perampanel Oral Dose (N=10)
n	10
C _{max} (ng/mL)	221 ± 54.4
AUC _{0-inf} (hr·ng/mL)	14000 ± 13900
t _{max} (hours)	1.00 (0.50–2.00)
AUC _{last} (hr·ng/mL)	12000 ± 9190
t _{1/2} (hours)	102 ± 78.3
MRT (hours)	103 (39.7–396)
CL/F (mL/hr)	894 ± 531
V _Z /F (L)	91.5 ± 32.4

Arithmetic mean ± SD is shown except for t_{max} and MRT. t_{max} and MRT are shown as median (range).

4. Plasma protein binding of unlabeled perampanel in vivo was 95.9% (1 hr post-dose); this is consistent with in vitro protein binding data. Plasma protein binding could not be assessed at 312 hours postdose due to low free concentrations in 9 of the 10 subjects.

Whole blood: plasma ratios of total radioactivity ranged from 0.601 at 1-hr post-dose, 0.867 at 132-hr, to 1.04 at 312-hr post-dose. The trend was similar to that observed in mass-balance study.

5. Quantification of Metabolites in Plasma by LC/MS/MS

The concentrations of parent drug and metabolites (M1, M2, M3, M4, M5 and M7) were analyzed with and without the addition of β-glucuronidase. M13 and M14 were also measured as these two are glucuronide conjugates of M4 and M5, respectively, and can be converted to M4 and M5 after incubation with β-glucuronidase. After incubation of the plasma samples with β-glucuronidase, the concentrations of perampanel were slightly lower than those before treatment rather than being higher, suggesting that in plasma there was no glucuronide metabolite directly conjugated with parent drug.

The plasma concentrations of metabolites of perampanel evaluated were below the LLOQ for the majority of subjects at the majority of time points (pre-dose to 480hr post-dosing, except 50 and 55 min post-dosing for which plasma concentrations of perampanel and its metabolites were not quantified). One subject had quantifiable concentrations of M4 at only the 24 and 48 hours post-dose time points, and another subject had quantifiable concentrations of M7 at only 1.25, 1.5, and 4 hours post-dose; these were only quantifiable after the addition of β-glucuronidase. In all cases, the values were just above the LLOQ (1 ng/mL), suggesting that these metabolites are present in trace amounts in plasma. It should be noted that though the level of M7 was very low, its detection suggests an epoxide (designated as M19) might be generated as a reactive intermediate.

6. Metabolite Profiling:

6.1. Plasma samples

Metabolite profiling of plasma was performed using AMS for the 1, 132, 216, 312, and 480-hr samples and LC/MS/MS for the 1 hour sample.

On radio-chromatograms, there was no major peak except that for parent drug, suggesting the absence of major metabolite with significant amount (i.e. >10% of total drug-related material) in circulation.

Figure 3. HPLC radio-chromatogram of Pooled Plasma (1 hr) following i.v. administration of 10 µg / 200 nCi [¹⁴C]-Perampanel

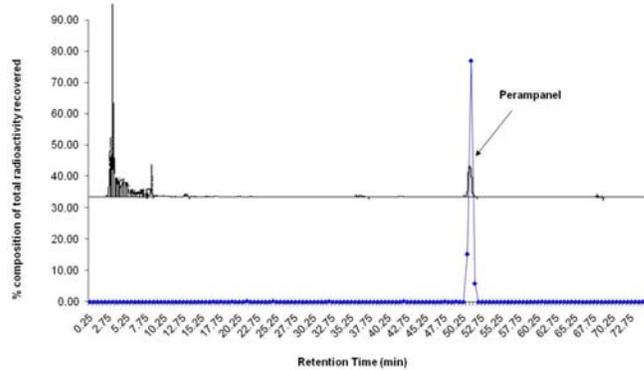


Figure 4. HPLC radio-chromatogram of Pooled plasma (132 hr) following i.v. administration

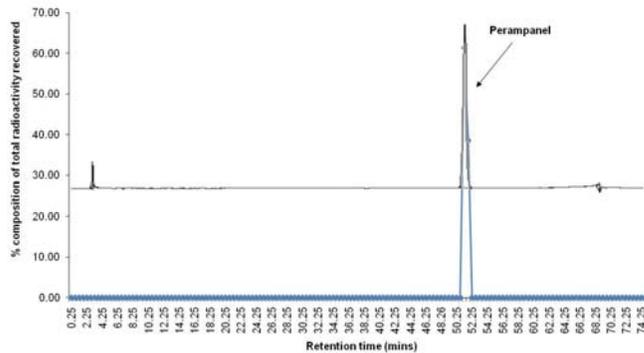


Figure 5. HPLC radio-chromatogram of Pooled plasma (216 hr) following i.v. administration

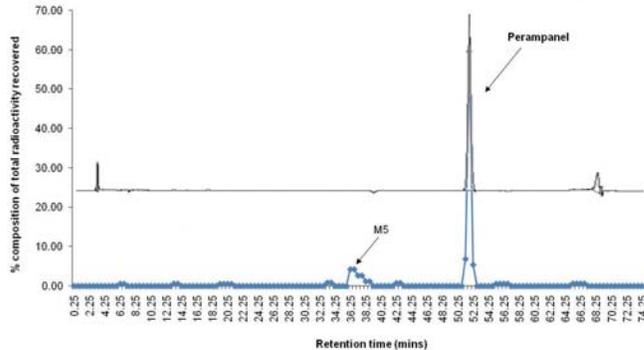


Figure 6. HPLC radio-chromatogram of Pooled plasma (312 hr) following i.v. administration

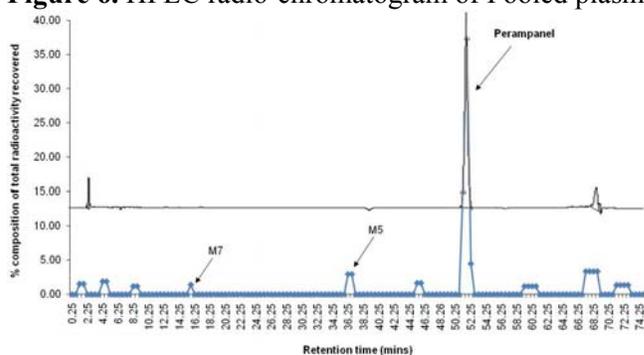


Figure 7. HPLC radio-chromatogram of Pooled plasma (480 hr) following i.v. administration

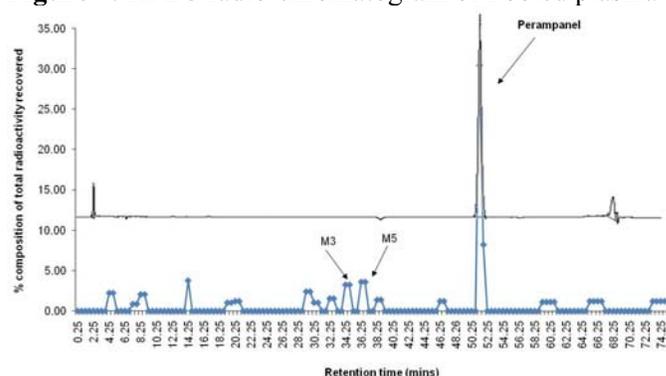


Table 3. Metabolite Profiling Results in Plasma

Analyte	AMS					LC/MS/MS 1 hour
	1 hour	132 hour	216 hour	312 hour	480 hour	
M2	–	–	–	–	–	–
M14	NA	NA	NA	NA	NA	–
M13	NA	NA	NA	NA	NA	–
M15	NA	NA	NA	NA	NA	–
M34	NA	NA	NA	NA	NA	–
M7	–	–	–	+	–	–
M1	–	–	–	–	–	–
M5	–	–	+	+	+	–
M3	–	–	–	–	+	–
M35	NA	NA	NA	NA	NA	–
M4	–	–	–	–	–	±
perampanel	+	+	+	+	+	+
% radioactivity of the sample	NA	NA	P>>M5	P>>M5>M7	P>>M5, M3	NA

AMS = accelerator mass spectrometry, LC/MS/MS = liquid chromatography with tandem mass spectrometry detection, NA = not applicable, P = perampanel.

Analytes are listed in the order of retention time under LC/MS/MS conditions.

See Figure 1 for structures of M2 to M15. M34 and M35 are not included in the diagram but M34 has two -OH groups on the benzene ring and M35 has one -OH group but the position has not been identified.

–: not detected.

±: detected at extremely low intensity (this marker is only applicable to LC/MS/MS analysis).

+: detected.

Reviewer's Note: Some metabolites were labeled with “NA” for AMS analysis. This is due to lack of authentic synthetic compounds as standards. Thus, it is impossible to tell which fractions eluted from HPLC or time points on radio-chromatograms correspond to these metabolites, even though their peaks, if there are any, should be present on the radio-chromatogram.

Reviewer's Comment: Metabolic profiling results of this study are more informative than those from the mass-balance study, as plasma samples collected across a wide span which covered more than 3 times of t_{1/2} (Table 1) were analyzed and thus the results reflected the whole profile of perampanel and its metabolites in circulation. Based on the AMS analyses and quantitative LC/MS-MS results, it seems that there were no major metabolites in plasma, and the 20-25% of total radioactivity not accounted by parent drug may be composed of many identified and unidentified metabolites present as low levels.

6.2. Urine Samples

AMS analyses suggested that there was little parent drug at earlier time points (0-24 hr and 132-156 hr). At later timepoint (300-324 hr), parent drug was detected with radioactivity comparable to a number of other peaks. Overall, there was minimal presence of parent drug in urine. AMS analysis found the peak with the highest ¹⁴C activity corresponded to M7. Following analysis of the results of the AMS and LC/MS/MS, it was concluded that, in addition to M7, this peak also included two glucuronides, M13 and M14.

Timepoint (h)	Percentage of radioactivity recovered					
	M7	M2	M3	M5	M4	Parent
0-24	28	5	1	1	1	1
132-156	17	3	8		3	1
300-324	12	3		13	Not Detected	5

Reviewer's Comment: The results from this study were more informative than that from the mass-balance study, as three urine samples spaced in time were used for metabolic profiling.

Figure 8. HPLC radio-chromatogram of Pooled urine (0-24h) following i.v. administration of 10 µg / 200 nCi [¹⁴C]-Perampanel

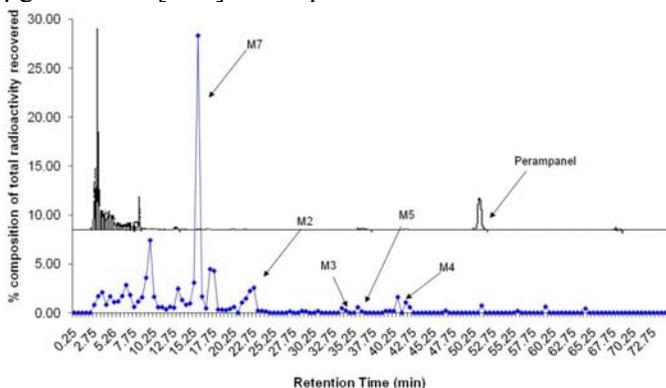
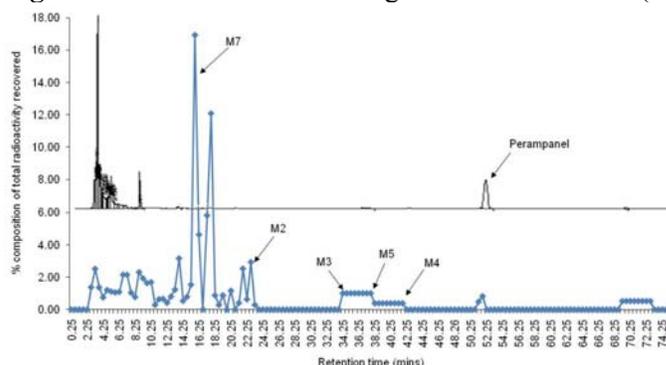


Figure 9. HPLC radio-chromatogram of Pooled urine (132-156h) following i.v. administration



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Figure 10. HPLC radio-chromatogram of Pooled urine (300-324h) following i.v. administration

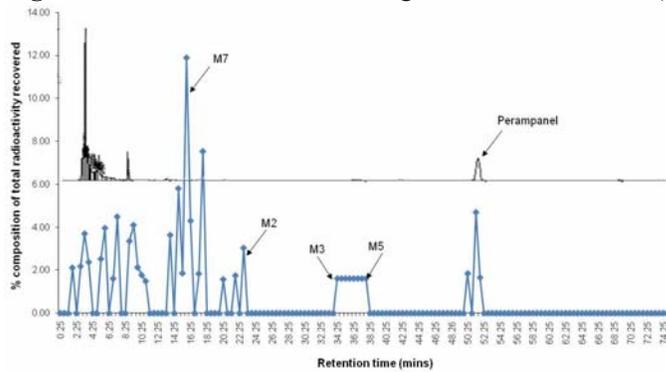


Table 4. Metabolite Profiling Results in Urine

Analyte	AMS			LC/MS/MS 0–24 hour
	0–24 hour	132–156 hour	300–324 hour	
M2	+	+	+	+
M14	NA	NA	NA	+
M13	NA	NA	NA	+
M15	NA	NA	NA	+
M34	NA	NA	NA	+
M7	+	+	+	+
M1	–	–	–	±
M5	+	+	+	–
M3	+	+	+	+
M35	NA	NA	NA	–
M4	+	+	–	+
perampanel	+	+	+	+
Radioactivity of the sample (dpm/mL)	10.5	4.29	0.848	NA
% radioactivity of the sample	M7>M2>M4 >M3, M5, P	M7>M3+M5 >M2>P>M4	M7>M3+M5>P> M2	

6.3. Metabolic Profiling in Feces

For feces homogenates, there were many peaks on radio-chromatograms. For samples collected during 0-24hr, the peak of parent drug seemed to have radioactivity more than other single metabolites. However, the proportion of total radioactivity of the samples accounted by parent drug was still low (Fig 11). In addition, in the mass-balance study (E2007-E044-007), only 3% of dose administered was recovered in feces for the first 48 hrs, suggesting that little of dose was excreted into feces as parent drug during this early period. Radio-chromatograms for samples of 48-72hr and 120-168hr showed that parent drug was present with smaller peak compared to the peaks of several known and unknown metabolites. Overall, these results indicated that parent drug was present with small amount in feces compared to metabolites.

Reviewer’s Comment: It should be noted that the extraction efficiencies for feces samples were very low (20-30%). Thus, it is very difficult to make quantitative interpretation about AMS analysis results. Also, it is impossible at this moment to make any conclusion about the relative importance of metabolic pathways of perampanel in humans (e.g, the pathways represented by M1, M2, M3, M4, M5, M7 and M15), as majority of dose administered (48%) was excreted into feces.

Timepoint (h)	Percentage of radioactivity recovered					
	M7	M2	M3	M5	M4	Parent
0-24	7	1.5	4	5	1	8
48-72	10	2	6	9	<1	1.5
120-168	7	4	7.5	6	<1	2

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Figure 11. HPLC radio-chromatogram of Pooled feces homogenate (0-24h) following intravenous administration of 10 µg / 200 nCi [14C]-Perampanel

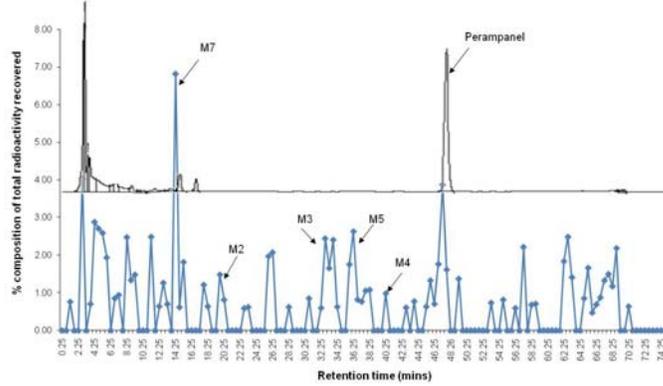


Figure 12. HPLC radio-chromatogram of Pooled feces homogenate (48-72h) following i.v. administration

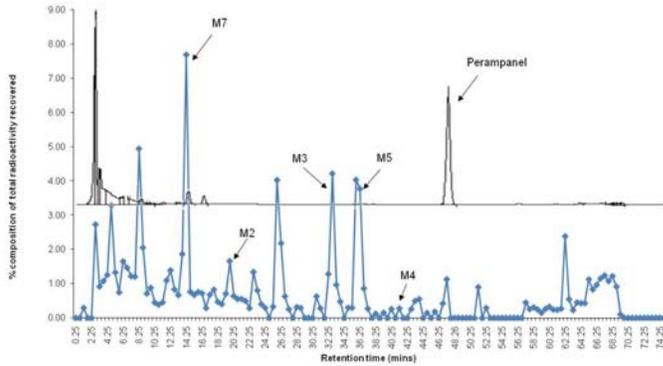
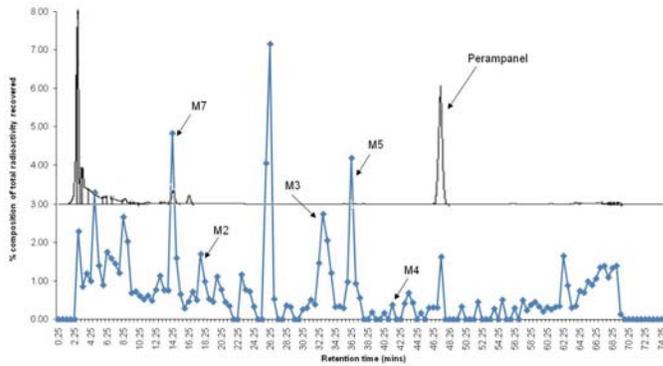


Figure 13. HPLC radio-chromatogram of pooled feces homogenate (120-168h) following i.v. administration



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Table 5. Metabolite Profiling Results in Feces

Analyte	AMS			LC/MS/MS					
	0–24 hour	48–72 hour	120–168 hour	0–24 hour	24–48 hour	48–72 hour	72–96 hour	120–168 hour	264–312 hour
M2	+	+	+	–	–	±	±	–	–
M14	NA	NA	NA	–	–	–	–	–	–
M13	NA	NA	NA	–	–	–	–	–	–
M15	NA	NA	NA	+	+	±	±	–	–
M34	NA	NA	NA	–	–	–	–	–	–
M7	+	+	+	–	–	±	±	–	–
M1	+	+	+	+	+	+	+	+	+
M5	+	+	+	+	+	+	+	+	+
M3	+	+	+	–	±	±	±	±	–
M35	NA	NA	NA	±	±	±	±	±	–
M4	+	+	+	+	+	+	+	+	+
perampanel	+	+	+	+	+	+	+	+	+
Radioactivity of the sample (dpm/mL)	8.10	36.2	27.0	/					
% radioactivity of the sample	P>M7>M5>M3>M1>M2>M4	M7>M5>M1>M3>M2>P>M4	M1>M7>M3>M5>M2>P>M4						

Safety Result

Four subjects reported a total of 5 TEAEs that were considered possibly related to study drug: dizziness (n=3), headache (n=1), and frequent bowel movements (n=1). One subject reported a TEAE that was moderate in severity: arthralgia. Overall, a single 8-mg oral dose of perampanel and 10- μ g ¹⁴C-perampanel solution administered as a single IV infusion were well-tolerated in this study.

Conclusions

- Absolute bioavailability of perampanel (116%), along with results of mass-balance study, indicating that perampanel absorption was almost complete.
- Unchanged perampanel accounted for about 75% of total drug-related material in plasma. There seemed to be no major metabolites with significant amount (>10% of total radioactivity) in circulation.
- Little of dose administered was excreted into urine as unchanged perampanel.
- Compared to metabolites, parent drug seemed to be present in feces only with small amount.
- Due to the low extraction efficiency from feces samples, quantitative results for parent drug and its metabolites were not available. Thus, it is difficult to delineate the relative importance of each metabolic pathway in perampanel total metabolism, considering that feces represent the major elimination pathway for perampanel and its metabolites.

Study E2007-E044-019: An open label, three treatment, fixed sequence crossover study to investigate the effect of E2007 on the combined ethinylestradiol and levonorgestrel oral contraceptive pill (Microgynon® 30 ED) in healthy pre-menopausal female volunteers

Objective	<p><i>Primary objective:</i> To determine the effect of E2007 on the PK of components of the combined ethinylestradiol and levonorgestrel oral contraceptive (OC) pill.</p> <p><i>Secondary objective:</i> To explore the safety and toleration of E2007 with the combined ethinylestradiol and levonorgestrel OC pill in healthy female subjects.</p>		
Study Design	<p>This was an open label, three-treatment, fixed-sequence, crossover study.</p> <p>Timeline: Scr. Bln. Treatment period Follow-up Days: -1 1 21 22 28 29 49 50</p> <p>Study centre attendance: ↓ at days -1, 1, 21, 28, 49, 50</p> <p>OC dosing: [Days 1-21] [Days 29-49]</p> <p>E2007 dosing: [Days 22-28]</p> <p>OC pharmacokinetics: H at days 21, 28, 49, 50</p> <p>All subjects received one cycle of dosing with the OC pill q.d for 21 days (Days 1–21, ‘OC’) followed by 2 mg E2007 and the OC <i>placebo</i> pill q.d. for seven days (Days 22–28, ‘E2007’) and one cycle for 21 days of dosing with the OC pill plus 4 mg E2007 q.d. (Days 29–49, ‘OC plus E2007’).</p>		
Study Population	<p>24 healthy pre-menopausal female subjects (age: 27.4 ± 7.0 yr, weight: 58.7 ± 7.4 kg, all Caucasians) were enrolled and 20 of them completed the study.</p>		
Dosage and Administration	<p>Study drug dosing on Days 21 and 49 was in the morning under fasted state. On all other days, dosing was at bedtime in the evening preferably after a substantial meal.</p> <p>Microgynon® 30 ED tablet (Ethinylestradiol 30 µg and levonorgestrel 150 µg) was taken orally in the morning while fasted on Days 21 and 49. On all other days, the tablet was taken in the evening at bedtime, preferably after a substantial meal.</p>		
PK Sampling	<p><i>Ethinylestradiol and Levonorgestrel:</i> blood samples were taken at the following times relative to study drug administration on Day 21 and on Day 49: -0.5 hr, could be taken up to 1 hr pre-dose, and 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 hrs after dosing.</p> <p><i>E2007:</i> blood samples were taken before the E2007 dose (up to -1 hr) on Day 49.</p>		
Bioanalytical Method	Analyze	Ethinylestradiol	Levonorgestrel
	Method	LC-MS/MS	LC-MS/MS
	Internal Std.	d4-17α-Ethinylestradiol-2,4,16,16	d6-Norgestrel
	LOQ (pg/mL)	2	50
	Calibration	2, 5, 10, 20, 50, 100,	50, 100, 250, 500, 1000,
	Range (pg/mL)	150, 250, 300	3000, 8000, 10,000
	QC (pg/mL)	6, 75, 225	150, 750, 7500
	Accuracy	100.9 – 103.3%	97.3 – 101.3%

	Precision	1.3 – 5.9%	3.1 – 5.1%
	Analyze	E2007	
	Method	HPLC-Fluorescence	
	Internal Std.	E2007 associated substance	
	LOQ (ng/mL)	1	
	Calibration Range (ng/mL)	1, 12, 33.8, 67.5, 112.5, 167.2, 231.5, 308.6, 398.7, 502	
	QC (ng/mL)	3, 73, 211, 428	
	Accuracy	90 – 99.7%	
Precision	1.73 – 6.49%		
PK Assessments	<i>Ethinylestradiol / Levonorgestrel</i> : AUC _{0–τ} , C _{max} , T _{max} , and C _{avg} on Days 21–22 and Days 49–50. <i>E2007</i> : plasma concentrations on Day 49 were summarized.		
Safety Assessment	Physical examination, 12-lead ECG, vital signs, laboratory safety tests and adverse events, pregnancy test at screening		
PK Results	E2007 – Ethinylestradiol / Levonorgestrel Interaction		

OC PK

Repeated doses of 4 mg E2007 did not have significant effect on the steady-state exposure (AUC_{0-tau} and C_{max}) of either component (ethinylestradiol or levonorgestrel) of the OC.

Figure 1. Ethinylestradiol Mean Plasma Concentrations (+/- SD)

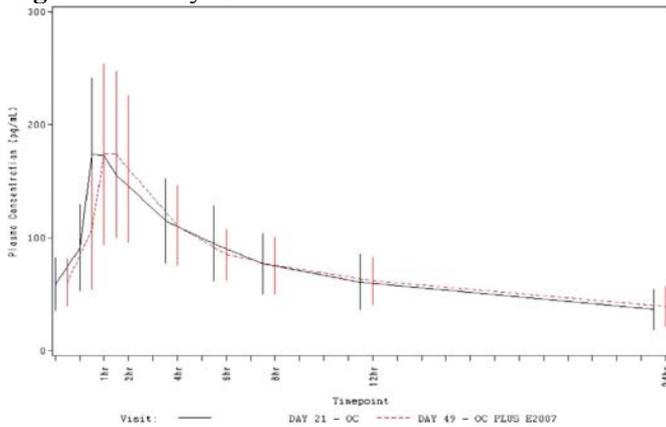


Figure 2. Levonorgestrel Mean Plasma Concentrations (+/- SD)

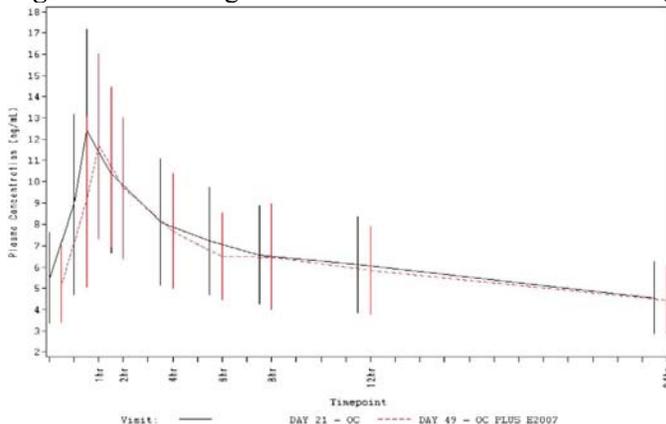


Table 1. Summary PK parameters of Ethinylestradiol and Levonorgestrel

Pharmacokinetic Parameter	Ethinylestradiol		Levonorgestrel	
	OC Alone (N=22)	OC + Perampanel 4 mg (N=20)	OC Alone (N=22)	OC + Perampanel 4 mg (N=20)
AUC_(0-τ)				
Mean	1772 pg-h/mL	1788 pg-h/mL	157 ng-h/mL	150 ng-h/mL
(SD)	(646.3 pg-h/mL)	(631.5 pg-h/mL)	(56.1 ng-h/mL)	(52.5 ng-h/mL)
C_{max}				
Mean	181 pg/mL	180 pg/mL	12.7 ng/mL	11.8 ng/mL
(SD)	(67.2 pg/mL)	(78.9 pg/mL)	(4.8 ng/mL)	(4.3 ng/mL)
C_{av}				
Mean	74 pg/mL	75 pg/mL	7 ng/mL	6 ng/mL
(SD)	(26.9 pg/mL)	(26.3 pg/mL)	(2.3 ng/mL)	(2.2 ng/mL)
t_{max}				
Median	1.5 h	1.3 h	1.0 h	1.0 h
(Min – Max)	(1.0 – 1.5 h)	(1.0 – 2.0 h)	(0.5 – 2.0 h)	(0.7 – 1.5 h)

Table 2. Statistical Analysis of Ethinylestradiol and Levonorgestrel PK Parameters

Drug PK Parameter	Geometric Least Square Means		Geometric Mean Ratio (%) (OC + Perampanel/OC Alone)	90% CI (%)
	OC + Perampanel 4 mg (N=20)	OC Alone (N=22)		
Ethinylestradiol				
AUC _(0-τ) (pg-h/mL)	1601	1660	96	91, 102
C _{max} (pg/mL)	162	169	96	90, 103
Levonorgestrel				
AUC _(0-τ) (ng-h/mL)	136.9	147	93	87, 100
C _{max} (ng/mL)	10.8	11.9	91	84, 98

E2007 PK: pre-dose plasma concentrations of E2007 at Day 49: 550.84 ± 143.1 ng/mL.

Safety Result	<p>14 subjects were enrolled into the initial part of the study (subsequently abandoned). The first five subjects were discontinued due to AEs after being dosed with 4 mg E2007. Four subjects had SAEs of somnolence and of these subjects, one subject also had SAEs of asthenia and dizziness. Other AEs reported included elevated mood, fatigue and thirst. The remaining nine subjects who had been dosed with the OC pill alone and had not received E2007 were discontinued at the request of sponsor. The study was then redesigned by incorporating dose titration from 2 mg and also dosing E2007 in the evenings.</p> <p>On study re-start, 24 were enrolled and 20 of them completed the study. Four subjects withdrew prior to completing the study, among them one subject was withdrawn due to elevated GPT levels on Day 21, and the other subject withdrawn due to muscle spasm in chest at the end of the 2 mg E2007 dosing period (Day 29). In the 2 mg E2007 dosing period, 5 subjects (24% of subjects) experienced mild TEAEs (most common ones, fatigue and dizziness) considered to be related to study treatment. In the OC plus 4 mg E2007 dosing period, the majority of TEAEs experienced by 14 subjects (70% of subjects) were considered to be mild in severity, with another subject experiencing moderate AE (vomiting, resolved without concomitant medication). Most commonly reported TEAEs were dizziness, headache, coordination abnormal, vomiting, fatigue and pharyngolaryngeal pain. Overall, 16 subjects (76%) experienced AEs that were considered to be related (probably or possibly) to E2007.</p>
Conclusion	Repeated doses of 4-mg E2007 did not significantly affect steady-state PK of either component (ethinylestradiol and levonorgestrel) of the OC pill.

E2007-A001-023: A Double-blind Ascending Single-Dose Safety and Tolerability Study to Find the Maximum Tolerated Dose of E2007 in Healthy Recreational Polydrug Users

Objective	<p><i>Primary objective:</i> To determine the safety and tolerability of single oral escalating doses of perampanel for the purposes of identifying the maximum tolerated dose (MTD) in healthy adult, recreational polydrug users.</p> <p><i>Secondary objective:</i> To make a preliminary evaluation of subjective effects following single oral escalating doses of perampanel.</p>																																																												
Study Design	<p>This study was a double-blind, fixed-order, single ascending-dose, within-subject, staggered-group pilot study consisting of 8 dosing periods in recreational polydrug users. The subjects were divided into staggered groups:</p> <ul style="list-style-type: none"> • Group 1 - received single oral doses of 8 mg and 16 mg of perampanel • Group 2 - received single oral doses of 12 mg and 20 mg perampanel • Group 3 - received single oral doses of 24 mg and 32 mg perampanel • Group 4 - received single oral doses of 28 mg and 36 mg perampanel <p>Group 1 subjects received 8 mg perampanel or placebo in Period 1. Group 2 subjects received 12 mg perampanel or placebo in Period 2, approximately 7 days after dosing in Period 1. Each subject underwent a minimum 2-week washout period between dosing. Group 1 subjects received 16 mg perampanel or placebo in Period 3. Group 2 subjects received 20 mg perampanel or placebo in Period 4, approximately 7 days after dosing in Period 3.</p> <p>Group 3 received 24 mg and 32 mg perampanel in Periods 5 and 7, respectively, and Group 4 received 28 mg and 36 mg perampanel in Periods 6 and 8, respectively. The staggered design with a minimum 7-day washout between each period and a 2-week washout for each subject remained as described above for Group 1 and Group 2.</p> <p>For each dosing period, 8 subjects were to be randomized to receive active treatment and 4 subjects were to receive placebo. No subjects received placebo in consecutive sessions.</p>																																																												
Dosing & Administration	<p>Perampanel was supplied as tablets containing 2 mg perampanel or over-encapsulated tablets containing 4 mg perampanel. Single oral doses of perampanel or placebo were administered in the morning on Day 1 of each Treatment Period (fasted from 8 hours pre-dose until 4 hours post-dose).</p>																																																												
Study Population	<p>Healthy male or female subjects, 21-55 yr, who were current recreational polydrug users with a history of psychedelic drug use.</p> <table border="1" data-bbox="488 1549 1391 1866"> <thead> <tr> <th></th> <th>Group 1 (N=19)</th> <th>Group 2 (N=13)</th> <th>Group 3 (N=12)</th> <th>Group 4 (N=12)</th> <th>Total (N=56)</th> </tr> </thead> <tbody> <tr> <td>Male, n (%)</td> <td>12 (63.2)</td> <td>8 (61.5)</td> <td>8 (66.7)</td> <td>10 (83.3)</td> <td>38 (67.9)</td> </tr> <tr> <td>Female, n (%)</td> <td>7 (36.8)</td> <td>5 (38.5)</td> <td>4 (33.3)</td> <td>2 (16.7)</td> <td>18 (32.1)</td> </tr> <tr> <td>Racial Designation</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td> White, n (%)</td> <td>12 (63.2)</td> <td>10 (76.9)</td> <td>12 (100)</td> <td>9 (75.0)</td> <td>43 (76.8)</td> </tr> <tr> <td> Asian, n (%)</td> <td>2 (10.5)</td> <td>1 (7.7)</td> <td>0 (0.0)</td> <td>1 (8.3)</td> <td>4 (7.1)</td> </tr> <tr> <td> Black or of African descent, n (%)</td> <td>2 (10.5)</td> <td>0 (0.0)</td> <td>0 (0.0)</td> <td>0 (0.0)</td> <td>2 (3.6)</td> </tr> <tr> <td> Other, n (%)</td> <td>3 (15.8)</td> <td>2 (15.4)</td> <td>0 (0.0)</td> <td>2 (16.7)</td> <td>7 (12.5)</td> </tr> <tr> <td>Age (years), Mean (SD)</td> <td>34.7 (7.5)</td> <td>31.1 (6.9)</td> <td>31.2 (8.1)</td> <td>34.9 (10.4)</td> <td>33.1 (8.2)</td> </tr> <tr> <td>BMI (kg/m²), Mean (SD)</td> <td>24.7 (2.9)</td> <td>23.4 (3.3)</td> <td>24.3 (3.0)</td> <td>25.1(3.2)</td> <td>24.4 (3.1)</td> </tr> </tbody> </table>		Group 1 (N=19)	Group 2 (N=13)	Group 3 (N=12)	Group 4 (N=12)	Total (N=56)	Male, n (%)	12 (63.2)	8 (61.5)	8 (66.7)	10 (83.3)	38 (67.9)	Female, n (%)	7 (36.8)	5 (38.5)	4 (33.3)	2 (16.7)	18 (32.1)	Racial Designation						White, n (%)	12 (63.2)	10 (76.9)	12 (100)	9 (75.0)	43 (76.8)	Asian, n (%)	2 (10.5)	1 (7.7)	0 (0.0)	1 (8.3)	4 (7.1)	Black or of African descent, n (%)	2 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	Other, n (%)	3 (15.8)	2 (15.4)	0 (0.0)	2 (16.7)	7 (12.5)	Age (years), Mean (SD)	34.7 (7.5)	31.1 (6.9)	31.2 (8.1)	34.9 (10.4)	33.1 (8.2)	BMI (kg/m ²), Mean (SD)	24.7 (2.9)	23.4 (3.3)	24.3 (3.0)	25.1(3.2)	24.4 (3.1)
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PK & PD measurements	<p><i>PK</i>: Blood samples were collected at pre-dose, 1, 2, 4, 8, 24 and 72 hours post-dose.</p> <p><i>PD</i>: The following visual analogue scales (VAS) were assessed at 1, 2, 4, 6, 12, and 24 hours post-dose:</p> <ul style="list-style-type: none"> • Drug Liking ('at this moment') visual analogue scale (VAS) • Good Drug Effects VAS • Bad Drug Effects VAS • Any Drug Effects VAS
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Bioanalytical Method	Analyze	E2007
	Method	LC/MS-MS
	Internal Std.	E2007 associated substance
	LOQ (ng/mL)	2.5
	Calibration Range (ng/mL)	2.5, 5, 10, 30, 100 300, 800 and 1,000
	QC (ng/mL)	2.5, 7.5, 150 and 750
	Accuracy	84.9 – 107.2 %
	Precision	3.3 to 9.1 %

PK & PD Assessments	<p><i>PK</i>: Cmax, Tmax, AUC0-last</p> <p><i>PD</i>: The peak responses (maximum effect [Emax] and minimum effect [Emin] for Drug Liking VAS only) and area under the effect curve (AUE) over the 24 hours from dosing for all pharmacodynamic measures.</p>
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Safety Assessment	Physical examination, 12-lead ECG, vital signs, laboratory safety tests, urine collection, and adverse events
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PK Results	E2007
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PK:
Tmax of perampanel was observed within 1 to 2 hours post-dose. Perampanel plasma concentrations declined in a biphasic manner; with a slower decline in concentrations observed after 8 hours post-dose.

Figure 1. Perampanel Plasma Concentrations over Time by Dose (8 mg to 20 mg)

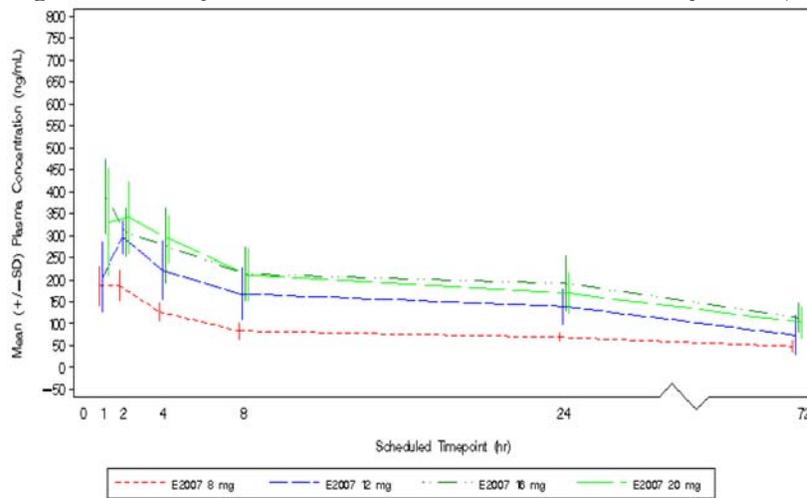


Figure 2. Perampanel Plasma Concentrations over Time by Dose (24 mg to 36 mg)

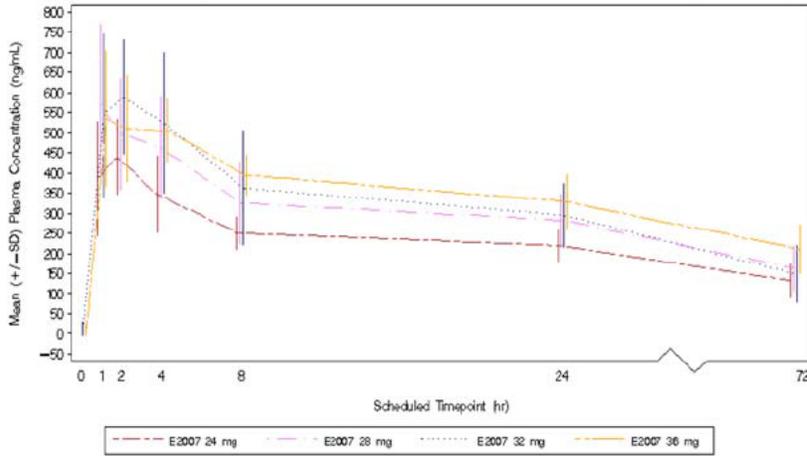


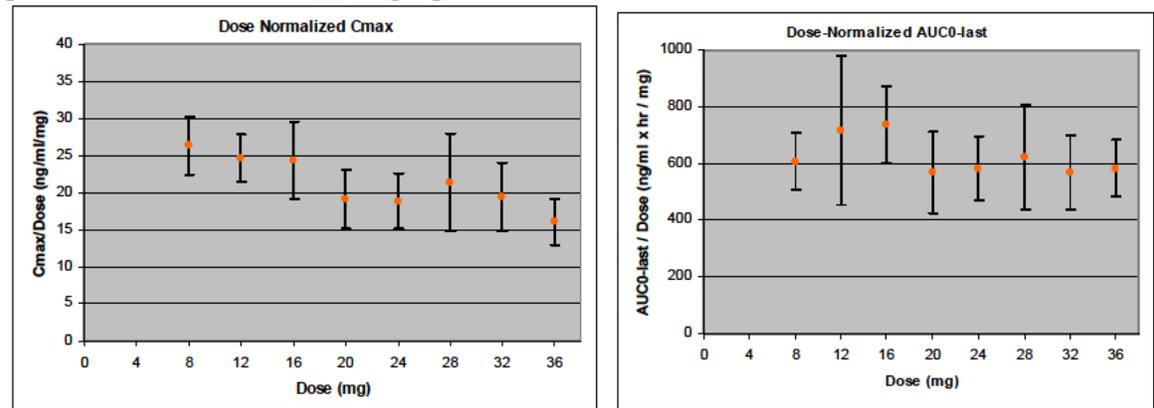
Table 1. Summary of Pharmacokinetic Endpoints for Perampanel (8 mg to 36 mg)

Parameter	Statistic	perampanel 8 mg (N=8)	perampanel 12 mg (N=6)	perampanel 16 mg (N=8)	perampanel 20 mg (N=8)	perampanel 24 mg (N=8)	perampanel 28 mg (N=8)	perampanel 32 mg (N=7)	perampanel 36 mg (N=8)
C_{max} (ng/mL)	Mean	210.6	295.5	388.7	382.1	451.5	599.3	623.9	578.3
	SD	31.0	38.1	83.0	79.7	89.0	184.8	146.2	113.1
	Median	208.9	300.8	398.2	369.8	469.3	595.5	577.0	621.5
	Range	160.4-248.1	232.9-341.2	289.5-506.1	262.9-524.3	309.6-608.0	379.2-957.0	494.9-873.8	376.1-711.4
	Geometric Mean (% CV)	208.5 (14.7)	293.3 (12.9)	380.8 (21.3)	374.9 (20.9)	443.7 (19.7)	575.9 (30.8)	610.5 (23.4)	567.5 (19.6)
t_{max} (hour)	Median	1.03	2.01	1.04	1.08	2.04	1.14	2.07	1.66
	Range	1.00-2.03	2.00-2.03	1.00-4.15	1.03-4.03	1.03-2.07	1.03-4.08	1.08-2.12	1.12-4.08
AUC_{0-t} (h*ng/mL)	Mean	4867.5	8615.5	11794.2	11411.3	14007.4	17432.8	18280.0	21016.5
	SD	814.5	3135.5	2151.9	2873.0	2706.9	5202.7	4190.1	3636.5
	Median	4918	9500	12147	10721	13241	15585	17603	21668
	Range	3731-5968	4400-11955	8681-14496	7726-17098	10784-19425	12281-25772	13718-24637	15552-25316
	Geometric Mean (% CV)	4807.4 (16.7)	8070.0 (36.4)	11616.3 (18.3)	11119.1 (25.2)	13795.6 (19.3)	16824.4 (29.8)	17884.9 (22.9)	20724.9 (17.3)

Reviewers' Comment:

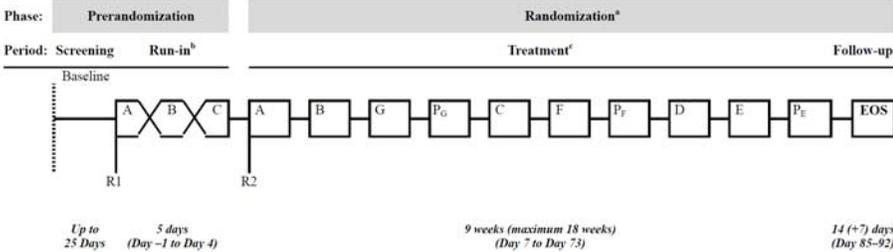
C_{max} increased less than dose proportionally as illustrated in the figure below (left panel). Dose-normalized C_{max} gradually decreased when dose increased from 8 mg to 36 mg. In contrast, AUC of perampanel increased in an approximately dose-proportional manner (right panel).

Figure 3. 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}



<p>PD: Please refer to the review documented by CSS reviewer, Dr. Alicja Lerner, for more details about the evaluation of the abuse potential of perampanel.</p>	
<p>Safety Result</p>	<p>At perampanel doses of 12 mg or greater, all subjects (100%) experienced at least one AE, while the incidence of AEs following perampanel 8 mg was slightly lower (87.5%). Placebo was associated with the lowest incidence of AEs (45.2%). The most common AEs were those classified as nervous system disorders, general disorders and administration site conditions, gastrointestinal disorders and psychiatric disorders, and the most common AEs reported were somnolence, dizziness, euphoric mood, headache, gait disturbance, fatigue, nausea, oral paresthesia and blurred vision. The most common AE associated with perampanel was somnolence, which occurred in greater than 60% of patients at all doses (8 mg to 36 mg). Following placebo treatments, the most common AE was dizziness (16.1%). Most subjects experienced mild to moderate AEs and 2 subjects experienced severe AEs. All perampanel-treated subjects had at least one AE that was considered at least possibly related to the study drug.</p>
<p>Conclusions</p>	<p>Tmax was observed within 1 to 2 hours post-dose. Cmax of perampanel increased in a less than dose-proportional manner from 8 mg to 36 mg doses, while AUC0-last seemed to increase approximately dose-proportional.</p>

E2007-A001-024: A Randomized, Double-Blind, Placebo- and Active-Controlled Crossover Study to Evaluate the Abuse Potential of Perampanel (E2007) in Healthy Recreational Polydrug Users

Objective	<p><i>Primary objective:</i> To evaluate the abuse potential of single doses of perampanel (8 mg, 24 mg, and 36 mg) compared to alprazolam (1.5 mg and 3 mg), oral ketamine (100 mg), and placebo in healthy recreational polydrug users</p> <p><i>Secondary objective:</i> To confirm the safety and tolerability following single oral doses of perampanel (8 mg, 24 mg, and 36 mg) and to assess the pharmacokinetics of perampanel in healthy recreational polydrug users</p>
Study Design	<p>The study consisted of 2 phases: Pre-randomization and Randomization. The total duration of the study from Screening until Follow-up was ~26 weeks.</p> <p>The Pre-randomization Phase was up to 4 weeks in duration and consisted of 2 periods: a Screening Period and a 5-day (4-night) inpatient Run-in Period. During the Run-in Period, subjects received single oral doses of each of the following treatments: 100 mg oral ketamine, 1.5 mg alprazolam, and placebo. The Run-in Period was conducted to ensure that subjects were able to distinguish the positive comparators from placebo in laboratory setting. Drug administrations in this Run-in Period were separated by a washout of 24 hours. A washout of at least 5 days separated last drug administration in the Run-in Period and the first drug administration in the Randomization Phase.</p>  <p>A=placebo; B=100 mg ketamine; C=1.5 mg alprazolam; D=3 mg alprazolam; E=8 mg perampanel; EOS=End of study; F=24 mg perampanel; G=36 mg perampanel; P_E=placebo arm fixed to follow 8 mg perampanel; P_F=placebo arm fixed to follow 24 mg perampanel; P_G=placebo arm fixed to follow 36 mg perampanel; R₁=Run-in Randomization; R₂=Randomization Phase randomization.</p> <p>a. Represents 1 of 10 possible treatment sequences for the Randomization Phase. Each Perampanel Treatment Period was followed by a placebo Treatment Period.</p> <p>b. Represents 1 of 6 possible treatment sequences for the Run-in Period</p> <p>The Randomization Phase of the study was ~9 to 18 weeks in duration. During this phase, subjects were randomized to 1 of 10 treatment sequences, according to two 7×7 Williams squares. To reduce the potential for accumulation of perampanel, the 4 random sequences where 3 perampanel doses would have been given in succession were removed.</p> <p>During the Randomization Phase, each subject received the following single</p>

	<p>oral dose treatments in a randomized, double-blind, crossover manner (1 at each Treatment Period): 8 mg perampanel, 24 mg perampanel, 36 mg perampanel, 1.5 mg alprazolam, 3 mg alprazolam, 100 mg oral ketamine, and placebo. Due to the long half-life of perampanel, additional placebo doses were fixed to follow each dose of perampanel, such that each subject participated in a total of 10 inpatient Treatment Periods (6 active treatments, 1 fully randomized placebo dose, and 3 "washout" placebo doses), each lasting 4 days (3 nights). Treatment Periods were separated by a 7-day washout (maximum 14 days). A safety Follow-up Period occurred 14 days (up to 21 days) after the last drug administration.</p>																																								
Dosing & Administration	<p>Perampanel was supplied as red, 8.1 mm diameter, biconvex film-coated tablets containing 4 mg perampanel that were over-encapsulated into gray opaque capsule shells.</p> <p>Alprazolam (Xanax®) was supplied as a lavender, single-score tablet containing 0.5 mg or 1 mg alprazolam. Alprazolam and placebo tablets were over-encapsulated with no overfill in Swedish Orange DBAA capsules. Each capsule contained one tablet (0.5 mg alprazolam tablet, 1 mg alprazolam tablet, or placebo tablet).</p> <p>Ketamine (Ketalar®) was supplied in 20 mL Steri-vials (each 1 mL contained ketamine HCl equivalent to 10 mg ketamine base). Ketamine was prepared as an oral solution for administration. 10 mL (100 mg) of 10 mg/mL ketamine solution was added to a strongly flavored juice up to a volume of approximately 240 mL (eg, Everfresh™ Orange Banana Strawberry Cocktail). The solution was administered to subjects within 4 hours of preparation.</p> <p>Following an overnight fast of at least 8 hours, subjects were administered the capsules with the 240 mL oral solution in the morning during the Run-in Period and each Treatment Period. No food was permitted for at least 2 hours post-dose.</p>																																								
Study Population	<p>Healthy male or female subjects, 18 - 55 yr, who were current recreational polydrug users with a history of CNS depressant and psychedelic drug use. 40 subjects were enrolled into the Randomization Phase, and 34 subjects provided valid data for the pharmacodynamic analyses.</p> <table border="1"> <thead> <tr> <th></th> <th>Safety Analysis Set (N=40)</th> <th>Pharmacokinetic Analysis Set (N=39)</th> <th>Pharmacodynamic Analysis Set (N=34)</th> </tr> </thead> <tbody> <tr> <td>Gender</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Male, n (%)</td> <td>31 (77.5)</td> <td>30 (76.9)</td> <td>28 (82.4)</td> </tr> <tr> <td>Female, n (%)</td> <td>9 (22.5)</td> <td>9 (23.1)</td> <td>6 (17.6)</td> </tr> <tr> <td>Age (years)^a, mean (SD)</td> <td>34.1 (9.77)</td> <td>34.3 (9.73)</td> <td>35.1 (9.89)</td> </tr> <tr> <td>BMI (kg/m²), mean (SD)</td> <td>25.37 (3.155)</td> <td>25.35 (3.193)</td> <td>25.34 (3.295)</td> </tr> <tr> <td>Race, n (%)</td> <td></td> <td></td> <td></td> </tr> <tr> <td>White</td> <td>33 (82.5)</td> <td>33 (84.6)</td> <td>30 (88.2)</td> </tr> <tr> <td>Black</td> <td>4 (10.0)</td> <td>4 (10.3)</td> <td>2 (5.9)</td> </tr> <tr> <td>Asian</td> <td>3 (7.5)</td> <td>2 (5.1)</td> <td>2 (5.9)</td> </tr> </tbody> </table>		Safety Analysis Set (N=40)	Pharmacokinetic Analysis Set (N=39)	Pharmacodynamic Analysis Set (N=34)	Gender				Male, n (%)	31 (77.5)	30 (76.9)	28 (82.4)	Female, n (%)	9 (22.5)	9 (23.1)	6 (17.6)	Age (years)^a, mean (SD)	34.1 (9.77)	34.3 (9.73)	35.1 (9.89)	BMI (kg/m²), mean (SD)	25.37 (3.155)	25.35 (3.193)	25.34 (3.295)	Race, n (%)				White	33 (82.5)	33 (84.6)	30 (88.2)	Black	4 (10.0)	4 (10.3)	2 (5.9)	Asian	3 (7.5)	2 (5.1)	2 (5.9)
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PK & PD measurements	<p><i>PK</i>: Blood samples were collected at pre-dose and 1.5, 3.5, 4.5, 8.5, 12.5, 24.5, and 48.5 hours post-dose during each Treatment Period, and Follow-up.</p> <p><i>PD</i>: Drug Liking Visual Analogue Scale (VAS), Good Drug Effects VAS,</p>																																								

Bad Drug Effects VAS, other subjects effects VASs (High VAS, Drowsiness VAS, and Dizziness VAS), ARCI (Addiction Research Center Inventory) VASs, NMDA-specific VASs, Overall Drug Liking VAS, Take Drug Again VAS, SDV (Subjective Drug Value), Drug Similarity VASs, CRT (Choice Reaction Time test), DA (Divided Attention test), and DSST (Digit Symbol Substitution Test) were measured/performed at pre-dose and different timepoints post-dose on each dosing day during the Run-in Period and Treatment Period.

Bioanalytical Method	Analyze	E2007
	Method	LC/MS-MS
	Internal Std.	E2007 associated substance
	LOQ (ng/mL)	2.5
	Calibration Range (ng/mL)	2.5, 5, 10, 30, 100 300, 800 and 1,000
	QC (ng/mL)	2.5, 7.5, 150 and 750
	Accuracy	84.9 – 107.2 %
	Precision	3.3 to 9.1 %

PK & PD Assessments

PK: Cmax, Tmax, AUC0-last

PD: Primary subjective variables included:

- Balance of effects: Drug Liking Visual Analogue Scale (VAS) ("at this moment"), Subjective Drug Value (SDV);
- Positive effects: ARCI Morphine Benzadrine Group (MBG) scale
- Sedative effects: ARCI Pentobarbital Chlorpromazine Alcohol Group (PCAG) scale

Safety Assessment Physical examination, 12-lead ECG, vital signs, laboratory safety tests and adverse events

PK Results E2007

PK:
Cmax and AUClast of perampanel appeared to increase in a less than dose-proportional manner. Tmax was reached later for 24 mg and 36 mg perampanel (median, 3.5 hours) compared to the 8 mg dose (median, 1.5 hours), indicating slower absorption at these higher dose levels.

Figure 1. Mean (SD) Plasma Perampanel Concentrations over Time by Dose (ng/mL)

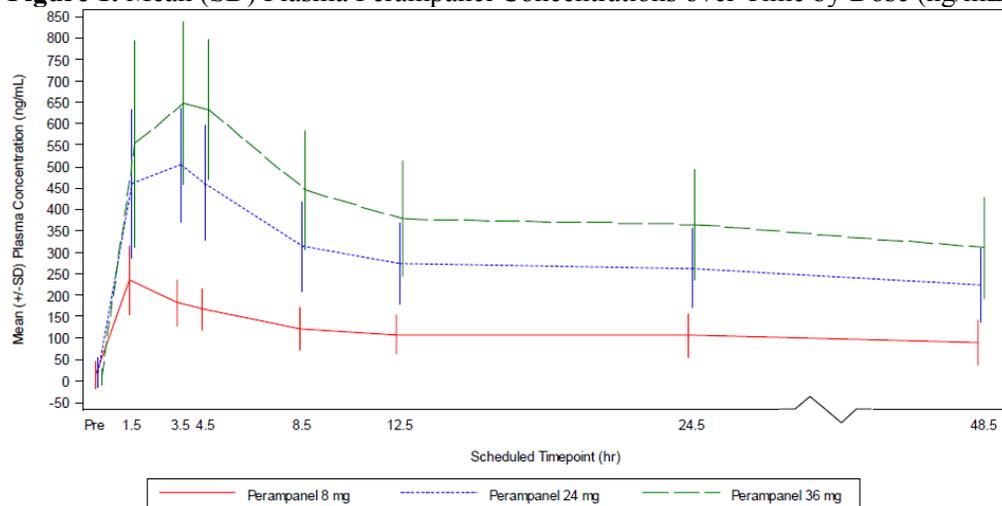


Table 1. Summary of Pharmacokinetic Parameters for Perampanel

Parameter/Statistic	Perampanel 8 mg (N=38)	Perampanel 24 mg (N=37)	Perampanel 36 mg (N=37)
C_{max} (ng/mL)			
Mean	246.1	541.8	708.7
SD	65.3	141.7	181.4
Range (min-max)	130 – 378	340 – 951	452 – 1196
T_{max} (hour)			
Median	1.5	3.5	3.5
Range (min-max)	1.5 – 3.5	1.5 – 4.5	1.5 – 4.5
AUC_{last} (ng*hr/mL)			
Mean	5461	13592	18635
SD	2370	4360	6040
Range (min-max)	2917 – 13506	9050 – 26413	10865 – 37153

Reviewers' Comment: It is speculated that the less than dose-proportional increases in C_{max} at higher doses of perampanel may be attributed to limited solubility of the drug and resulted delay in dissolution/absorption. Solubility of perampanel (weak base, pKa=3.24) is pH-dependent and is higher in acidic condition, as shown in the following table. Complete dissolution was not observed at pH 4.5 or above because of insufficient solubility of perampanel.

Table 2. 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

PK-PD:

Scatter plots of E_{max} values for primary pharmacodynamic measures vs. perampanel C_{max} are shown in the following figures for Drug Liking VAS, SDV, ARCI MBG (Morphine Bazedrine Group), and ARCI PCAG (Pentobarbital Chlorpromazine Alcohol Group). Overall, the effects of perampanel increased slightly with increasing C_{max}. The strongest relationships were observed with ARCI MBG and PCAG scales. Please refer to the review documented by CSS reviewer, Dr. Alicja Lerner, for more details about the evaluation of the abuse potential of perampanel.

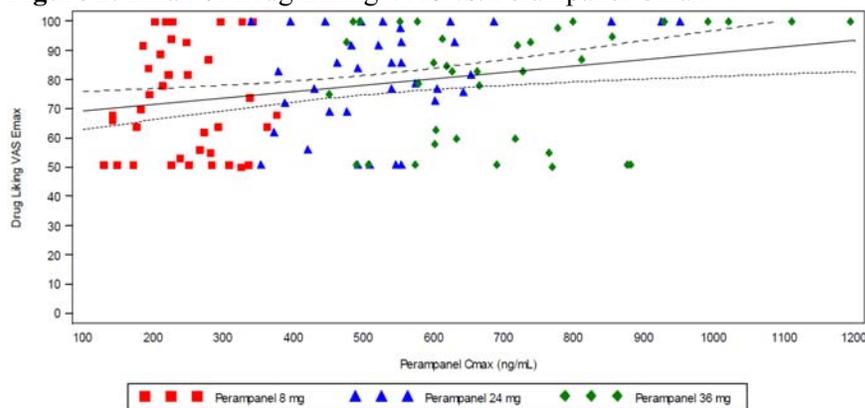
Figure 2. E_{max} of Drug Liking VAS vs. Perampanel C_{max}

Figure 3. Emax of SDV vs. Perampanel Cmax (Regression line with 95% CI of the mean)

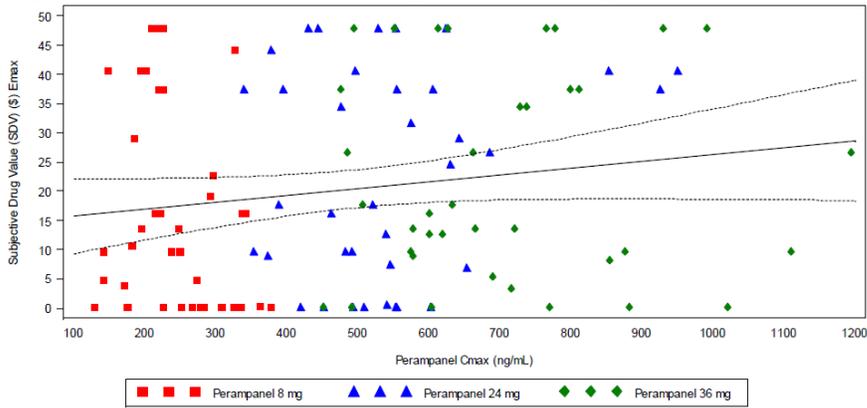


Figure 4. Emax of ARCI MBG vs. Perampanel Cmax

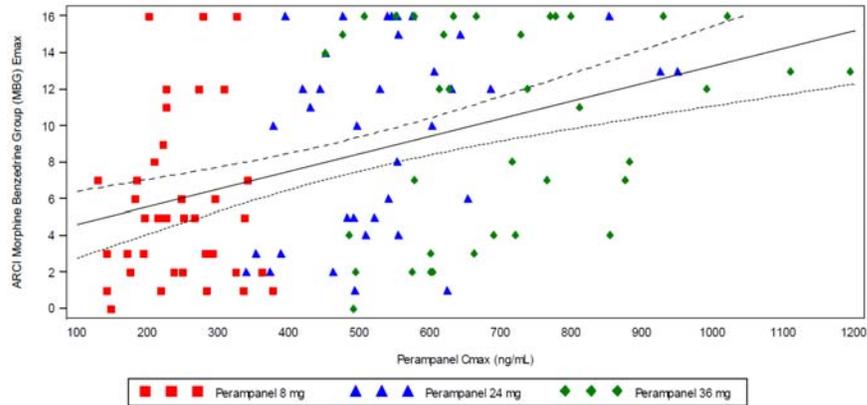
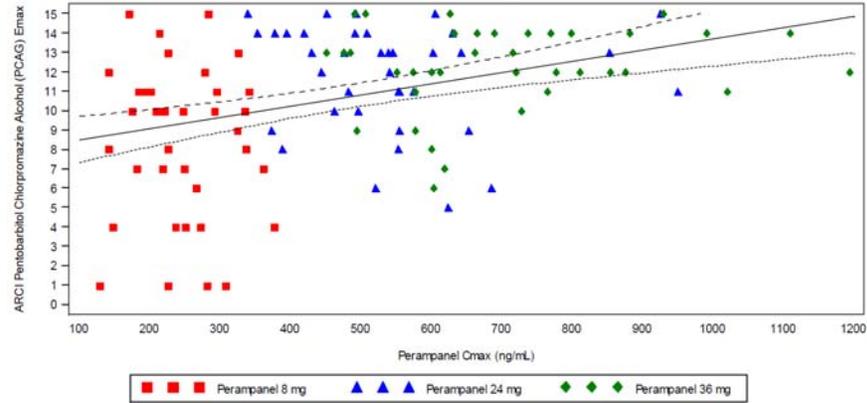


Figure 5. Emax of ARCI PCAG vs. Perampanel Cmax (Regression line with 95% CI of the mean)



Safety Result

Treatment-emergent AE (TEAE) incidence was very high in subjects who received 1.5 mg and 3 mg alprazolam (97.2% and 100.0%, respectively), 100 mg ketamine (97.1%), and 24 mg and 36 mg perampanel (both 100.0%). The incidence was lower with 8 mg perampanel (86.8%), while the incidence of TEAEs observed following the randomized placebo (30.6%) and placebo fixed to follow perampanel doses (18.9% to 32.4%) was much lower.

	<p>The most common TEAEs reported with 8 mg perampanel were somnolence, euphoric mood, fatigue, dizziness, hypoaesthesia oral, and nausea. In addition to these TEAEs, gait disturbance was also commonly reported with 24 mg perampanel, while vision blurred, dysarthria, coordination abnormal, and ataxia were also common with 36 mg perampanel. The incidence of somnolence was similar between 24 mg and 36 mg perampanel and alprazolam doses and higher than that the incidence observed with 100 mg ketamine. Perampanel, particularly at the 36 mg dose, was also associated with higher incidences of other TEAEs compared to the other active treatments, primarily dizziness, nausea, hypoaesthesia (oral), vision blurred, dysarthria, gait disturbance, vomiting, coordination abnormal, and ataxia. Of these TEAEs, dizziness, vision blurred, dysarthria, coordination abnormal, and ataxia showed dose-related increases with perampanel, and somnolence, euphoric mood, nausea, and gait disturbance showed higher incidences with the 2 higher doses compared to 8 mg perampanel. Most TEAEs had a maximum severity of mild or moderate.</p>
<p>Conclusions</p>	<ul style="list-style-type: none"> • C_{max} and AUC_{last} of perampanel appeared to increase in a less than dose-proportional manner. T_{max} was delayed for 24 mg and 36 mg perampanel (median 3.5 hours) compared to the 8 mg dose (median 1.5 hours), indicating slower absorption at these higher dose levels. • Perampanel E_{max} values for pharmacodynamic measures, Drug Liking VAS, SDV, ARCI MBG (Morphine Benezdrine Group) and ARCI PCAG (Pentobarbital Chlorpromazine Alcohol Group), increased slightly with increasing C_{max} of perampanel, with stronger relationships observed for APCI MBG and APCI PCAG.

Study E2007-E044-025: An open-label, three treatment, fixed sequence study to investigate the pharmacokinetic interaction between E2007 and levodopa in healthy volunteers

Objective	To determine the effect of steady-state E2007 on the pharmacokinetics of current Parkinson's disease therapy levodopa in healthy volunteers.		
Study Design	<p>This was an open-label, three-period, fixed-sequence study.</p> <ul style="list-style-type: none"> • Levodopa alone: a single dose of 100 mg levodopa (Sinemet® 110 tablets, containing 10.8 mg carbidopa and 100 mg levodopa) on the morning of Day 1 following an overnight fast of at least 10 hours. • E2007 alone: repeated dosing with 4 mg E2007 (4-mg tablet) for 19 days dosed in the evening after food on Days 2 to 20. • E2007 and levodopa: a single dose of 100 mg levodopa (Sinemet® 110 tablets) on the morning of Day 21 following an overnight fast 		
Study Population	60 subjects were recruited and 59 subjects completed the study. Age (mean±SD): 30.4 ± 9.1 yr; Weight: 71.6 ± 10.6 kg; Race: Caucasian (87%); Gender: male (72%)		
PK Sampling	<p>Levodopa: for Day 1 and Day 21, blood samples were collected at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours after dosing levodopa on Day 1 for analysis of levodopa.</p> <p>E2007: pre-dose on Days 19 (within 60 minutes) and 20; and at 12 (prior to levodopa dose) and 24 hours following the evening dose on Day 20 (i.e. on Day 21) for analysis of E2007 concentration.</p> <p>Urine was collected for 24 hours after the last dose of E2007 (Day 20) for metabolite identification purposes.</p>		
Bioanalytical Method	Analyze	E2007	Levodopa
	Method	LC/MS/MS	LC/MS/MS
	Internal Std.	E2007-d5	L-Dopa-d3
	LOQ (ng/mL)	5	49.1
	Calibration Range (ng/mL)	5, 15.7, 38, 71, 115, 169 236, 314, 402, 501	49, 71, 113, 177, 260, 369 491, 642, 805, 996
	QC (ng/mL)	15, 83, 222, 426	149, 266, 507, 861
	Accuracy	92.9 – 97.2%	96.1 – 106.9%
	Precision	2.40 – 7.57%	4.71 – 10.67%
PK Assessments	Levodopa: AUC _{0-∞} , C _{max} , T _{max} , AUC _{0-t} , and t _{1/2} .		
Safety Assessment	Physical examination, 12-lead ECG, vital signs, laboratory safety tests and adverse events		
Pharmacokinetic Results	E2007 – Levodopa Interaction		
<p>Levodopa PK Repeated doses of 4-mg E2007 did not affect PK of levodopa (AUC, C_{max}, T_{max}, t_{1/2}).</p> <p>Figure 1. Mean (±SD) Levodopa Plasma Concentration versus Time Profile</p>			

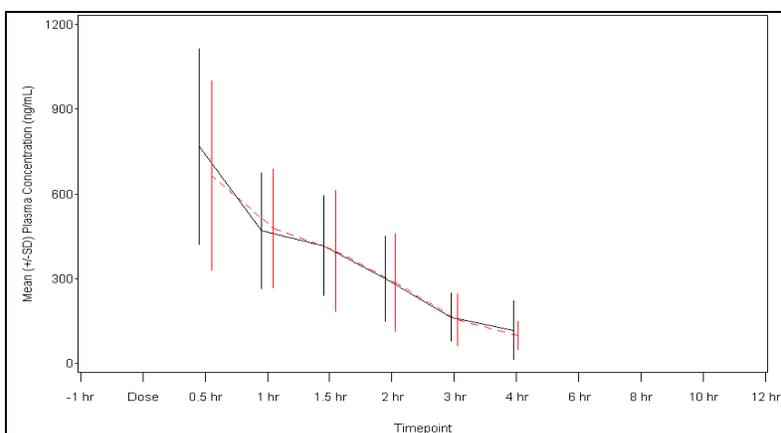


Table 1. Summary PK parameters of Levodopa

Parameter		Levodopa (N = 59)	E2007 plus Levodopa (N = 59)
AUC(0-t) (ng.hr/mL)	n	59	59
	Mean	1335.717	1230.954
	Geometric	1268.525	1163.908
	SD	435.0425	452.9609
	CV %	33.5459	33.6495
	Median	1244.54	1131.85
	Minimum	572.21	607.54
AUC(0-inf) (ng.hr/mL)	n	57	59
	Mean	1445.457	1356.839
	Geometric	1383.785	1291.417
	SD	424.6786	463.5490
	CV %	30.9054	31.6636
	Median	1341.54	1261.99
	Minimum	642.61	694.46
Cmax (ng/mL)	n	59	59
	Mean	841.267	804.483
	Geometric	803.797	777.427
	SD	268.1104	214.2257
	CV %	30.7708	26.8938
	Median	768.40	807.94
	Minimum	411.81	470.86
tmax (hr)	n	59	59
	Median	0.50	0.50
	Minimum	0.50	0.42
	Maximum	4.00	2.00
t1/2 (hr)	n	57	59
	Mean	1.257	1.268
	SD	0.2892	0.3291
	Median	1.20	1.25
	Minimum	0.58	0.65

Table 2. Statistical Analysis of Primary Levodopa Pharmacokinetic Parameters

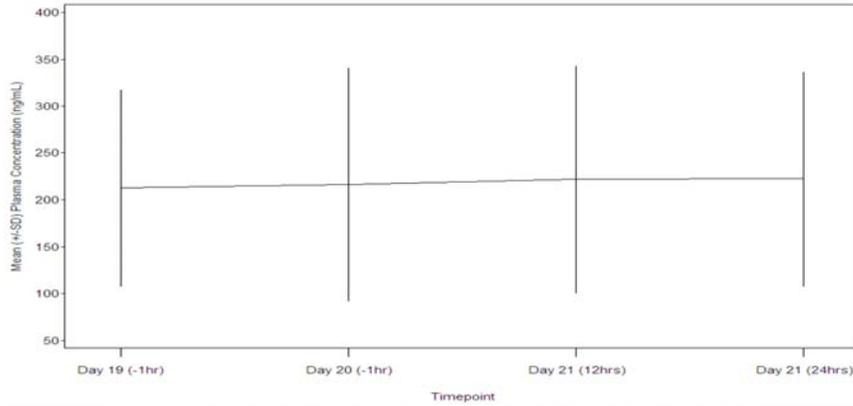
Pharmacokinetic Parameter	Geometric Least Square Means		Geometric Least Square Means Ratio (%) ^a	90% CI
	Perampanel + Levodopa	Levodopa Alone		
AUC _(0-inf) (n=57)	1291	1389	93	88, 99
C _{max} (n=59)	777	804	97	89, 105

Pharmacokinetic Parameter	Least square means		Ratio of treatment means ¹	90% CI
	E2007 plus Levodopa	Levodopa		
AUC _{0-t} (n = 59)	1163.91	1268.52	0.92	0.86, 0.98

¹ Ratio of treatment LS means is E2007 plus levodopa:levodopa

E2007 PK:

Mean Ctrough values for E2007 were comparable between Day 19 (212.5 ± 104 ng/mL), Day 20 (216 ± 124 ng/mL) and Day 21 (224 ± 120 ng/mL at 12hr post-dose, 222 ± 114 ng/mL at 24 hr post-dose), suggesting steady-state was likely to have been reached prior to Day 21.

Figure 2. Mean (\pm SD) E2007 Plasma Concentration versus Time Profile**Safety Result**

There were no SAEs or withdrawals due to AEs during the study. Most AEs were mild in severity and brief in duration. The most common TEAEs were headaches, dizziness, fatigue, nausea, insomnia, epistaxis and somnolence (over 10% incidence in any treatment category). Seventeen (28.3%) subjects had TEAEs which were related (either possibly or probably related) to study drug treatment (levodopa) on Day 1, 40 (66.7%) subjects had related TEAEs when treated with E2007 alone, 25 (42.4%) subjects had related TEAEs when treated with E2007 plus levodopa.

Conclusion

Repeated doses of 4-mg E2007 did not alter levodopa PK.

Study E2007-J081-026: Phase I Ascending Repeated-Dose Study of E2007 in Japanese Healthy Adult Male Volunteers

Objective	<p><i>Primary objective:</i> To evaluate the safety, tolerability and pharmacokinetics of E2007 when administered orally at dosages of 2 and 4 mg once daily to Japanese healthy adult male volunteers</p> <p><i>Secondary objective:</i> To evaluate the pharmacodynamic effects of E2007 when administered orally at dosages of 2 and 4 mg once daily to Japanese healthy adult male volunteers</p>														
Study Design	<p>This was a repeated-dose, randomized, double-blind, placebo-controlled study.</p> <table border="1" data-bbox="495 577 1388 730"> <thead> <tr> <th>Step</th> <th>Dose</th> <th colspan="2">Dosage form and frequency of dosing/day (number of tablets)</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>2 mg</td> <td colspan="2" style="text-align: center;">Days 1-14 2 mg E2007 tab×1 or placebo tab×1</td> </tr> <tr> <td rowspan="2">2</td> <td rowspan="2">4 mg</td> <td style="text-align: center;">Days 1-14</td> <td style="text-align: center;">Days 15-28</td> </tr> <tr> <td>2 mg E2007 tab ×1 or placebo tab ×1</td> <td>2 mg E2007 tab ×2 or placebo tab ×2</td> </tr> </tbody> </table> <p>The test drugs were administered once daily at 30 minutes after the start of breakfast. On Days 1, 7 and 14 of Step 1 and Days 1, 14, 21 and 28 of Step 2, E2007 or placebo were administered after a 10-hour or longer fasting and the fasting was maintained until 4 hours after the administration.</p>	Step	Dose	Dosage form and frequency of dosing/day (number of tablets)		1	2 mg	Days 1-14 2 mg E2007 tab×1 or placebo tab×1		2	4 mg	Days 1-14	Days 15-28	2 mg E2007 tab ×1 or placebo tab ×1	2 mg E2007 tab ×2 or placebo tab ×2
Step	Dose	Dosage form and frequency of dosing/day (number of tablets)													
1	2 mg	Days 1-14 2 mg E2007 tab×1 or placebo tab×1													
2	4 mg	Days 1-14	Days 15-28												
		2 mg E2007 tab ×1 or placebo tab ×1	2 mg E2007 tab ×2 or placebo tab ×2												
Study Population	<p>12 subjects were randomized to Step 1 (9 on drug, 3 on placebo). Age: 23 – 37 yr, mean: 26.5 yr; Weight: 54 – 77.4 kg, mean: 65.9 kg</p> <p>12 subjects were enrolled for Step 2 (9 on drug, 3 on placebo). Age: 21 – 40 yr, mean: 27.5 yr; Weight: 53.2 – 71 kg, mean: 62.3 kg</p>														
PK & PD Measurements	<p><i>PK:</i></p> <p>Step 1: Blood samples were taken at the following time points Day 1: pre-dose and at 15, 30 and 45 min, 1, 1.5, 2, 3, 4, 6, 8, 12 hr post-dose Days 2, 4, 6: Pre-dose Day 7: Pre-dose and at 1, 2, 4, 8, and 12 hr after drug administration Days 8, 10, 12: Pre-dose Day 14: predose and at 15, 30 and 45 min, 1, 1.5, 2, 3, 4, 6, 8, 12 hr postdose Days 15, 16, 17, 19, 23, 28, 42: at 24, 48, 72, 120, 216, 336, and 672 hr post-dosing on Day 14</p> <p>Step 2: Blood samples were taken at the following time points Day 1: pre-dose and at 15, 30 and 45 min, 1, 1.5, 2, 3, 4, 6, 8, 12 hr post-dose Days 2, 4, 6, 8, 10, 12: pre-dose Day 14: predose and at 15, 30 and 45 min, 1, 1.5, 2, 3, 4, 6, 8, 12 hr postdose Days 15, 16, 18, 20: pre-dose Day 21: pre-dose and at 1, 2, 4, 8 and 12 hr post-dose Days 22, 24, 26: pre-dose Day 28: predose and at 15, 30 and 45 min, 1, 1.5, 2, 3, 4, 6, 8, 12 hr postdose Days 29, 30, 31, 33, 37, 42 and 56: at 24, 48, 72, 120, 216, 336, and 672 hr post-dosing on Day 28</p> <p><i>PD:</i> Saccadic Eye Movements (SEM) & Visual Analogue Mood Scale (VAMS)</p> <p>Step 1: Day 1: pre-dose [-1.5 hour] and at 1, 2, 4, 8 and 12 post-dose</p>														

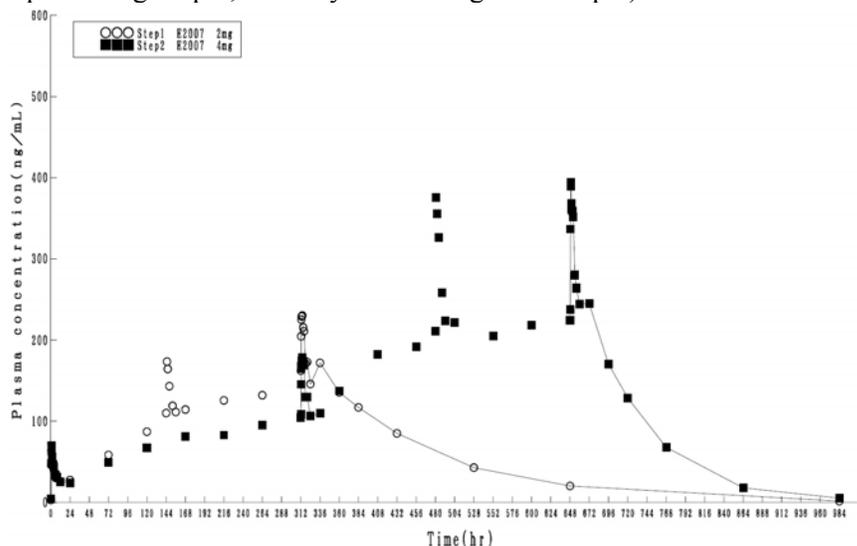
	Days 7 and 14: pre-dose [-1 hour] and at 1, 2, 4, 8 and 12 post-dose Step 2: Day 1: pre-dose [-1.5 hour] and at 1, 2, 4, 8 and 12 post-dose Days 14, 21 and 28: pre-dose [-1 hour] and at 1, 2, 4, 8 and 12 post-dose		
Bioanalytical Method	Analyze	E2007 (plasma)	
	Method	LC/MS-MS	
	Internal Std.	(b) (4)	
	LOQ (ng/mL)	0.25	
	Calibration Range (ng/mL)	0.25, 1, 3, 10, 30, 60, 120, 200	
	QC (ng/mL)	1, 30, 160	
	Accuracy	75 – 122.5%	
	Precision	3.6 - 14.3%	
PK & PD Assessments	<p><i>Pharmacokinetics:</i> Cmax, C_{ss,min}, C_{ss,avg}, T_{max}, AUC, λ_z, t_{1/2}, V_z/F, MRT, CL/F, Rac, PTF were determined using model independent methods.</p> <p><i>Pharmacodynamic:</i> Peak saccadic velocity (PSV) and percentage of failed saccades were determined for saccadic eye movements. Sub-scores for anxiety, sedation and dysphoria were calculated from the VAMS.</p>		
Safety Assessments	12-lead ECG, EEG, vital signs, laboratory safety tests, adverse events, Ophthalmological evaluation		
PK & PD Results	E2007		

E2007 PK

PK Profiles and Parameters

Plasma E2007 concentration reached C_{max} after 0.75 to 1.5 hrs (median) after the first dosing and multiple dosing, with a long terminal half-life after the final drug administration (mean t_{1/2}: 101.7 hrs and 63.9 hrs for 2 mg and 4 mg, respectively).

Figure 1. Geometric Mean Plasma E2007 concentration-time profiles (linear scale; open symbols representing Step 1; Close symbols designated Step 2)



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Figure 2. Arithmetic Mean (+SD) plasma E2007 concentration-time profiles on frequent blood sampling days (Left panel: Step1 E2007 2 mg, on days 1 and 14; Right panel; Step2 E2007 2 mg on day 1 and 4 mg on days 14 and 28)

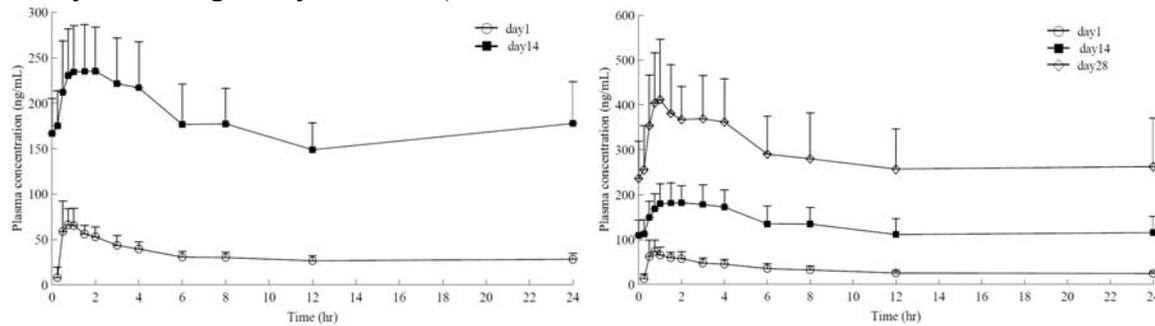


Table 1. Summary pharmacokinetic parameters of E2007 after the first dosing

Dose	2 mg		
Day	Day 1		
Step	Step 1	Step 2	2 mg Total
n	9	9	18
C_{max} (ng/mL)	73.2 ±22.7	80.3 ±23.3	76.7 ±22.6
t_{max} (hr)	0.75 0.50-2.00	0.75 0.50-1.50	0.75 0.50-2.00
AUC_{0-24} (ng-hr/mL)	757 ±155	761 ±164	759 ±155

Arithmetic mean ± standard deviation except for t_{max} . Median in the upper column and minimum-maximum in the lower column for t_{max} .

Table 2. Summary pharmacokinetic parameters of E2007 when repeated dosing

Dose	2 mg			4 mg
Day	Day 14			Day 28 ^{a)}
Step	Step 1	Step 2	2 mg Total	Step 2 ^{b)}
n	9	9	18	9
$C_{ss,max}$ (ng/mL)	254.6 ±53.6	194.2 ±40.1	224.4 ±55.4	433.0 ±126.6
$t_{max,ss}$ (hr)	1.00 0.75-3.00	1.50 0.75-3.00	1.00 0.75-3.00	1.00 0.75-3.00
$AUC_{0-\tau,ss}$ (ng-hr/mL)	4234 ±930	3104 ±857	3669 ±1044	6845 ±2294
$C_{ss,min}$ (ng/mL)	148.5 ±29.9	102.7 ±32.7	125.6 ±38.5	228.8 ±86.9
$C_{ss,av}$ (ng/mL)	176.4 ±38.7	129.3 ±35.7	152.9 ±43.5	285.2 ±95.6
PTF (%)	60.1 ±7.2	74.4 ±18.9	67.3 ±15.7	74.3 ±15.2
$t_{1/2,ss}$ (hr)	101.7 ±22.2	- ^{c)}	- ^{c)}	63.9 ±30.0
Cl_{ss}/F (mL/hr)	496.0 ±123.9	693.0 ±204.6	594.5 ±192.9	635.4 ±180.6
$R_{ac}(C_{max})$	3.59 ±0.59	2.52 ±0.51	3.05 ±0.77	- ^{d)}
$R_{ac}(AUC)$	5.68 ±1.26	4.18 ±1.18	4.93 ±1.42	- ^{d)}

Arithmetic mean ± standard deviation except for t_{max} . Median in the upper column and minimum-maximum in the lower column for t_{max} .

$PTF(\%) = (C_{ss,max} - C_{ss,min}) / C_{ss,av} \times 100$, $R_{ac}(C_{max}) = C_{ss,max} / C_{max}$, $R_{ac}(AUC) = AUC_{0-\tau,ss} / AUC_{0-24}$

- a) 14 days after ascending to 4 mg
 b) Once daily oral administration of E2007 2 mg for 14 days followed by once daily oral administration of E2007 4 mg for 14 days
 c) Not determined because 4 mg was administered on Day 15 or later in Step 2.
 d) Not determined because C_{max} and AUC_{0-24} were not obtained after the first administration of 4 mg.

Time to reach steady state

As shown in Figure 1, concentrations of E2007 approached steady-state after 2-week once-daily dosing. In Step 1, mean trough (pre-dose) concentrations on days 12 and 14 were 135.3 ng/mL and 166.8 ng/mL, respectively. The mean concentration of E2007 at 24 hours after drug administration on day 14 were 177.6 ng/mL. In Step 2, mean E2007 concentrations before drug administration on day 12, and before and after administration on day 14 of 2 mg E2007 treatment were 99.7 ng/mL, 109.5 ng/mL and 115.6 ng/mL, respectively. In Step 2, after the dose was increased to 4 mg, mean E2007 concentrations were similar before and 24 hours after drug administration on Days 26 and 28 (230.1 ng/mL, 236.6 ng/mL and 261.9 ng/mL, respectively).

Accumulation after multiple dosing

The AUC_{0-24hr} values after 14-day treatment with 2 mg E2007 were 5.68 times and 4.18 times as high as the AUC₀₋₂₄ values following the first dose, respectively, in Steps 1 and 2. The accumulation ratio for C_{max} after E2007 administered at a dosage of 2 mg once daily for 14 days was 3.59 and 2.52, respectively, in Steps 1 and 2 (Table 2).

Fluctuation Index

The FI% value, calculated as $(C_{max,ss} - C_{min,ss}) / C_{avg} \times 100\%$, was 67% and 74%, for 2 mg and 4 mg doses, respectively.

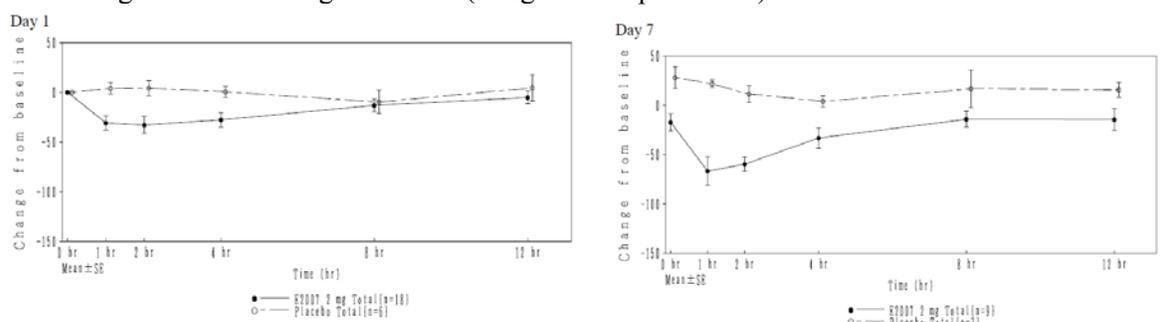
Dose Proportionality

The C_{max} and AUC_{0-24hr} values on Day 28 were approximately 2.2 times of those on Day 14, indicating dose-proportional increase of E2007 exposure between 2 mg and 4 mg.

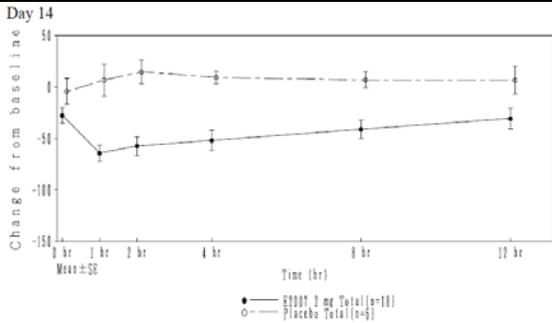
Pharmacodynamics:

Peak Saccadic Velocity (PSV): Sedative effect measured as change in PSV from baseline increased over time after treatment with E2007 starting at a dose of 2 mg (Figure 3). It seemed that the effects were similar between Day 7 and Day 14. When the dose was increased to 4 mg, the sedative effects were further augmented (Figure 4). The effects were similar between Day 21 and Day 28 (i.e., Day 7 and Day 14 for 4-mg dosing).

Figure 3. Changes over time in Δ PSV (changes from pre-treatment baseline (Day 1: 0 hr)) with a unit of degrees/sec for 2 mg dose level (Integrated Steps 1 and 2)

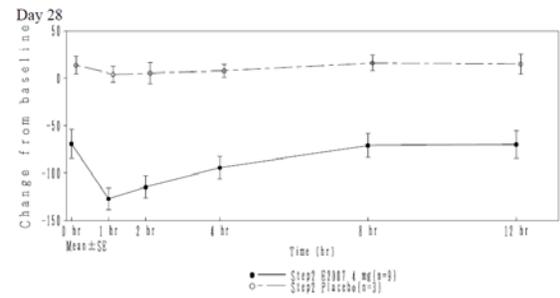
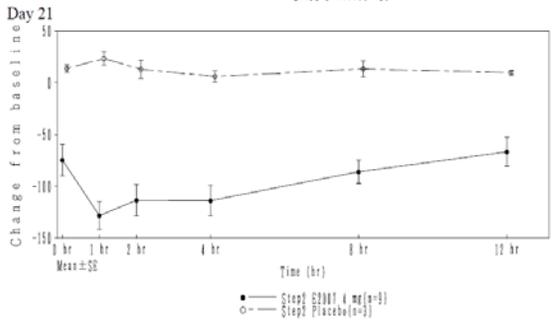
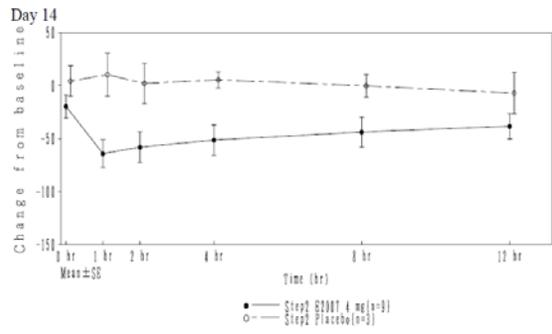
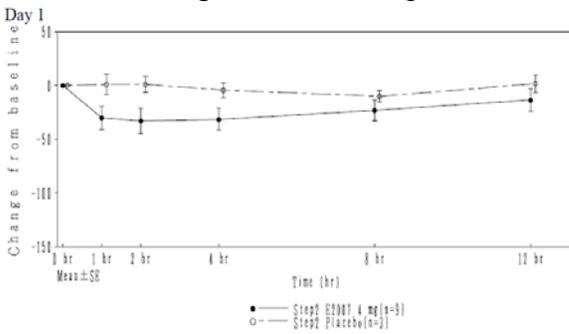


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Note: Data for Day 7 are based on the measurements only from the 12 subjects participating in Step 1, because PSV was not determined in Step 2.

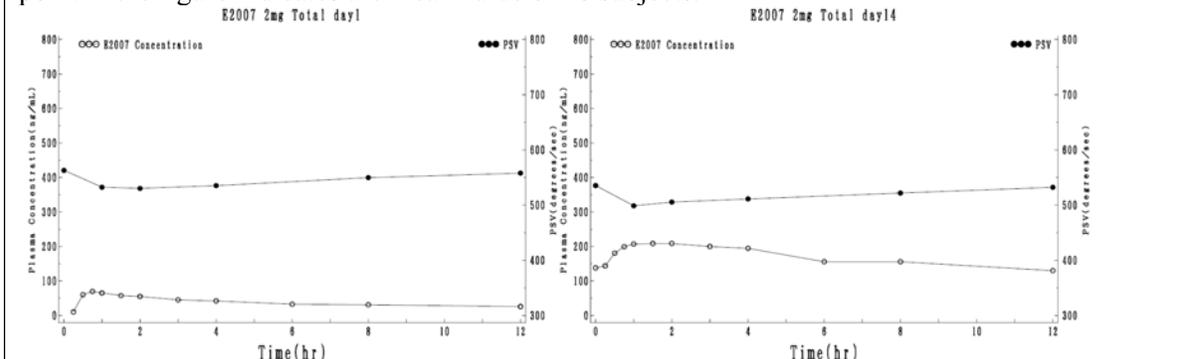
Figure 4. Changes over time in Δ PSV (changes from pre-treatment baseline (Day 1: 0 hr)) with a unit of degrees/sec for Step 2



In the 4 mg group, E2007 was administered as 2 mg q.d. for 14 days and thereafter 4 mg q.d. for 14 days.

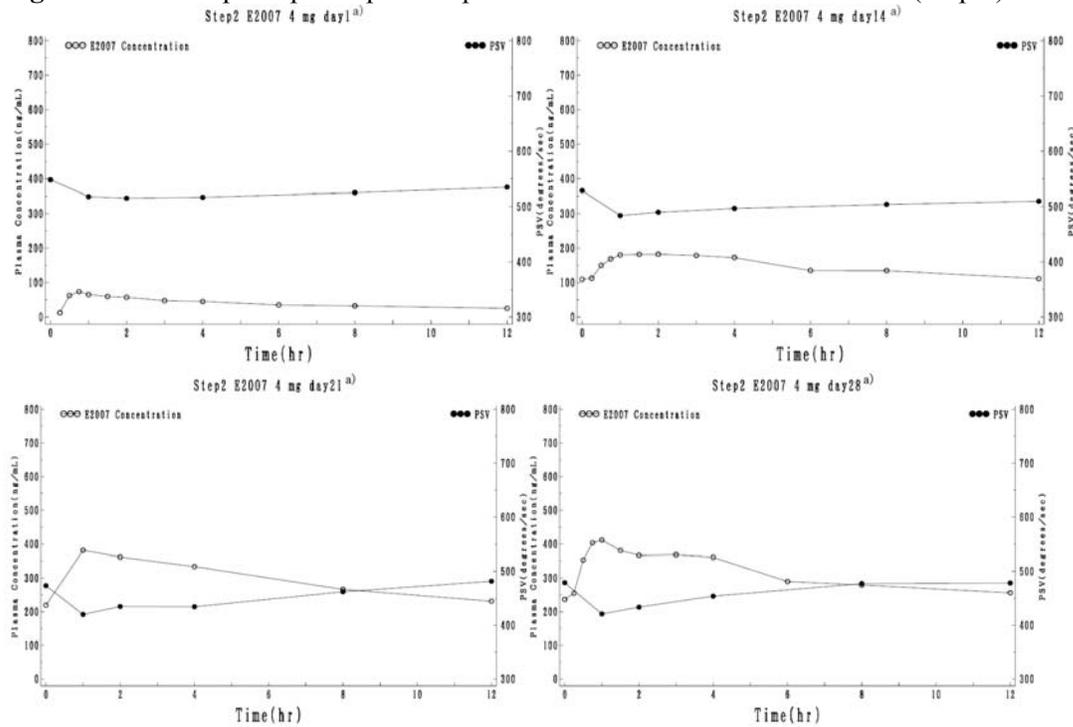
A correlation between E2007 concentrations and PSV was observed for both Steps 1 and 2.

Figure 5. Mean superimposed plots of plasma E2007 concentration and PSV (2 mg Total). Each point in the figure indicates the mean value of 18 subjects.



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Figure 6. Mean superimposed plots of plasma E2007 concentration and PSV (Step 2)

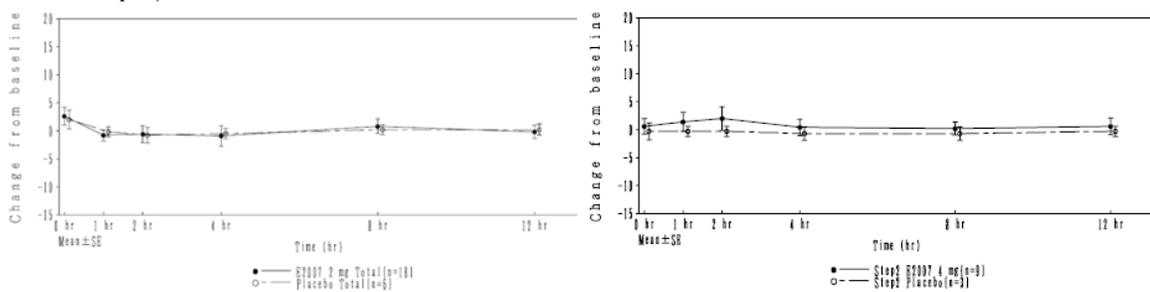


In the 4 mg group, E2007 was administered as 2 mg q.d. for 14 days and thereafter 4 mg q.d. for 14 days.

Bond and Lader Sedation Sub-score:

On the final evaluation day (Day 14) of Integrated Steps 1 and 2, Δ VAMS-sedation sub-score was generally same in 2 mg and placebo treated groups. On the final evaluation day (Day 28) of Step 2, Δ VAMS-sedation sub-score was higher in the 4 mg group, as compared with the placebo group, but the difference was small.

Figure 7. Intraday changes in Δ VAMS- sedation sub-score (changes from pre-treatment baseline (Day 1: 0 hr)) (mm) (Left panel: 2 mg, Day 14 of Integrated Steps 1 and 2; Right Panel: 4 mg, Day 28 for Step 2)



Safety Results

All the AEs were mild or moderate in severity. The frequently observed AEs were somnolence and dizziness. In the group titrated from 2 mg to 4 mg, the frequency increased according to the increased doses. All of these events were mild and recovered with no medical treatment.

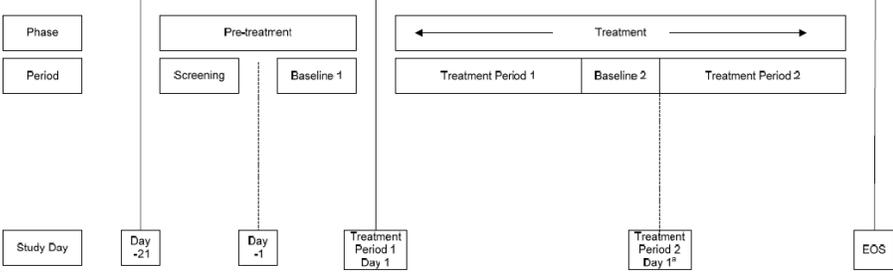
Conclusions

- E2007 was rapidly absorbed with (median) T_{max} of 0.75 to 1.5 hours. Mean terminal $t_{1/2}$ after the final drug administration was long shown as 101.7 hours and 63.9 hours for 2 mg and 4 mg, respectively.

	<ul style="list-style-type: none">• Steady state of E2007 plasma concentrations was approached by day 14 of once-daily dosing. Accumulation ratio for AUC_{0-24hr} and C_{max} after 2-week daily dosing was 4.93 and 3.05, respectively. Fluctuation index (FI%) after 14-day dosing was 67% and 74%, for 2 mg and 4 mg, respectively.• Repeated doses of 2 mg or 4 mg E2007 did not show any notable change in VAMS scores including sedation sub-score (a qualitative measure of the sedative effect of the drug). Decreased PSV (a quantitative measure of the sedative effect of the drug) with dose escalation from 2 mg to 4 mg was shown and the sedative effect was persistently shown from the 7th day of multiple dosing. In addition, changes in PSV over time were correlated with E2007 plasma concentrations.
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Study E2007-E044-029: An Open-label Study to Investigate the Potential Pharmacokinetic Interaction of Perampanel with Oral Contraceptives in Healthy Female Subjects

Objective	<p><i>Primary objectives:</i> (Part A) To investigate the effect of steady state perampanel on the PK of a single-dose oral contraceptive (OC) containing ethinylestradiol (EE) and levonorgestrel (LN) (Microgynon® 30) (part B) To investigate the effect of repeated dosing of an OC containing EE and LN (Microgynon 30) on the PK of a single dose of perampanel. <i>Secondary objective:</i> To investigate the effect of steady state perampanel on QT interval duration relative to pre-dose baseline.</p>
Study Design	<p>This was an open-label, non-randomized, fixed sequence study in healthy female subjects. The study had two parts (A and B), both of which had two phases: pre-treatment and treatment. The Pretreatment Phases comprised screening and baseline period 1. The Treatment Phases comprised: treatment Period 1, baseline period 2, and treatment Period 2.</p>  <p>The diagram illustrates the study timeline. It is divided into three main phases: Pre-treatment, Treatment, and End of Study (EOS). The Pre-treatment phase includes a Screening period (Day -21) and Baseline 1 (Day -1). The Treatment phase is divided into Treatment Period 1 (Day 1), Baseline 2, and Treatment Period 2 (Day 1^a). The timeline starts at Study Day and ends at EOS.</p> <p><small>EOS=end of study. ^a Follows a minimum 7-day washout after dosing in Treatment Period 1.</small></p> <p>Part A Subjects received a single dose of OC (Microgynon 30: containing 30 µg EE and 150 µg LN) on the morning of Treatment Period 1, Day 1. Following a post-dosing washout of at least 7 days, subjects proceeded to Baseline Period 2 when subjects reported to the study unit on the day before dosing (Day -1) for Treatment Period 2. Subjects began receiving perampanel orally in the evening of Treatment Period 2, Day 1. Perampanel doses were up-titrated via weekly 4-mg increments to a maximum of 12 mg/day for total treatment duration of at least 35 days (4 mg x 7 days, followed by 8 mg x 7 days and finally 12 mg x 21 days, once daily). On the last day of perampanel treatment (Day 35), subjects received a single oral dose of the OC.</p> <p><i>Note:</i> Subjects who did not tolerate 12 mg/day were allowed to revert to 8 mg/day and were then to remain on 8 mg/day for an additional week. After this additional week, subjects could remain at 8 mg or up-titrate to 12 mg/day. Later on, it was decided that any subject that did not tolerate 12 mg/day would remain on 8 mg/day for the rest of the study and would not up-titrate to 12 mg/day.</p> <p>Part B Subjects received a single 6 mg dose of perampanel on the morning of Treatment Period 1, Day 1 after an overnight fast. Following a post-dosing</p>

	washout of at least 7 days, subjects proceeded to Baseline Period 2 when subjects reported to the study unit on the day before dosing (Day -1) for Treatment Period 2. Subjects began receiving the OC (Microgynon 30) on the morning of Treatment Period 2, Day 1. OC was administered for 21 consecutive days. On Day 21 subjects also received a single 6 mg dose of perampanel following an overnight fast.																																		
Study Population	<p>Part A: 28 subjects were enrolled (Age: 21 – 43 yr, mean 30.6 yr; Weight: 51 – 95 yr, mean: 63.7 yr; Race: White (68%)). 10 subjects were titrated to and remained on 12 mg, with 2 of them withdrawn due to protocol violation and withdrawn consent. 14 subjects were down titrated to 8 mg, among whom 2 subjects were discontinued due to AEs. Eventually, 20 subjects completed the study.</p> <p>Part B: 24 subjects were enrolled and completed the study. Age: 20 – 42yr, mean 27.4 yr; Weight: 56.6 – 85.5 yr, mean: 67.5 yr; Race: White (80%)</p>																																		
Dosage and Administration	<p>Part A: All doses of perampanel were administered in the evening with a standard evening meal. It was acceptable to administer perampanel within 30 minutes of the end of an evening snack. Microgynon 30 was administered in the morning as directed by the instructions on the label.</p> <p>Part B: Perampanel was administered in the morning, following an overnight fast. Microgynon 30 was administered once-daily as directed by the instructions on the label.</p>																																		
PK Sampling	<p>Part A <i>EE and LN:</i> blood samples for PK analysis were collected at pre-dose and 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 hours post-dose on Treatment Period 1 Day 1 and Treatment Period 2 Day 35. <i>Perampanel:</i> blood samples to confirm steady state were collected pre-dose on Treatment Period 2, Days 33, 34, and 35.</p> <p>Part B <i>Perampanel:</i> blood samples for PK analysis were collected at pre-dose and 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 48, and 72 hours post-dose on Treatment Period 1 Day 1 and Treatment Period 2 Day 21 <i>EE and LN:</i> pre-dose on Days 19, 20, and 21 of Treatment Period 2</p>																																		
Bioanalytical Method	<table border="1"> <tr> <td>Analyze</td> <td>Ethinylestradiol</td> <td>Levonorgestrel</td> </tr> <tr> <td>Method</td> <td>LC-MS/MS</td> <td>LC-MS/MS</td> </tr> <tr> <td>Internal Std.</td> <td>Ethinylestradiol-d4</td> <td>Levonorgestrel-d6</td> </tr> <tr> <td>LOQ (ng/mL)</td> <td>0.01</td> <td>0.1</td> </tr> <tr> <td>Calibration Range (ng/mL)</td> <td>0.01, 0.02, 0.05, 0.1, 0.5, 1.0, 1.7, 2</td> <td>0.1, 0.2, 0.5, 1, 5, 10, 17, 20</td> </tr> <tr> <td>QC (ng/mL)</td> <td>0.025, 0.3, 1.5</td> <td>0.25, 3, 15</td> </tr> <tr> <td>Accuracy</td> <td>93.3 – 97.6%</td> <td>95.6 – 98.7%</td> </tr> <tr> <td>Precision</td> <td>8.3 – 11.4%</td> <td>7.6 – 10.5%</td> </tr> </table> <table border="1"> <tr> <td>Analyze</td> <td>E2007</td> </tr> <tr> <td>Method</td> <td>LC/MS-MS</td> </tr> <tr> <td>Internal Std.</td> <td>Perampanel-d5</td> </tr> <tr> <td>LOQ (ng/mL)</td> <td>1</td> </tr> </table>			Analyze	Ethinylestradiol	Levonorgestrel	Method	LC-MS/MS	LC-MS/MS	Internal Std.	Ethinylestradiol-d4	Levonorgestrel-d6	LOQ (ng/mL)	0.01	0.1	Calibration Range (ng/mL)	0.01, 0.02, 0.05, 0.1, 0.5, 1.0, 1.7, 2	0.1, 0.2, 0.5, 1, 5, 10, 17, 20	QC (ng/mL)	0.025, 0.3, 1.5	0.25, 3, 15	Accuracy	93.3 – 97.6%	95.6 – 98.7%	Precision	8.3 – 11.4%	7.6 – 10.5%	Analyze	E2007	Method	LC/MS-MS	Internal Std.	Perampanel-d5	LOQ (ng/mL)	1
Analyze	Ethinylestradiol	Levonorgestrel																																	
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		Calibration Range (ng/mL)	1, 2, 8.4, 20, 80 140, 210, 250
		QC (ng/mL)	3, 80, 200
		Accuracy	98 – 101.5%
		Precision	8.8 – 10.1%
PK Assessments	Part A - EE and LN: Cmax, Tmax, AUC0-24, AUC0-inf; Perampanel: Ctrough Part B – Perampanel: Cmax, Tmax, AUC0-72, AUC0-inf EE and LN: Ctrough		
Safety Assessment	Physical examination, 12-lead ECG, vital signs, laboratory tests and AEs		
PK Results	Perampanel – Ethinylestradiol / Levonorgestrel Interaction		

Part A
OC PK

- The 8 mg dose of perampanel had no significant effect on EE and on LN PK, with a small reduction of LN AUC0-24hr and AUC0-inf by 9% and 12%, respectively.
- In contrast, the 12 mg dose of perampanel reduced AUC0-24 and Cmax of LN by 40 and 42%, respectively. Perampanel did not affect t1/2 and Tmax of LN.
- At 12-mg dose level, perampanel also decreased Cmax of EE by 18%, but did not have effect on AUC0-24hr of EE.

Figure 1. Mean (\pm SD) Plasma Concentration-Time Curve of Ethinylestradiol (EE) - Linear Scale

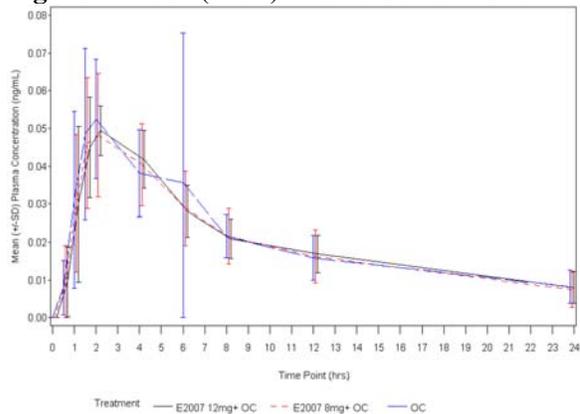


Figure 2. Mean (\pm SD) Plasma Concentration-Time Curve of Levonorgestrel (LN) – Linear Scale

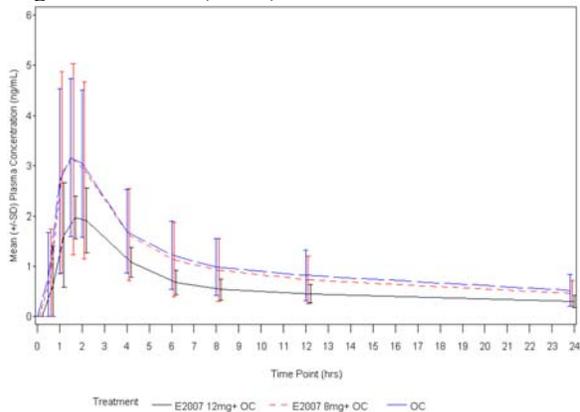


Table 1. Summary of Pharmacokinetic Parameters for Ethinylestradiol (EE)

Pharmacokinetic Parameter	OC alone (N = 28)	Perampanel + OC	
		Perampanel 8 mg (N = 12)	Perampanel 12 mg (N = 8)
AUC ₍₀₋₂₄₎ (ng•h/mL)	0.458 (29.7)	0.439 (34.7)	0.472 (21.4)
C _{max} (ng/mL)	0.060 (38.7)	0.052 (26.7)	0.051 (17.6)
t _{max} (h)	2.00 (1.0-6.3)	2.00 (1.0-4.1)	2.00 (1.0-4.0)

Geometric means (% CV) except median (min-max) for t_{max}.

Table 2. Effect of Steady-State Perampanel (E2007) on the PK of Levonorgestrel

Levonorgestrel PK Parameters	E2007 8 mg group			E2007 12 mg group		
	OC alone	+ E2007	Geomean Ratio	OC alone	+ E2007	Geomean Ratio
n	12	12	12	8	8	8
C _{max} (ng/mL)	3.65 ± 1.78	3.43 ± 1.78	0.949 (0.846-1.064)	4.01 ± 1.35	2.29 ± 0.72	0.570 (0.492-0.660)
T _{max} (hours)	1.5 (1.0-4.0)	1.5 (1.0-2.0)		1.75 (1.0-2.0)	1.5 (1.0-2.0)	
AUC _{0-24hr} (ng/mL x hr)	25.47 ± 13.74	23.36 ± 13.54	0.910 (0.824, 1.005)	26.63 ± 14.02	14.87 ± 4.68	0.592 (0.520, 0.674)
AUC _{0-inf} (ng/mL x hr)	40.04 ± 21.31	34.06 ± 17.42	0.876 (0.777, 0.986)	43.50 ± 25.99	23.76 ± 8.21	0.588 (0.498, 0.693)
t _{1/2} (hours)	17.8 ± 4.3	17.3 ± 4.6	0.90 (0.54,2.05)*	20.3 ± 6.0	20.6 ± 8.5	1.05 (0.43,1.55)*
AUC Extrapolate (%)	35.0 ± 8.6	32.7 ± 5.9		36.9 ± 8.7	36.0 ± 1.2	

* Ratio of t_{1/2} was expressed as median (min – max) of individual ratios of t_{1/2},OC+E2007 / t_{1/2}, OC alone

Table 3. Statistical Evaluation of the Effect of a Steady-State Perampanel the PK of a Single Dose of an Ethinylestradiol- and Levonorgestrel-Containing OC

OC Drug PK Parameter	Treatment Contrast (Test: Reference)	n		Geometric LS Means		Geometric LS Means Ratio (%) [90% CI]
		Test	Reference	Test	Reference	
Ethinylestradiol						
C _{max} (ng/mL)	12 mg perampanel + OC: OC	8	28	0.049	0.060	82.3 [72.6, 93.2]
AUC _(0-24h) (ng•h/mL)	12 mg perampanel + OC: OC	8	28	0.482	0.458	105 [96.7, 114]
C _{max} (ng/mL)	8 mg perampanel + OC: OC	12	28	0.056	0.060	94.2 [85, 105]
AUC _(0-24h) (ng•h/mL)	8 mg perampanel + OC: OC	12	28	0.455	0.458	99.2 [92.6, 106]
Levonorgestrel						
C _{max} (ng/mL)	12 mg perampanel + OC: OC	8	28	1.95	3.35	58.2 [50.2, 67.4]
AUC _(0-24h) (ng•h/mL)	12 mg perampanel + OC: OC	8	28	13.2	22.1	59.7 [52.4, 68.0]
C _{max} (ng/mL)	8 mg perampanel + OC: OC	12	28	3.17	3.36	94.5 [83.7, 107]
AUC _(0-24h) (ng•h/mL)	8 mg perampanel + OC: OC	12	28	20.1	22.1	91.1 [81.9, 101]

Perampanel PK

The trough levels of perampanel were similar in the time interval from Day 33 to Day 35.

Table 4. Trough Levels of Perampanel at Steady-State

Trough Level	Dose perampanel	Perampanel		
		Day 33	Day 34	Day 35
Concentration (ng/mL)	8 mg (N = 12)	715 ± 281	789 ± 265	762 ± 351
Concentration (ng/mL)	12 mg (N = 8)	775 ± 435	855 ± 411	821 ± 446

Reviewer's Comment: The exact mechanism of perampanel at 12 mg dose level reducing LN AUC and Cmax remains unclear. Per the labeling of LoSeasonique®, following absorption, levonorgestrel is conjugated at the 17β-OH position to form sulfate conjugates and, to a lesser extent, glucuronide conjugates in plasma. Levonorgestrel and its Phase I metabolites are excreted primarily as glucuronide conjugates. *In vitro* enzyme induction study conducted in human hepatocytes (study XT093050) showed that perampanel at concentrations of 3 μM and above induced mRNA expression of UGT1A1. Perampanel also increased mRNA of UGT1A4, though the induction extent seemed to be less than the effect of perampanel on UGT1A1.

Per the labeling of LoSeasonique®, ethinylestradiol is partially metabolized by CYP3A4. First-pass metabolism of ethinylestradiol involves formation of ethinylestradiol-3-sulfate in the gut wall, followed by 2-hydroxylation of a portion of the remaining untransformed ethinylestradiol by hepatic CYP3A4. Drugs or herbal products that induce CYP3A4 can decrease the plasma concentrations of ethinylestradiol, such as carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifampin and topiramate etc. In the current study, perampanel at 12 mg dose level did not affect AUC0-24hr of EE while decreasing Cmax of EE by 18%, indicating that perampanel is likely to be a weak CYP3A4 inducer.

Part B.

Perampanel PK:

Steady-state OC did not significantly affect Cmax, AUC0-72hr and Tmax of single-dose perampanel.

Figure 3. Mean (± SD) Plasma Concentration-Time Curve of Perampanel – Linear Scale

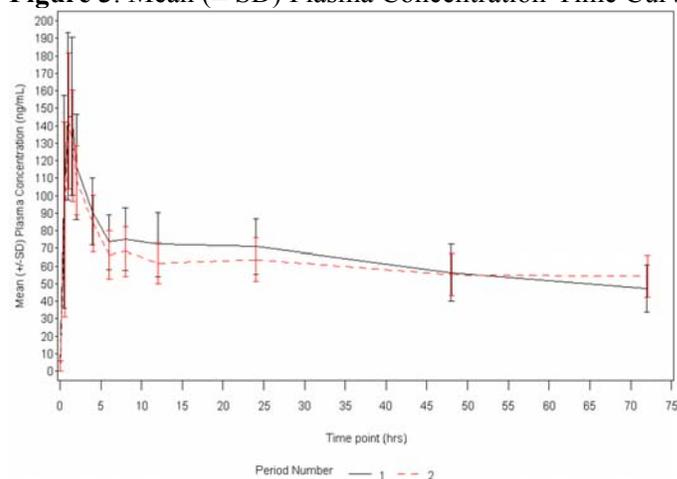


Table 5. Effect of Steady-State OC Administration on the PK of Perampanel 6 mg

Pharmacokinetic Parameter	Perampanel 6 mg (N = 24)	Perampanel 6 mg + OC (N = 23 ^a)
AUC _(0-72h) (ng•h/mL)	4546 (22.7)	4302 (17.8)
C _{max} (ng/mL)	160 (29.6)	146 (25.4)
t _{max} (h)	1.28 (1.20)	1.05 (1.00)

Geometric means (% CV) except mean (median) for t_{max}.

a: One subject was excluded as the predose perampanel concentration in Treatment Period 2 was beyond 5% of C_{max}

PK Parameter	Treatment Contrast (Test: Reference)	n		Geometric LS Means		Geometric LS Means Ratio (%) [90% CI]
		Test ^a	Reference	Test	Reference	
C _{max} (ng/mL)	Perampanel + OC: Perampanel	23 ^a	24	147	160	91.9 [82.5, 102]
AUC _(0-72h) (ng•h/mL)	Perampanel + OC: Perampanel	23 ^a	24	4380	4546	96.4 [92, 101]

OC PK:

The trough levels of EE or LN were similar in the time interval from Day 19 to Day 21.

Table 6. Trough Levels of Ethinylestradiol (EE) Following Multiple Dosing of OC to Steady-state

Trough Level	Perampanel dose	Trough levels (ng/mL)		
		Day 19	Day 20	Day 21
Ethinylestradiol (EE) Concentration (ng/mL)	E2007 6 mg + OC	0.022 ± 0.0059	0.021 ± 0.0059	0.020 ± 0.0056

Table 7. Trough Levels of Levonorgestrel (LN) Following Multiple Dosing of OC to Steady-state

Trough Level	Perampanel dose	Trough levels (ng/mL) (n=24)		
		Day 19	Day 20	Day 21
Levonorgestrel (LN) Concentration (ng/mL)	E2007 6 mg + OC	2.81 ± 0.970	2.74 ± 1.009	2.74 ± 0.987

Safety Result

Part A

In Treatment Period 2, the incidence of TEAEs increased as the dose of perampanel was up titrated from 4 mg to 8 mg (from 66.7% to 92.3%). Daily doses of 4 mg perampanel were relatively well tolerated; 1 subject was withdrawn due to TEAEs (abdominal pain and rash pruritic). 26 subjects were up titrated to 8 mg perampanel; 1 subject was withdrawn due to elevated liver enzymes and 1 subject withdrawn due to TEAEs (memory impairment). For the 24 subjects who were up titrated to 12 mg (for at least 1 dose) the incidence of TEAEs was 92%. The 12-mg dose was tolerated poorly with only 8 (33.3%) of the subjects remaining at this dose for the full 21 days. 14 subjects (58.3%) were down titrated to 8 mg perampanel; 12 subjects completed the treatment and 2 were withdrawn due to TEAEs (mood swings and feeling drunk).

Dizziness, lethargy, headache, and feeling drunk were the most frequently reported TEAEs (≥ 50% of subjects). Other common AEs (≥ 20% of subjects) among subjects receiving perampanel were somnolence, memory impairment, feeling hot, disturbance in attention, dysarthria, nausea, and abdominal pain. Five subjects receiving perampanel reported falls; the

	<p>incidence of fall was greatest in subjects receiving 12 mg perampanel (16.7%).</p> <p>Part B</p> <p>In Treatment Period 1, a total of 45.8% of subjects reported at least one TEAE following treatment with a single dose of 6 mg perampanel. The most frequently reported TEAEs ($\geq 8\%$ of subjects) were dizziness, somnolence, headache, and constipation. In Treatment Period 2 (daily doses of Microgynon 30) 45.8% of subjects reported TEAEs over the 21-day period; the most frequently reported TEAEs ($\geq 8\%$ of subjects) were constipation and headache. Following treatment with a 6 mg dose of perampanel at OC steady-state, the incidence of TEAEs was 33.3%. The most frequently reported AEs ($\geq 8\%$ of subjects) following combined OC and perampanel administration were headache, dizziness, and nausea.</p>
<p>Conclusions</p>	<ul style="list-style-type: none"> • Perampanel 12 mg at steady-state decreased the C_{max} and AUC₀₋₂₄ of LN by 42% and 40%, respectively. Perampanel 8 mg at steady-state had no significant effect on PK of LN, with small decrease of 9% and 12% in LN AUC_{0-24hr} and AUC_{0-inf}, respectively. • Perampanel 12 mg at steady-state decreased C_{max} of EE by 18%, but did not affect AUC₀₋₂₄ of EE. Perampanel 8 mg did not have an effect on PK of EE. • After 3-week consecutive administration of oral contraceptives (ethinylestradiol and levonorgestrel), PK of a single dose of perampanel 6 mg administered on Day 21 was not affected. • Due to significant reduction of levonorgestral plasma concentrations with co-administration of 12 mg perampanel, effectiveness of oral or implant contraceptives containing levonorgestrel may be impaired, and thus non-hormonal contraceptive method should be used.

Study E2007-A001-037: A Randomized, Open-label, Crossover Study to Demonstrate Bioequivalence Between 6 × 2-mg Tablets of Perampanel and a Single 12-mg Tablet of Perampanel in Healthy Subjects

Objective	<p><i>Primary objective:</i> To demonstrate bioequivalence between 6 × 2-mg tablets of perampanel and a single 12-mg tablet of perampanel.</p> <p><i>Secondary objective:</i> To evaluate and compare the PK profile, safety, and tolerability of 6 × 2-mg tablets of perampanel with a single 12-mg tablet.</p>			
Study Design	<p>This was a single center, open-label, 2-period, 2-sequence crossover BE study. Subjects were randomized to one of two treatment sequences (AB or BA) in a 1:1 ratio to receive a single 12-mg dose of perampanel as either 6 × 2-mg tablets (Formulation C, reference) or as a single 12-mg tablet (Formulation D, test) on Day 1 of Treatment Period 1, and then received the alternative treatment on Day 1 of Treatment Period 2. The two periods were separated by a 6-week washout. Study drug was administered after an overnight fast.</p>			
Study Population	<p>28 subjects received at least one treatment. A total of 22 subjects received both treatments. Six subjects withdrew after Treatment Period 1 (3 subjects from each treatment). Therefore, 25 subjects were dosed with 6 × 2-mg tablets, and 25 were dosed with the 12-mg tablet.</p> <p>Age: 21-54 yr, mean 41 yr; Weight: 59-94 kg, mean, 77.5 kg; Gender: Male (75%); Race: Most White (96%)</p>			
PK Sampling	<p>Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 120, 168 hours post-dose, and at Visit 8 (Day 29 +3).</p>			
Bioanalytical Method	Analyze Method	Internal Std.	(b) (4)	
	LOQ (ng/mL)	Calibration Range (ng/mL)		
	QC (ng/mL)	Accuracy		
	Precision			
PK Assessments	<p>Plasma concentrations of perampanel were analyzed by non-compartmental methods to determine the following PK parameters: C_{max}, AUC_{0-t}, AUC_{0-inf}, T_{max}, t_{lag}, and t_{1/2}</p> <p>C_{max}, AUC_{0-t} and AUC_{0-inf} of perampanel were compared between the 6 × 2-mg tablets (reference) and the 12-mg tablet (test) using a linear mixed effects model (with log-transformed PK parameter values as response). The model included terms for treatment, sequence, and period as fixed effects and subject nested within sequence as a random effect.</p>			
Safety Assessment	Physical examination, ECG, vital signs, laboratory safety tests and AEs			
PK Results	Perampanel			
<p>Perampanel PK</p> <p>The study failed to demonstrate BE between 12-mg tablet (Formulation D) and 6 x 2-mg tablets (Formulation C), sine the lower bound of 90% CI for geometric mean ratio of C_{max} slightly exceeded the pre-specified criterion (78.4% < 80%). Formulation D was bioequivalent to Formulation C in terms AUC_{0-t} and AUC_{0-inf}.</p>				



Safety Result	The most frequently reported treatment-emergent AEs (TEAEs) comprised nervous system disorders (21 subjects), general disorders and administration site conditions (14 subjects), and gastrointestinal disorders (9 subjects). The majority of TEAEs were possibly or probably related to study drug. The incidence of treatment related TEAEs was similar after dosing with the 12-
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	mg perampanel tablet and 6 × 2-mg perampanel tablets (20 subjects vs. 19 subjects, respectively). Six TEAEs were moderate in intensity (two instances each of headache and feeling drunk, and one instance each of decreased appetite and upper abdominal pain); these were all reported by subjects after dosing with 6 × 2-mg perampanel tablets. The remaining AEs were mild in severity.
Conclusion	Although AUC _{0-t} and AUC _{0-inf} satisfied the bioequivalence criteria, C _{max} slightly deviated from the criteria. Therefore, the bioequivalence of the 12-mg tablet (Formulation D) and 6 × 2-mg tablets (Formulation C) could not be concluded from this study.

Study E2007-A001-039: A Randomized, Open-label, Crossover Study to Demonstrate Bioequivalence Between 3 × 2-mg Tablets of Perampanel and a Single 6-mg Tablet of Perampanel in Healthy Subjects

Objective	<p><i>Primary objective:</i> To demonstrate bioequivalence between 3 × 2-mg tablets of perampanel and a single 6-mg tablet of perampanel.</p> <p><i>Secondary objective:</i> To evaluate and compare the PK profile, safety, and tolerability of 3 × 2-mg tablets of perampanel with a single 6-mg tablet.</p>		
Study Design	<p>This was a single center, open-label, 2-period, 2-sequence crossover BE study. Subjects were randomized to one of two treatment sequences (AB or BA) in a 1:1 ratio to receive a single 6-mg dose of perampanel as either 3 × 2-mg tablets (Formulation C, reference) or as a single 6-mg tablet (Formulation D, test) on Day 1 of Treatment Period 1, and then received the alternative treatment on Day 1 of Treatment Period 2. Study drug was administered after an overnight fast. The two treatment periods were separated by 6-week washout.</p>		
Study Population	<p>54 subjects were enrolled. 52 subjects received the 6-mg tablet and 51 subjects received 3 × 2-mg tablets.</p> <p>Age: 18-55 yr, mean 28 yr; Weight: 47-105 kg, mean, 77.4 kg; Gender: Male (63%); Race: Majority White (72%)</p>		
PK Sampling	<p>Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 120, 168 hours post-dose.</p>		
Bioanalytical Method	Analyze	Perampanel	
	Method	LC/MS-MS	
	Internal Std.	(b) (4)	
	LOQ (ng/mL)	1	
	Calibration Range (ng/mL)	1, 2, 5, 20, 100 200, 400, 500	
	QC (ng/mL)	3, 50, 380	
	Accuracy	95.8 – 98.3%	
	Precision	4.8 – 7.8%	
PK Assessments	<p>Plasma concentrations of perampanel were analyzed by non-compartmental methods to determine the following PK parameters: C_{max}, AUC_{0–t}, AUC_{0–inf}, T_{max}, t_{lag}, and t_{1/2}.</p> <p>C_{max}, AUC_{0–t} and AUC_{0–inf} of perampanel were compared between the 3 × 2-mg tablets (reference) and the 6-mg tablet (test) using a linear mixed effects model (with log-transformed PK parameter values as response). The model included terms for treatment and period as fixed effects and subject as a random effect.</p>		
Safety Assessment	<p>Physical examination, 12-lead ECG, vital signs, laboratory safety tests and adverse events</p>		
PK Results	Perampanel		
<p>Perampanel PK</p> <p>Bioequivalence between 6-mg (Formulation D) and 3 x 2-mg tablets (Formulation C) was demonstrated.</p> <p>Figure 1. Mean (+/-SD) E2007 Plasma Concentration versus Nominal Time by Treatment</p>			

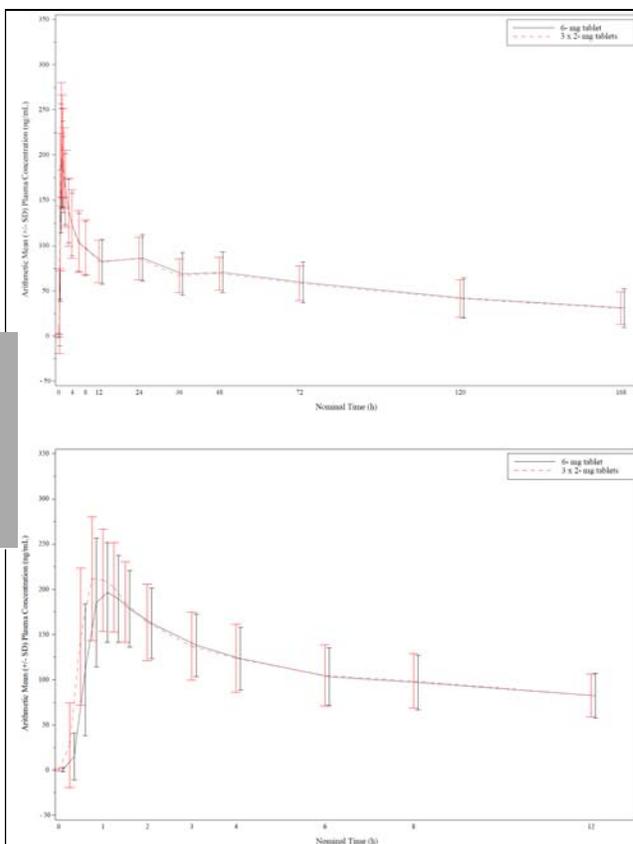


Table 1. Summary PK parameters of Perampanel

Pharmacokinetic Parameter	6-mg tablet (N=52)		3 × 2-mg tablets (N=51)	
	n		n	
Mean ± SD C _{max} (ng/mL)	51	218.37 ± 50.579	51	235.04 ± 51.895
Mean ± SD AUC _{0-t} (ng•h/mL)	51	9637.0 ± 3352.6	50	9592.0 ± 2891.2
Mean ± SD AUC _{0-inf} (ng•h/mL)	51	15794 ± 10336	50	16719 ± 13467
Median (range) t _{max} (h)	51	1.00 (0.50 – 3.00)	51	0.77 (0.50 – 2.00)
Median (range) t _{1/2} (h)	51	98.0 (27.0 – 273)	51	92.5 (25.0 – 519)
Median (range) t _{lag} (h)	51	0.00 (0.00 – 0.28)	50	0.00 (0.00 – 0.25)

Table 2. Results of the Statistical Analysis

Pharmacokinetic Parameter	Geometric Least-Square Mean		Ratio of Geometric Means (%) (Test:Reference)	90% Confidence Interval
	6-mg Tablet (Formulation D) Test (N=52)	3× 2-mg Tablets (Formulation C) Reference (N=51)		
C _{max} (ng/mL)	213 (n=51)	231 (n=51)	92.3	88.8, 95.9
AUC _(0-t) (ng•h/mL)	9153 (n=51)	9211 (n=50)	99.4	95.7, 103.2
AUC _(0-inf) (ng•h/mL)	13833 (n=51)	14172 (n=50)	97.6	92.7, 102.7

Safety Result

There was no notable difference between the 6-mg perampanel tablet and 3 × 2-mg perampanel tablets in any of the safety parameters assessed. All TEAEs reported during the study were mild in severity. The most frequently reported TEAEs comprised nervous system disorders (27 [50.0%] subjects). Overall, 27 (50%) of 54 subjects reported TEAEs considered to be probably

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	related to study drug. The incidence of treatment-related TEAEs was slightly lower after administration of the 6-mg perampanel tablet than that observed after administration of 3 × 2-mg perampanel tablets: 13 (24.5%) vs 18 (35.3%), respectively.
Conclusion	AUC _{0-t} , AUC _{0-inf} and C _{max} satisfied the bioequivalence criteria. Therefore, bioequivalence between the 6-mg tablet (Formulation D) and 3 × 2-mg (Formulation C) tablets is concluded.

Study E2007-A001-040: A Randomized, Open-label, Crossover Study to Demonstrate Bioequivalence Between 6 × 2-mg Tablets of Perampanel and a Single 12-mg Tablet of Perampanel in Healthy Subjects

Objective	<p><i>Primary objective:</i> To demonstrate bioequivalence between 6 × 2-mg tablets of perampanel and a single 12-mg tablet of perampanel. <i>Secondary objective:</i> To evaluate and compare the PK profile, safety, and tolerability of 6 × 2-mg tablets of perampanel with a single 12-mg tablet.</p>		
Study Design	<p>This was a single center, open-label, 2-period, 2-sequence crossover BE study. Subjects were randomized to one of two treatment sequences (AB or BA) in a 1:1 ratio receive a single 12-mg dose of perampanel as either 6 × 2-mg tablets (Formulation C, reference) or as a single 12-mg tablet (Formulation D, test) on Day 1 of Treatment Period 1, and then received the alternative treatment on Day 1 of Treatment Period 2. Study drug was administered after an overnight fast. The treatment periods were separated by a 6-week washout.</p>		
Study Population	<p>Of the 54 subjects randomized into the study, 51 subjects administered the 12-mg tablet and 48 subjects receiving 6 × 2-mg tablets were included in PK analysis set. A total of 47 subjects received both treatments. Age: 18-54 yr, mean 29 yr; Weight: 51-110 kg, mean, 75.4 kg; Gender: Male (59%); Race: Majority White (70%)</p>		
PK Sampling	<p>Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 120, 168 hours post-dose.</p>		
Bioanalytical Method	Analyze	Perampanel	
	Method	LC/MS-MS	
	Internal Std.	(b) (4)	
	LOQ (ng/mL)	1	
	Calibration Range (ng/mL)	1, 2, 5, 20, 100 200, 400, 500	
	QC (ng/mL)	3, 50, 380	
	Accuracy	94.9 – 97.9%	
	Precision	5.3 – 8.3%	
PK Assessments	<p>Plasma concentrations of perampanel were analyzed by non-compartmental methods to determine the following PK parameters: C_{max}, AUC_{0–t}, AUC_{0–inf}, T_{max}, t_{lag}, and t_{1/2} C_{max}, AUC_{0–t} and AUC_{0–inf} of perampanel were compared between the 6 × 2-mg tablets (reference) and the 12-mg tablet (test) using a linear mixed effects model (with log-transformed PK parameter values as response). The model included terms for treatment and period as fixed effects and subject as a random effect.</p>		
Safety Assessment	Physical examination, ECG, vital signs, laboratory safety tests and AEs		
PK Results	Perampanel		
	<p>Perampanel PK Bioequivalence between 12-mg (Formulation D) and 6 x 2-mg tablets (Formulation C) was demonstrated. Small but statistically significant differences in C_{max} values between treatments were noted. C_{max} values were approximately 9% lower for Formulation D vs. Formulation C.</p>		

Figure 1. Mean (+/-SD) E2007 Plasma Concentration versus Nominal Time by Treatment

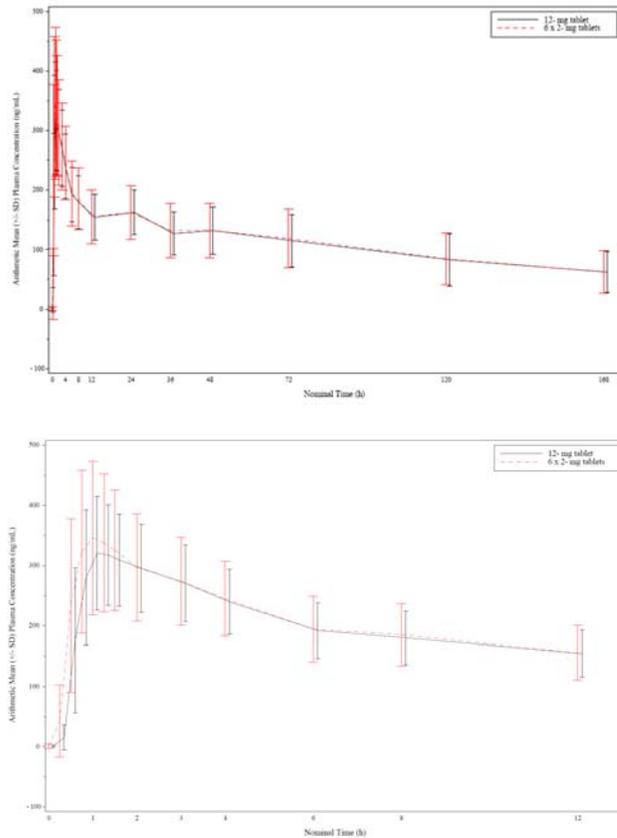


Table 1. Summary PK parameters of Perampanel

Pharmacokinetic Parameter	12-mg tablet (N=51)	6 × 2-mg tablets (N=48)
Mean ± SD C _{max} (ng/mL)	357.51 ± 77.594	396.73 ± 105.38
Mean ± SD AUC _{0-t} (ng·h/mL)	18432 ± 6197.2	18688 ± 6540.9
Mean ± SD AUC _{0-inf} (ng·h/mL)	31452 ± 17859	31221 ± 16845
Median (range) t _{max} (h)	1.00 (0.50 – 4.00)	1.00 (0.47 – 4.00)
Median (range) t _{1/2} (h)	95.0 (32.0 – 327)	101 (37.0 – 282)
Median (range) t _{1/2g} (h)	0.00 (0.00 – 0.25)	0.00 (0.00 – 0.25)

Table 2. Results of the Statistical Analysis

Pharmacokinetic Parameter	Geometric Least-Square Mean		Ratio of Geometric Means (%) (Test:Reference)	90% Confidence Interval
	12-mg Tablet (Formulation D) Test (N= 51)	6 × 2-mg Tablets (Formulation C) Reference (N=48)		
C _{max} (ng/mL)	346	382	90.7	86.3, 95.3
AUC _(0-t) (ng·h/mL)	17486	17483	100.0	95.9, 104.3
AUC _(0-inf) (ng·h/mL)	27398	26760	102.4	96.0, 109.2

Safety Result	There was no notable difference between the 12-mg perampanel tablet and 6 × 2-mg perampanel tablets in any of the safety parameters assessed. Most of the AEs were mild in severity. The most frequently reported treatment emergent AEs (TEAEs) comprised nervous system disorders (37 [68.5%] subjects), general disorders and administration site conditions (15 [27.8%]
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	<p>subjects), and gastrointestinal and eye disorders (7 [13.0%] subjects each). The incidence of treatment-related TEAEs was slightly higher after dosing with the 12-mg perampanel tablet than with 6 × 2-mg perampanel tablets: 37 (71.2%) subjects vs 29 (59.2%) subjects, respectively. The majority of TEAEs were possibly or probably related to study drug.</p>
Conclusion	<p>AUC_{0-t}, AUC_{0-inf} and C_{max} satisfied the bioequivalence criteria. Therefore, bioequivalence between the 12-mg tablet (Formulation D) and 6 × 2-mg (Formulation C) tablets is concluded.</p>
Additional Comments	<p>A request was sent to the Office of Scientific Investigations (OSI) on February 21, 2012 for inspecting clinical and bioanalytical sites for this study. Please refer to the memorandum documented by Dr. Sripal Mada (dated August 28, 2012) for details.</p> <p>In the memorandum it was concluded that, Following evaluation of the inspectional findings and response from (b) (4) (the firm conducted the bioanalysis for this study), the DBGC (Bioequivalence Branch) reviewers recommend the following:</p> <ul style="list-style-type: none"> • The accuracy of the data from the -20°C and -70°C freeze-thaw stability experiment cannot be assured since (b) (4) failed to document complete details of sample processing (see Form FDA-483, items 1, 2, and 3). (b) (4) needs to confirm the freeze-thaw stability at -20°C and -70°C by conducting a systematic study. • The clinical and other analytical data from this study are <u>acceptable</u> for review. <p>Dr. Mada further commented in a communication that, ‘Overall, the data generated from the freeze-thaw stability study during validation is not assured. As a result, all the clinical samples will have no effect except the ones with more than 1 freeze-thaw cycle (examples are the repeat analysis samples (if any) as they underwent more than 1 freeze-thaw cycle). To confirm, (b) (4) need to repeat the freeze-thaw stability experiment with proper study conduct’.</p> <p>Study samples were shipped frozen on dry ice from the clinical site to (b) (4) and were stored in -70°C freezer before analyzed. In the analytical report, there were 40 samples re-analyzed for different reasons. Among these, 13 samples had perampanel concentrations measurable during the first round of assay. The re-assay results for these samples were all within +/- 15% of the value derived from the first assay except one sample.</p> <p>An incurred sample reanalysis (ISR) evaluation was also performed by the firm on 192 plasma samples. All of these ISR samples had no more than +/- 20% difference compared to the original analysis results. Actually, 175 out of 192 samples had repeated values less than 10% different from the original values, and 189 samples had repeated values within +/- 15% of the original values.</p> <p>These samples subject to re-assay or ISR evaluation were likely to undergo more than 1 freeze-thaw cycle. The consistency between re-analyzed values and original values supports that the sample stability obtained from this study was not significantly affected by freeze-thaw conditions.</p>

	<p>Further, four validated analytical methods (b) (4)-US/BTM-1076-R0, (b) (4)/45-0603, (b) (4)/105-001 and (b) (4) 101589-2) developed by different contractor research companies including (b) (4) were used to analyze the plasma samples for most of the clinical studies, including this study, conducted by the Sponsor. Perampanel was shown to be stable in plasma for 3 cycles at -20°C and up to 7 cycles at -70°C.</p> <p>Considering the above information, this reviewer concluded that the bioanalytical data for this study are acceptable.</p>
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/s/

XINNING YANG

10/22/2012

This file is related to Clin Pharm QBR review DARRTSed earlier.

TA-CHEN WU

10/22/2012

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
OND Division:	OND-1/Division of Neurology Drug Products
OCP Divisions:	OCP/Division of Clinical Pharmacology-1 (DCP-1)
Primary Reviewer:	Xinning Yang, Ph.D.
Secondary Reviewer:	Ta-Chen Wu, Ph.D.
Team Leader:	Angela Yuxin Men, M.D., Ph.D. Ta-Chen Wu, Ph.D. (Acting)
Pharmacometrics Reviewer:	Joo-Yeon Lee, Ph.D.
Pharmacometrics Team Leader:	Atul Bhattaram, Ph.D. (Acting)

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-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-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 (CL_{Cr}: 50 – 80 mL/min) and 3 patients with moderate renal impairment (CL_{Cr}: 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 levonorgestrel-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 μ M and including clinical relevant concentration of \sim 3 μ M) 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. 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. 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 α 1-acid glycoprotein and to a much lesser extent with γ -globulin. Saturable binding of perampanel was found for α 1-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_{0-24hr}) 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 \geq 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-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-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 ($IC_{50} > 30 \mu\text{M}$) and is not expected to result in clinically significant DDI. Perampanel was a time-dependent inhibitor of CYP3A4. At a concentration of $30 \mu\text{M}$, 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 $1.89 \mu\text{M}$ 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 $3 \mu\text{M}$ and above, but the inducing effect was weak compared to the positive control, rifampicin. Perampanel may induce UGT1A1 ($\geq 3 \mu\text{M}$) and to a lesser extent induce UGT1A4 ($30 \mu\text{M}$).

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_{0-24hr} and C_{max} of single-dose levonorgestrel by 40% and 42%, respectively. At 12-mg dose level, perampanel decreased C_{max} of single-dose ethinylestradiol by 18% but not affected its AUC_{0-24hr}, 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 ethinylestradiol or levonorgestrel, with 8-mg perampanel slightly reducing AUC_{0-24hr} and AUC_{0-inf} of single-dose levonorgestrel 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

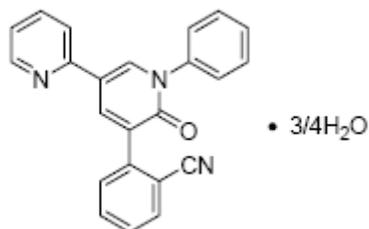
2.1.1 What are therapeutic indication(s) and the proposed mechanisms of action?

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 $C_{23}H_{15}N_3O \cdot 3/4H_2O$ and the molecular weight is 362.90 (3/4 hydrate) or (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				
Weight	105 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

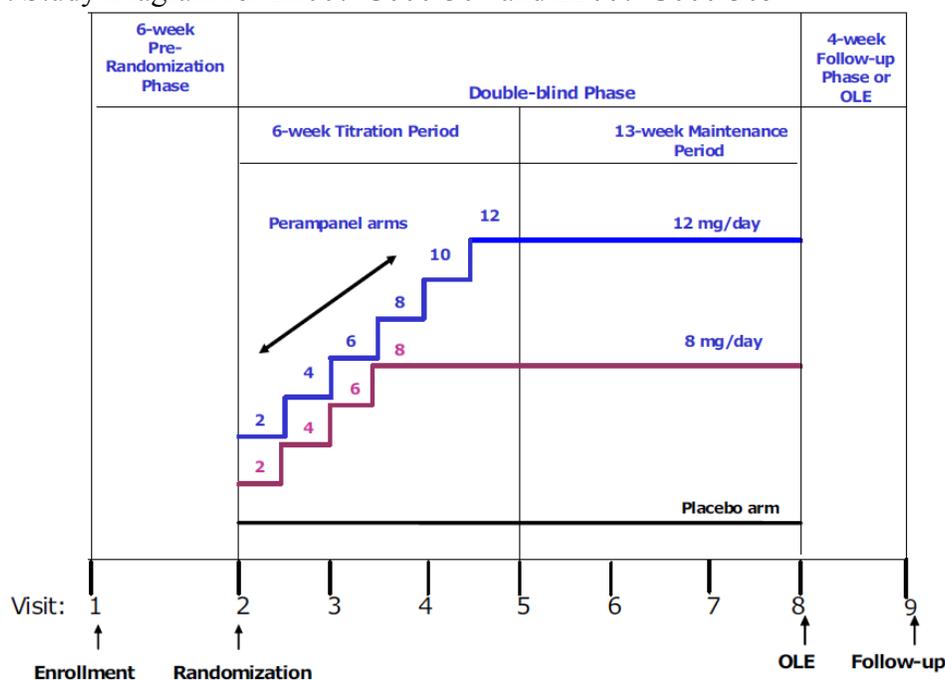
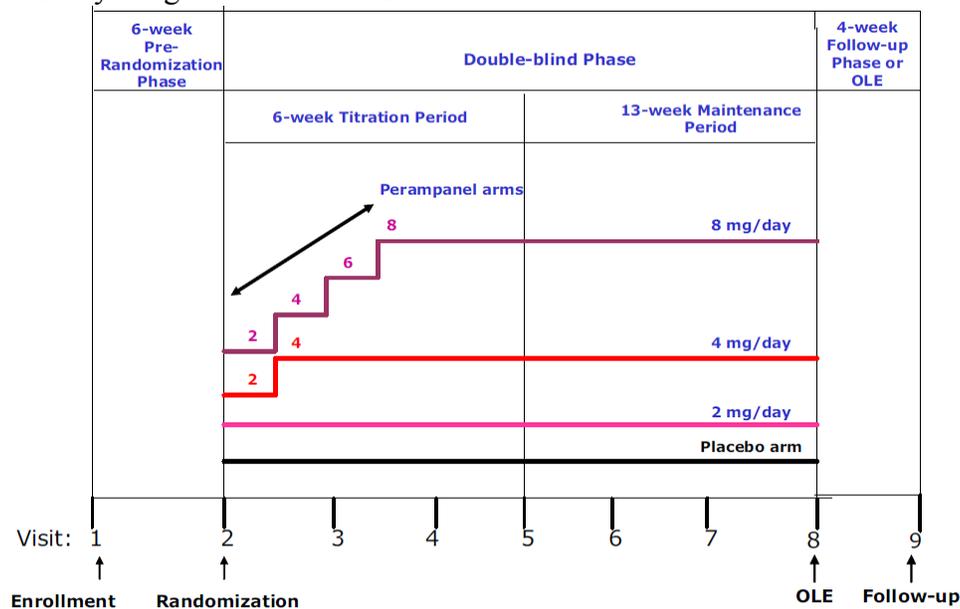


Figure 2. Study Diagram for E2007-G000-306



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

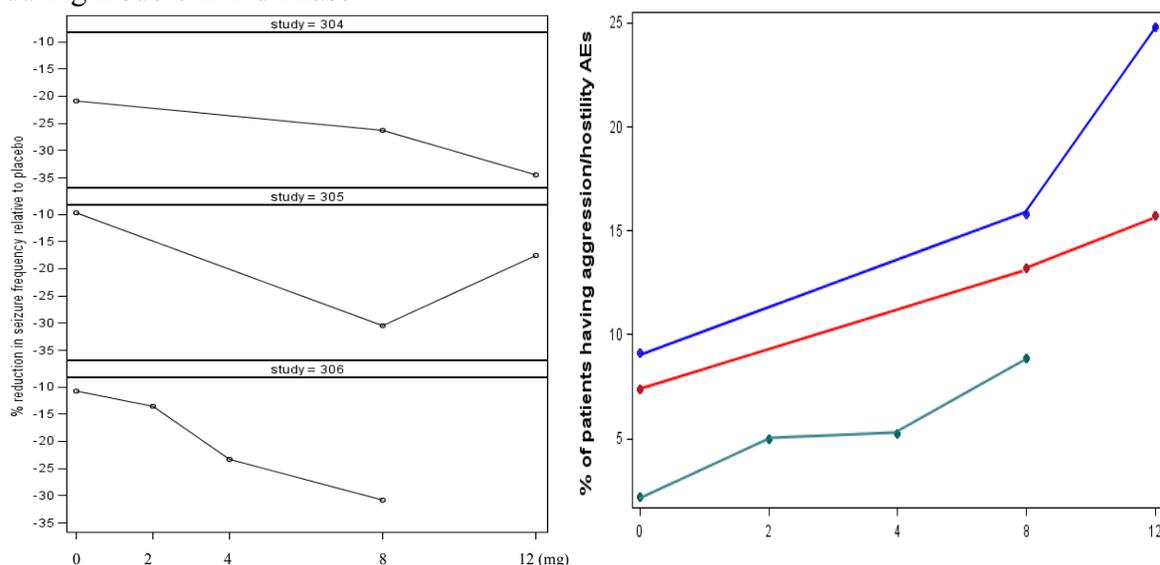
2.2.3.1. Is there any significant exposure-response relationship? And does the relationship support the proposed dosing regimen?

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.

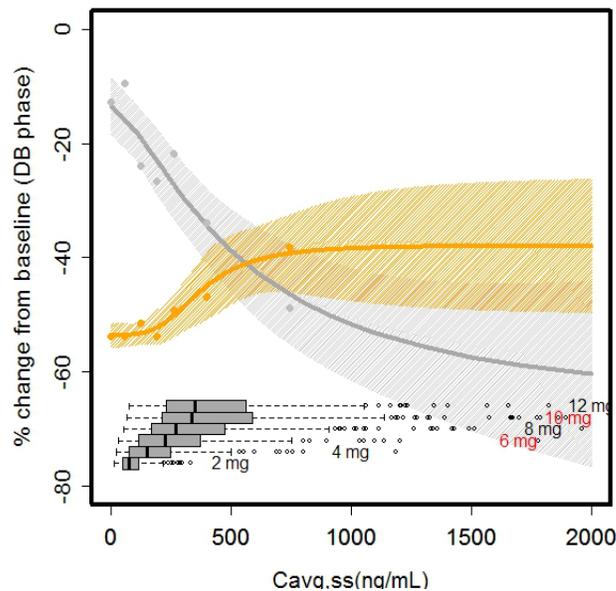
Table 3. Summary of Results of Primary Efficacy Analyses (based on Full ITT analysis set) The numbers are the median percent reduction of seizure frequency during double-blind phase from the baseline relative to placebo with p-values in parentheses.

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 ($C_{ss,avg}$) 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).



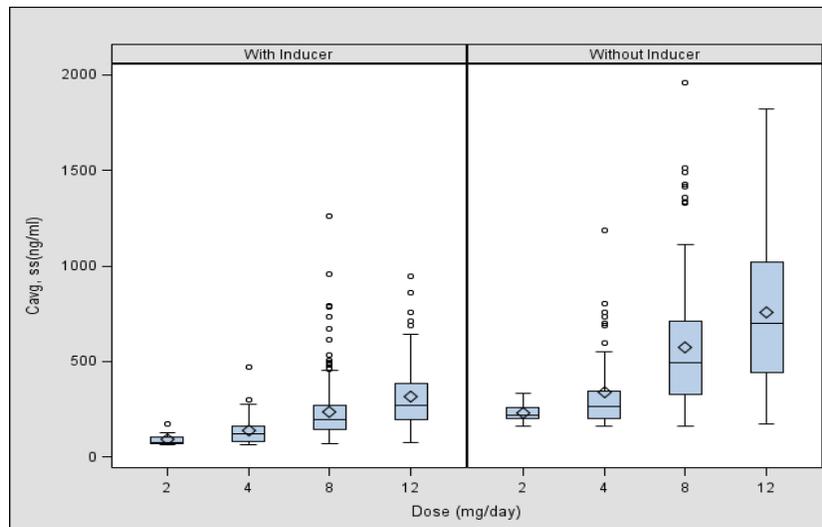
Sub-group Analysis by Inducer and Non-inducer AEDs

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 $C_{ss,avg}$ in the two groups shows that the $C_{ss,avg}$ 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



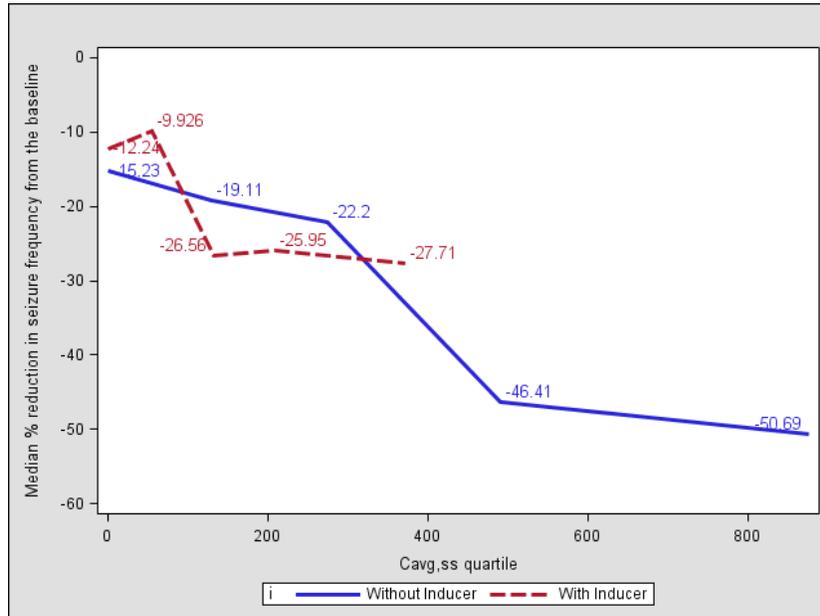
The $C_{ss,avg}$ was binned by quartiles for inducer and non-inducer groups. The median concentration with range in each bin is displayed by groups in the following table.

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)
1 st	55 ng/ml (10-88)	129 ng/ml (21-203)
2 nd	132 ng/ml (92-167)	275 ng/ml (204-365)
3 rd	209 ng/ml (168-267)	491 ng/ml (367-650)
4 th	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 μ M) was predicted for perampanel administered under fasted condition following the dosing regimen proposed for clinical use (i.e, 2 mg \times 7 days \rightarrow 4 mg \times 7 days \rightarrow 6 mg \times 7 days \rightarrow 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)

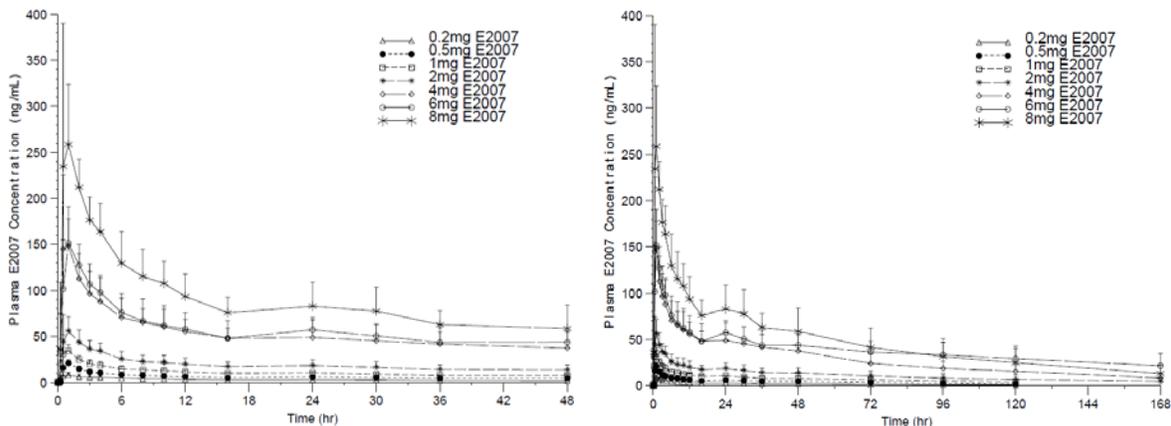
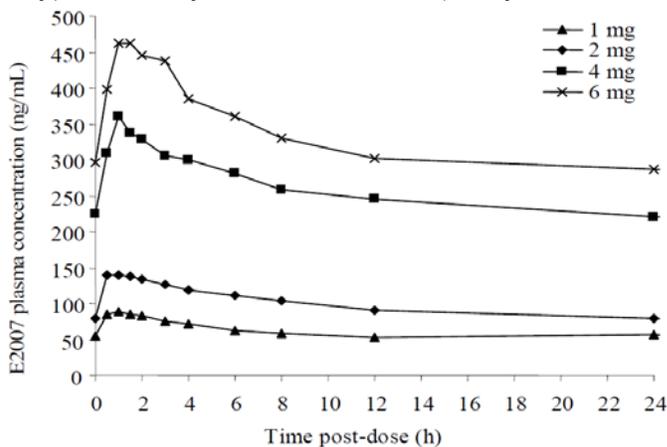


Figure 8. Mean Perampanel Plasma Concentration-Time Profiles after 14 Days Repeated Dosing (once daily) in Healthy Male Volunteers (Study E2007-E044-002)



[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)

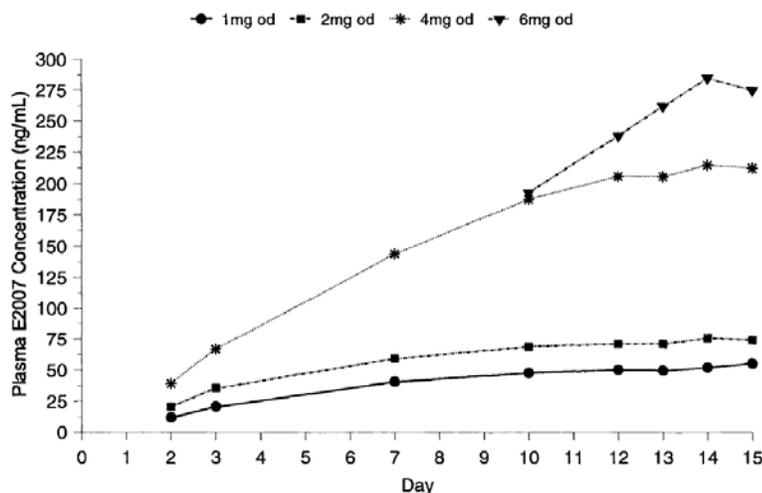
Perampanel dose	t_{max}^a (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC _(0-inf) (ng·h/mL)	CL/F (mL/min)
Single Dose					
1 mg (N=24)	1.00 (0.50-3.00)	36.8 (12.2)	111 (59.6)	2251 (1189)	9.77 (5.75)
2 mg (N=106)	1.00 (0.50-8.00)	60.7 (20.7)	85.2 (44.2)	3379 (156)	12.0 (5.73)
4 mg (N=68)	1.00 (0.50-6.00)	123 (46.5)	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 $(C_{\max,ss} - C_{\min,ss})/C_{av,ss} \times 100\%$) 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, C_{av,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- μ g (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 (V_d/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 α 1-acid glycoprotein and to a lesser extent to γ -globulin in human serum. Saturable binding was observed with α 1-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.

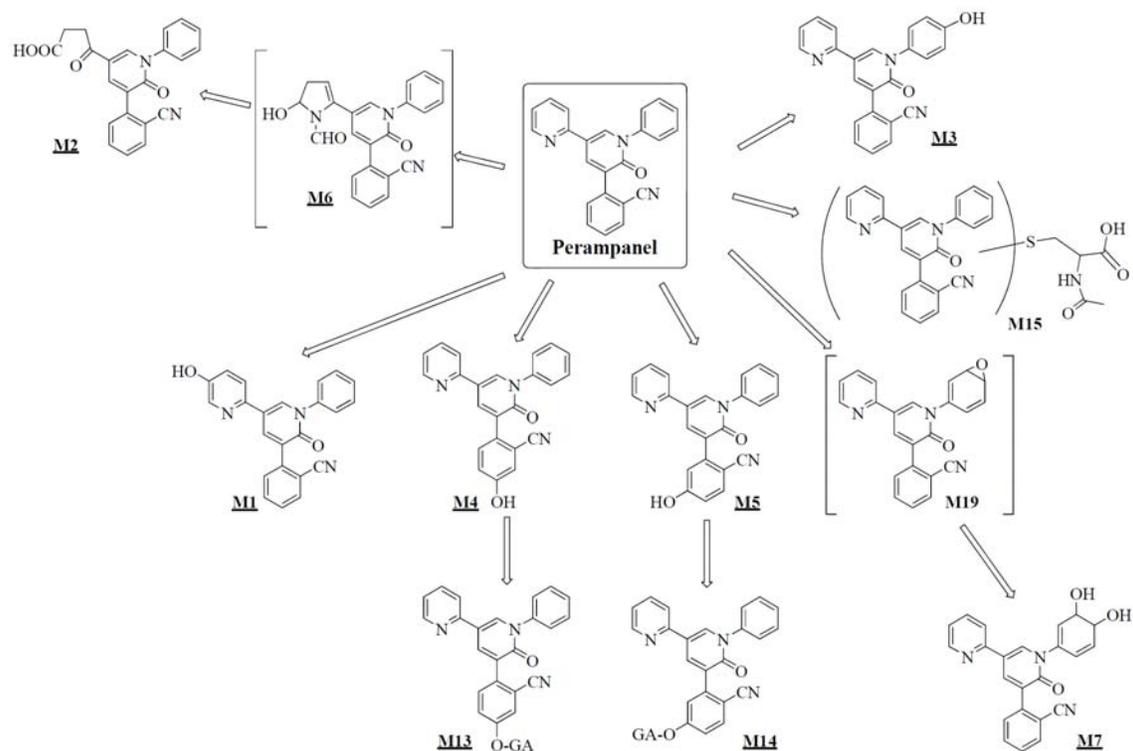
2.2.4.4 What are the characteristics of drug metabolism?

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 glucuronide 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 μ M 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 result 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 IC₅₀ 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 μ M (refer to Pharmacology and Toxicology review documented by Dr. Christopher D. Toscano for details).

Recommendation: 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?

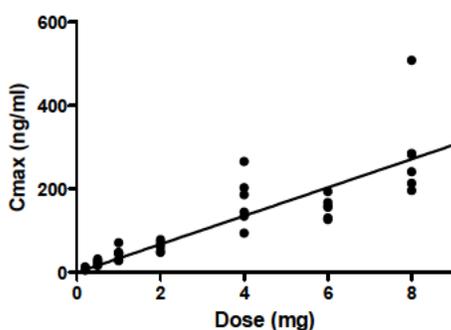
AUC of perampanel increased dose-proportionally over the range of 0.2-12 mg after single-dose administration and 1-12 mg after multiple-dose administration. C_{max} of perampanel increased in a dose-proportional manner after single-dose administration of 0.2-8 mg and increased less than dose-proportionally 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 $AUC_{0-\tau}$ for 4 mg dose group were double of corresponding parameters for 2 mg dose.

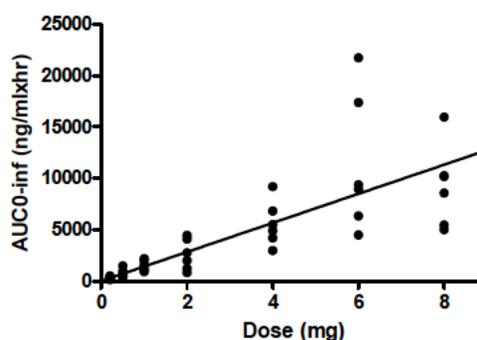
Table 9. Evaluations of Potential Nonlinearity in Perampanel PK

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)

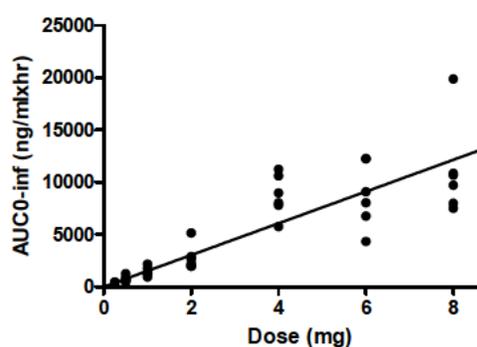
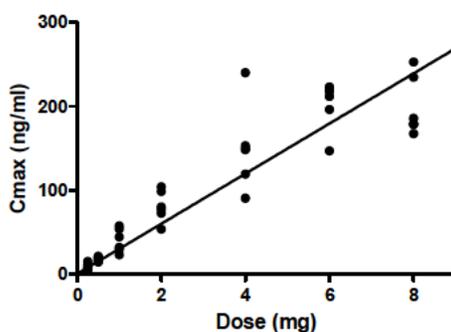
Figure 11. Dose-Exposure Relationship of Perampanel after Single Doses from 0.2-8 mg C_{max} (Study E2007-E04-001) AUC (Study E2007-E044-001)



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,

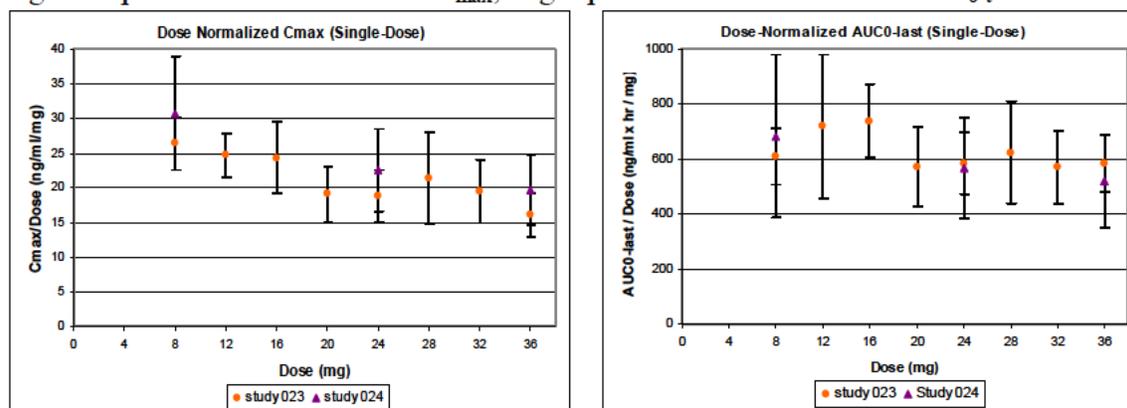
indicating that C_{max} increased less than dose proportionally. Of note, in Study E2007-A001-024, median T_{max} was prolonged from 1.5 hrs after 8 mg dose to 3.5 hrs after 24 mg or 36 mg. The less than dose-proportional increases in C_{max} at higher doses of perampanel may be attributed to the delayed absorption due to limited solubility of the drug. Solubility of perampanel ($pK_a=3.24$) 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} .

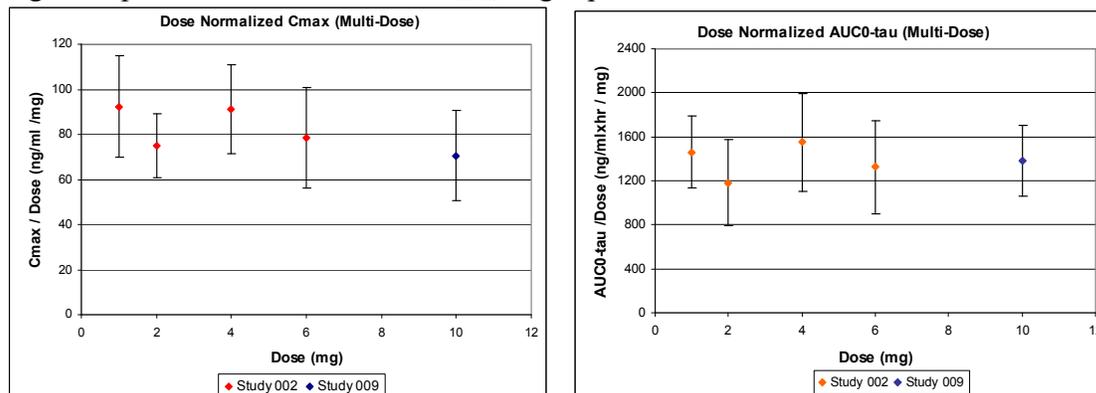
Figure 12. Dose-Exposure Relationship of Perampanel after Single Dose from 8 mg to 36 mg. Left panel: Dose-normalized C_{max} ; Right panel: Dose-normalized AUC_{0-t}



[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, oxcarbazepine, 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-inf} for majority of the studies fell within 30-60%. The CV% of AUC_{0-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

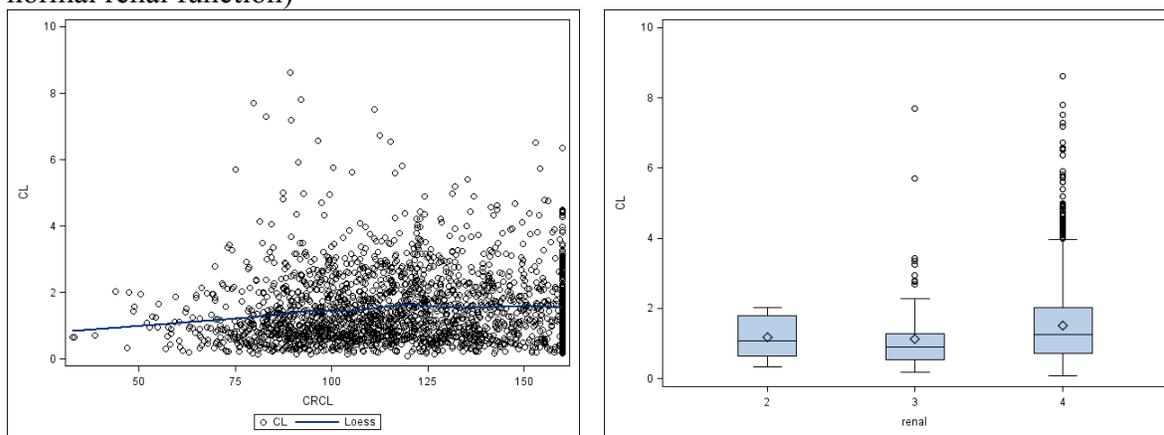
No dedicated study has been conducted in subjects with renal impairment. Effect of renal impairment on perampanel clearance was evaluated via population PK approach using Phase 3 data. As shown in the Table 13, median CL/F of perampanel was 27% lower in patients with mild renal impairment compared to 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 (CL_{cr}, 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 (CL _{cr} , 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 (CL_{cr}). 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.

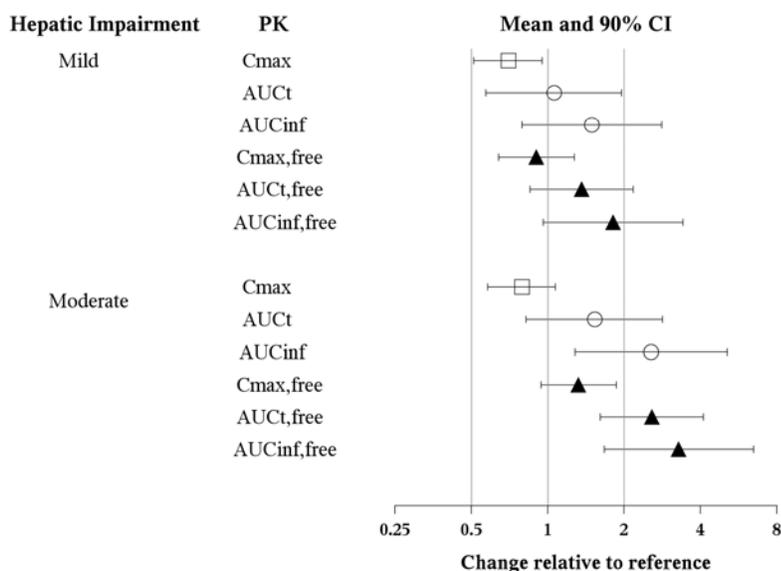
2.3.1.7 Hepatic impairment

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-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-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 $AUC_{0-\infty}$ 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., bupropion) 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., bupropion) 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 ($\geq 3 \text{ μM}$) 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.

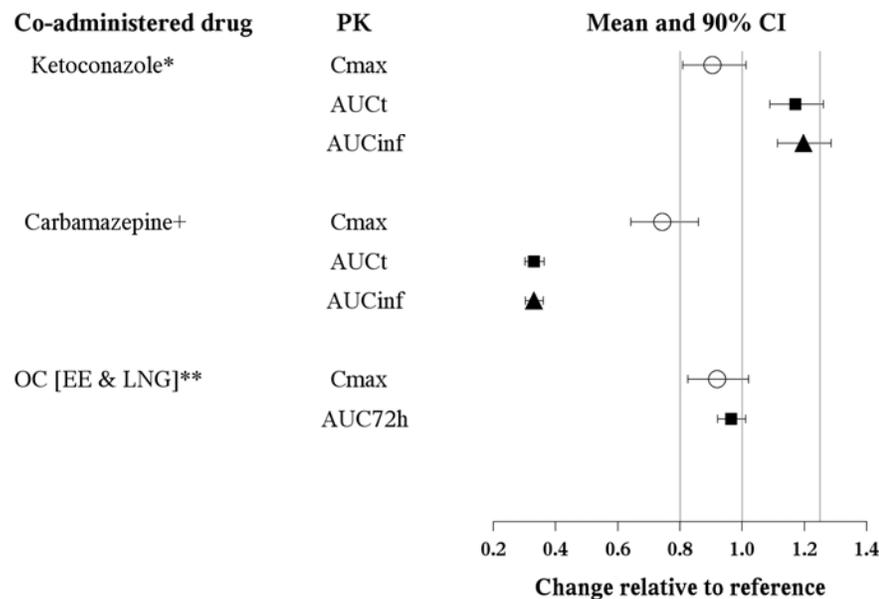
2.4.3 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered? If yes, is there a need for dosage adjustment?

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:

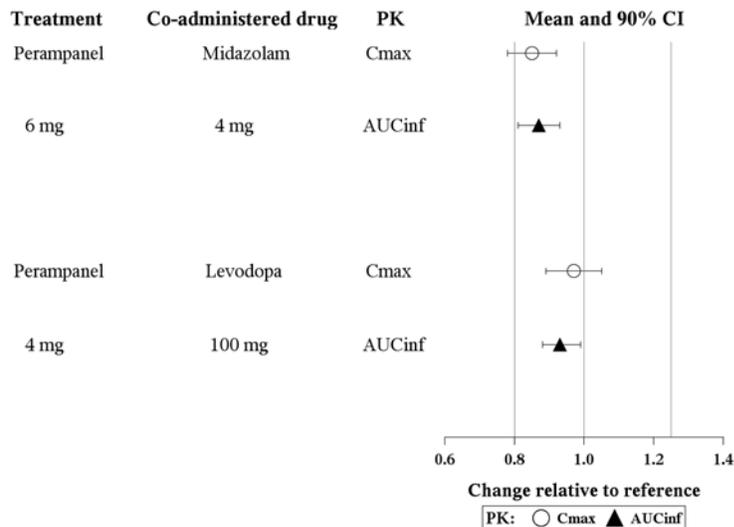
The Phase 3 population PK analysis (CPMS-E2007-2011-003) reported no significant effects of perampanel on the clearance of clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate, or zonisamide. On the other hand, perampanel increased the clearance of carbamazepine, clobazam, lamotrigine, and 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.

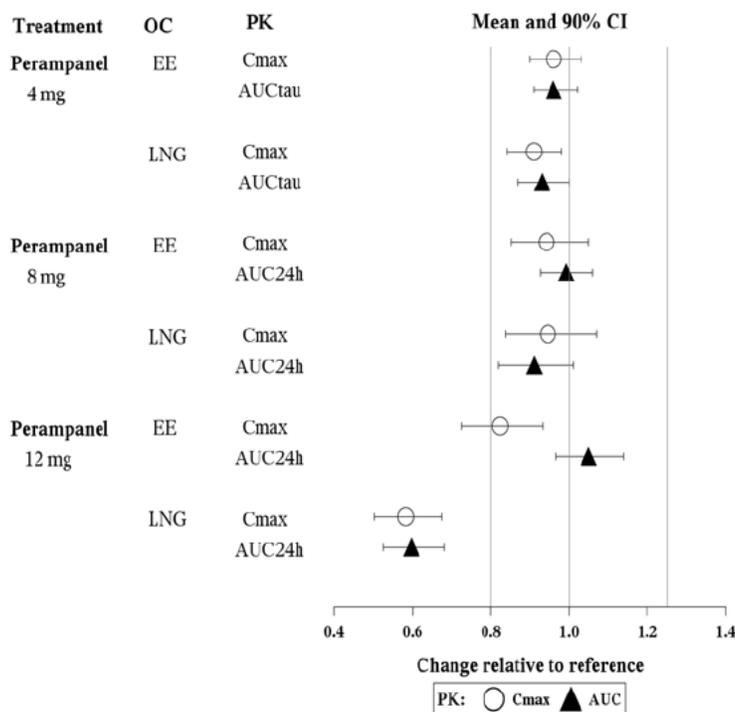
(4) Oral contraceptives:

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 $AUC_{0-\tau}$ 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_{0-24hr} of LNG by 42% and 40%, respectively, and decreased C_{\max} of EE by 18% without affecting AUC_{0-24hr} 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 $AUC_{0-24 hr}$ and AUC_{0-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

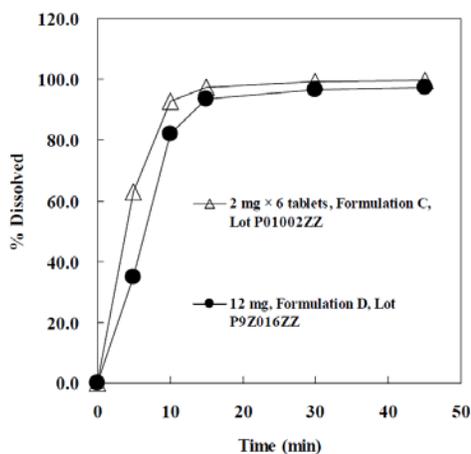
2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation?

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

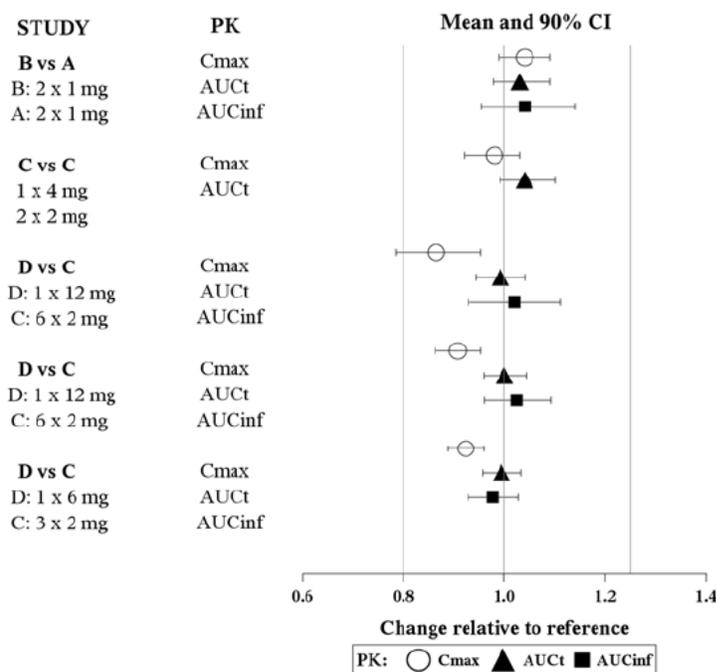


Formulation A (0.1, 1, and 5 mg tablets) was developed to initiate clinical study and used in the early stage of clinical trials (mainly in Phase 1 studies). Formulation A was then reformulated to Formulation B (b) (4)

(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 ($AUC_{0-168hr}$ and AUC_{0-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_{0-24hr} .

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

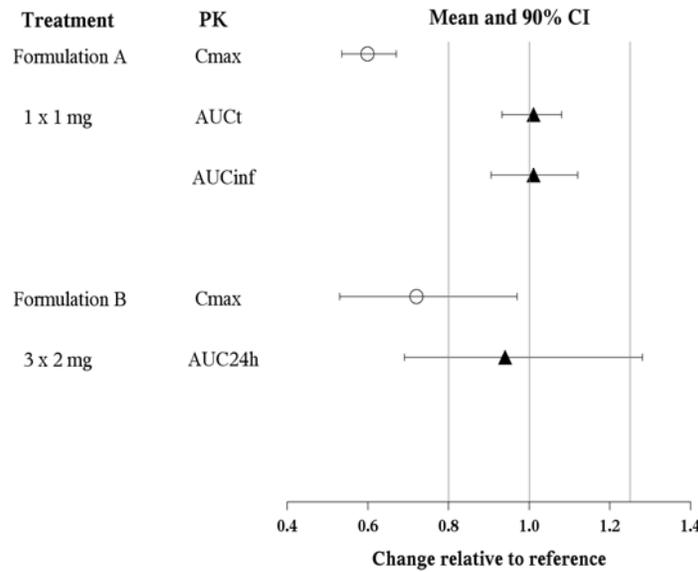
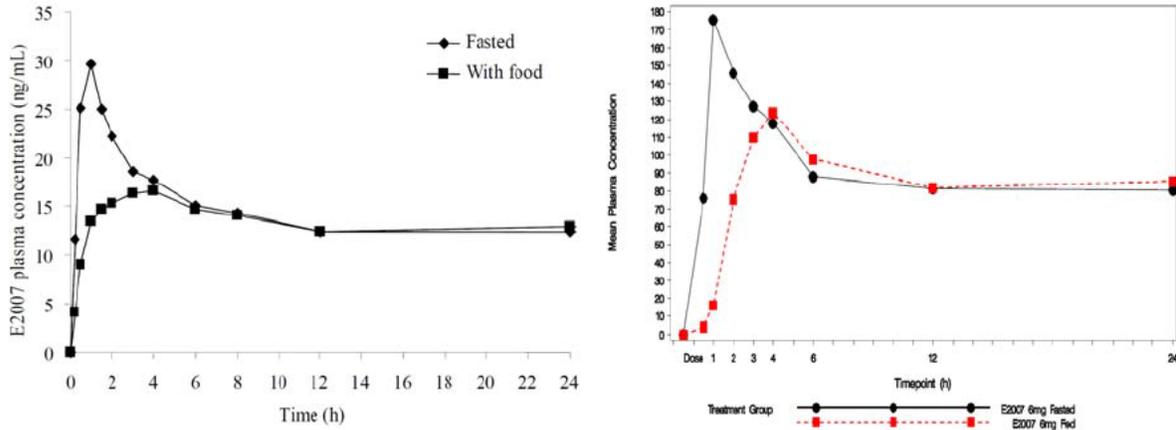
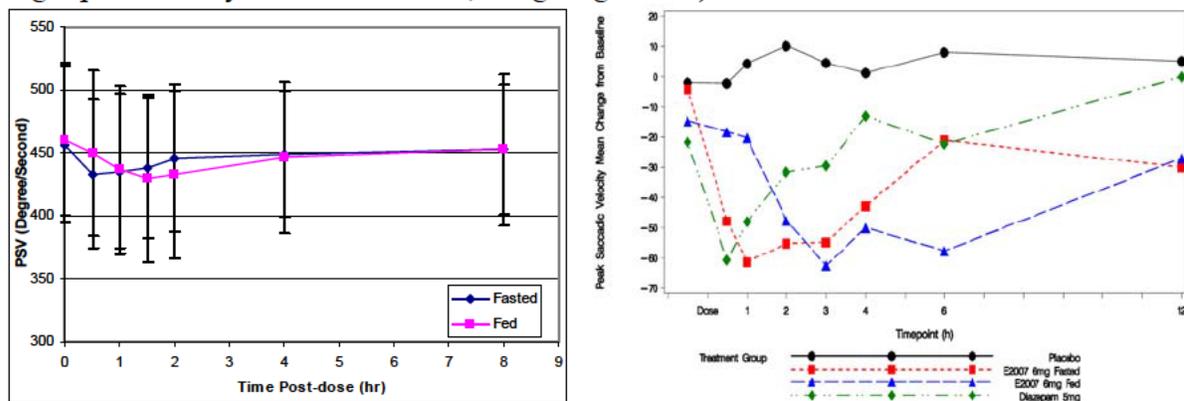


Figure 22. Concentration versus Time Profiles of Perampanel under Fasted and Fed Conditions (Left panel: Study E2007-044-003 (Formulation A); Right panel: Study E2007-044-009 (Formulation B))



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 dosing 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 (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 (b) (4) (b) (4) 101589-2) 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 ¹⁴C-radioactivity for ¹⁴C-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 (b) (4) -US/BTM-1076-R0, (b) (4) /45-0603, (b) (4) (b) (4) /105-001 and (b) (4) 101589-2) 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) (b) (4) 101589-2
Analyte Names	perampanel	perampanel	perampanel	Perampanel, Metabolite M1, M2, M3, M4, M5 and M7
Internal Standard (IS)	Perampanel associated substance	Perampanel associated substance	Perampanel associated substance	Perampanel-d5; M4-d5
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)	(b) (4)
Analyte Names	Perampanel (E2007)	Perampanel (E2007)
Internal Standard (IS)	Perampanel associated substance	NA
Analytical Method Type	LC-FI	LC-MS/MS
Stock solution solvent	ethanol	ethanol
Extraction Method	Liquid/liquid	Liquid/liquid
Linear range	0.2555 to 102.2 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 to 103%	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).

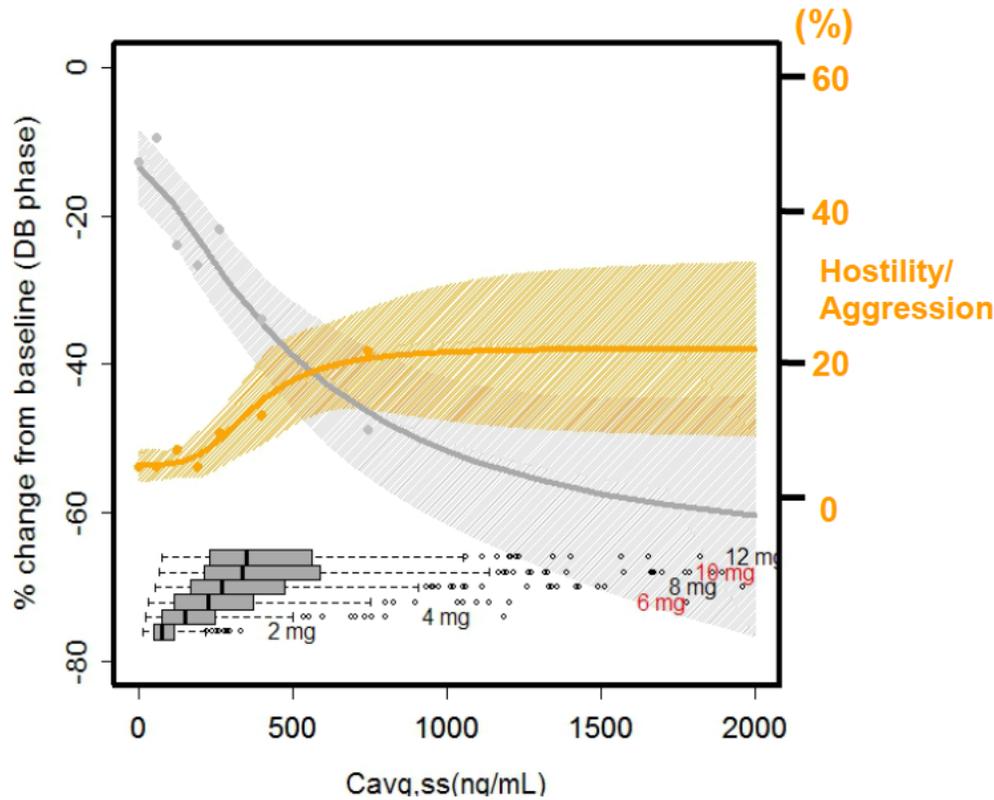


Table 2. Predicted % reduction in seizure frequency and % hostility/aggression-related adverse event based on the modeling results shown in Figure 1. The prediction was made at the median concentration at each dose. (6 mg and 10 mg were predicted based on the simulated exposure range).

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					All
		2 mg	4 mg	8 mg	12 mg	Placebo	
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

$$COV1 = -0.138 \times (FBM/17.1)+0.0220 \times (DOS-2)-0.162 \times (SEX-1)-0.0231*(VIS-6)$$

$$COV2 = 1.67*CAR+0.841*OXC+0.942*FENC/16204+0.228*TOP$$

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 topiramate 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]	
Effect 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 (centralized to 16204)	θ_{10}	0.942	0.137	15	[0.673; 1.211]	
Effect of topiramate 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 (Table 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:

$$C_{avss} = (DDOS/24) * 1000 / (CL/F)$$

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.

$$\text{Log}_e(\text{seizures frequency}/28\text{days})$$

$$= \text{Log}(\text{seizures frequency}/28\text{days of baseline}) + 0.245 * C_{LOB} - 0.368 - 0.000595 * C_{avss}(\text{ng/mL})$$

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	
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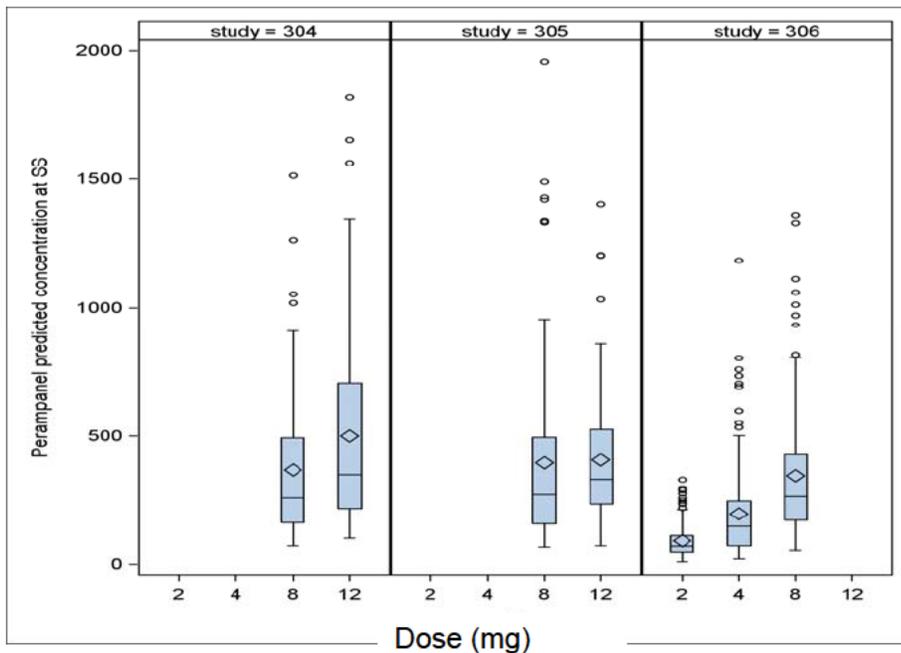
4.3.2 Software

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.

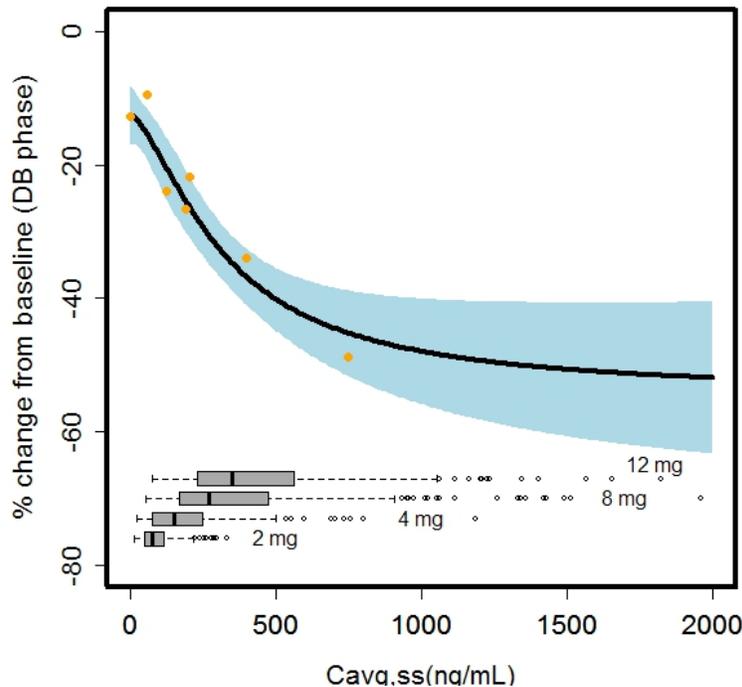
Figure 2. The distribution of Cavss (ng/ml) by study and dose.



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		
	Placebo	Perampanel Last Dose		Placebo	Perampanel Last Dose		Placebo	Perampanel Last Dose	
		8 mg	12 mg		8 mg	12 mg		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 (20.6)	29 (30.9)	26 (32.9)	17 (18.7)	27 (35.1)	24 (35.8)	12 (15.0)	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

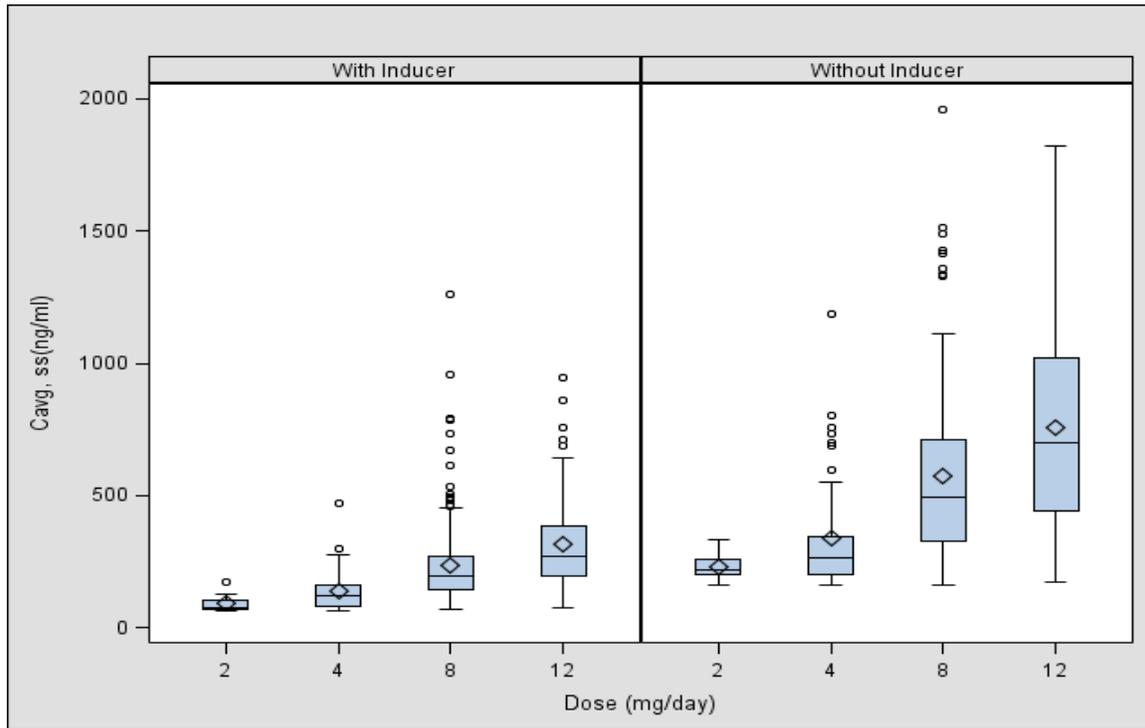
Statistics	All Partial Seizure Frequency per 28 days				Responder Rate	
	Total N	Median Prerandomization frequency	Median % change in Maintenance Period	Median difference to placebo (95% CI) ^a	Total N	Responder, n (%)
Concomitant CBZ, OXC, PHY						
Placebo	94	11.27	-14.39	--	94	17 (18.1)
Perampanel 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.



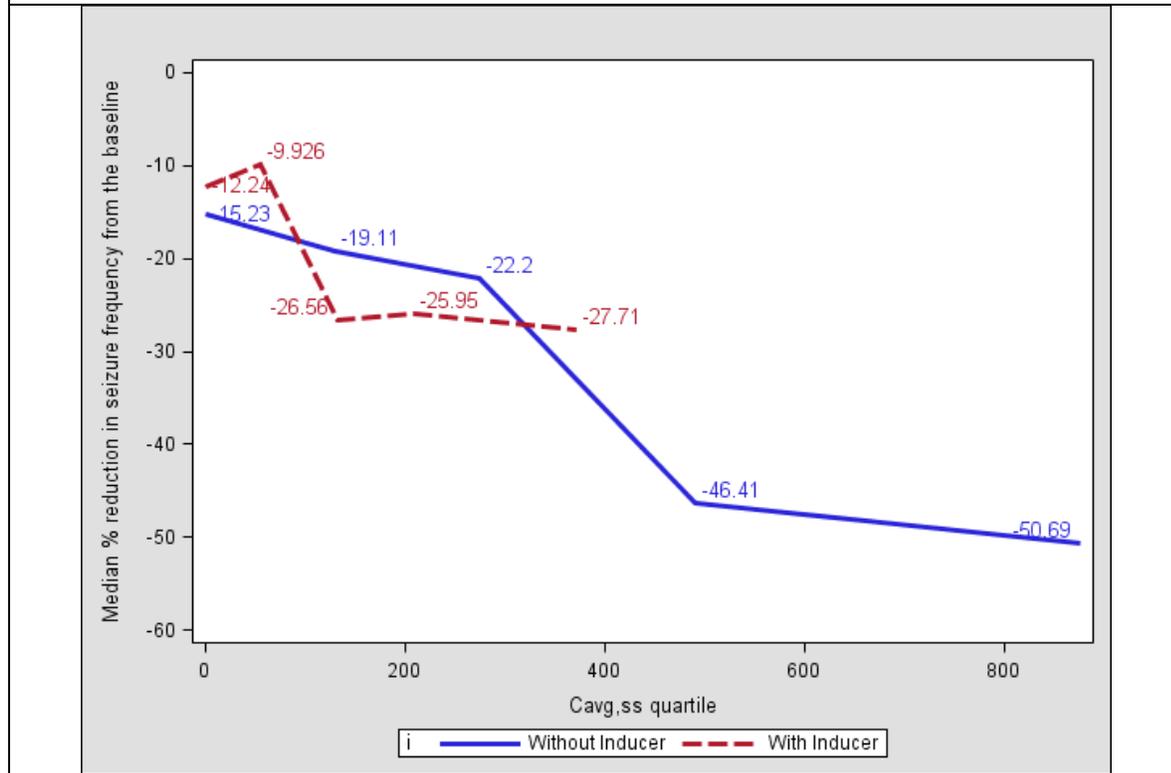
The steady-state average concentration was binned by quartiles by with-inducer and without-inducer groups. The median concentrations with range in each bin by groups are displayed in Table 10.

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)
1 st	55 ng/ml (10-88)	129 ng/ml (21-203)
2 nd	132 ng/ml (92-167)	275 ng/ml (204-365)
3 rd	209 ng/ml (168-267)	491 ng/ml (367-650)
4 th	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.

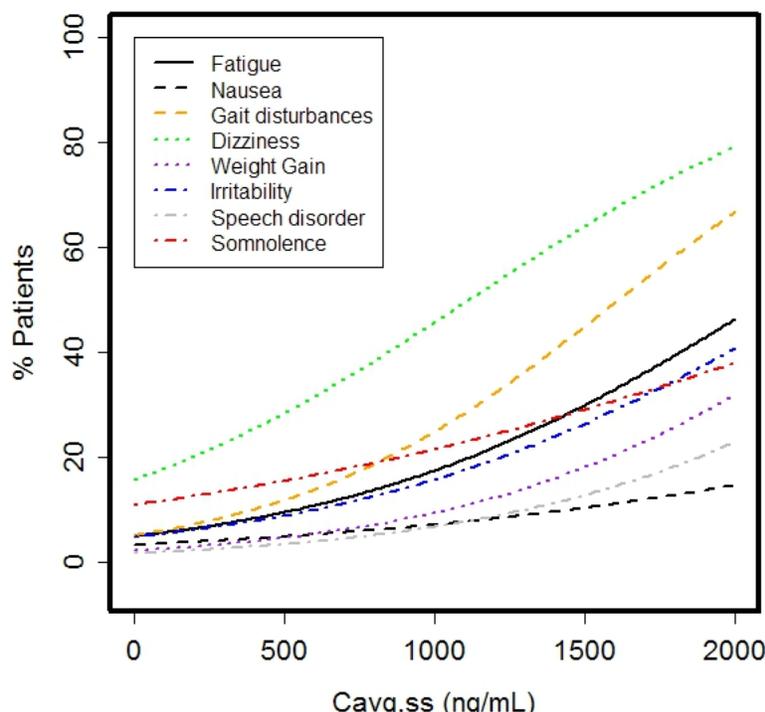
Figure 5. Median change in seizure frequency versus steady state average perampanel concentrations in studies of 304/305/306. The effect size is displayed at the median concentrations at each bin.



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.

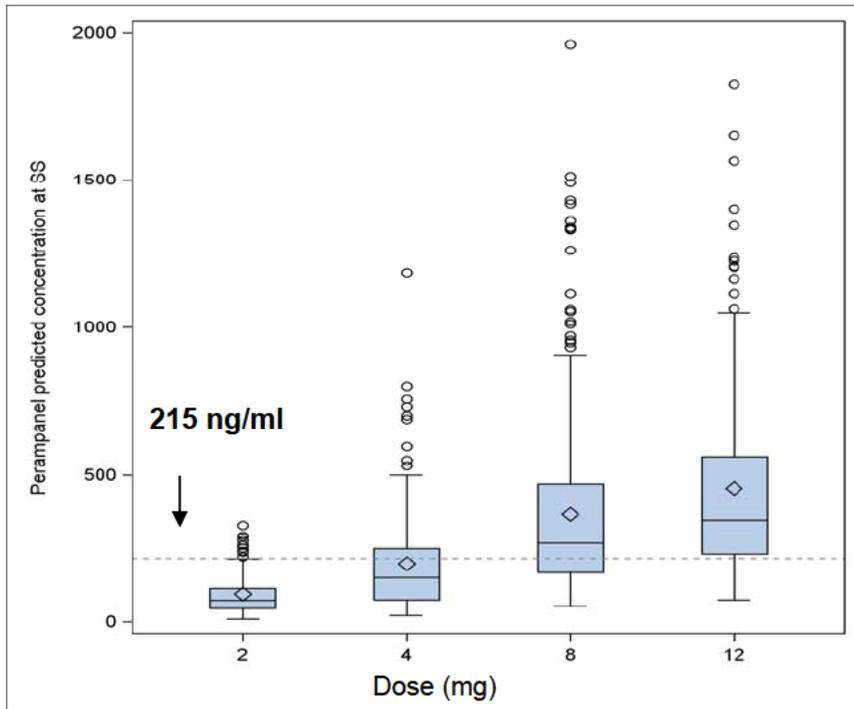
Study	Placebo	2 mg	4 mg	8 mg	12 mg	Total
304	9% (11/121)	—	—	16% (21/133)	25% (33/134)	17% (65/388)

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.

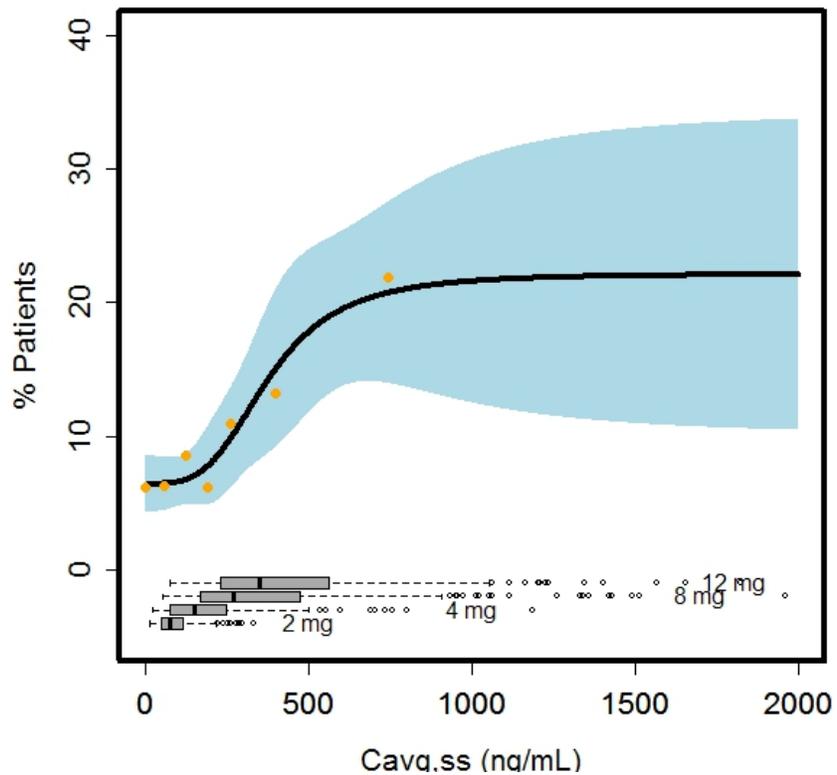


Figure 9 shows the benefit and risk profiles of perampanel, and based on the benefit and risk profile, the reviewer predicted the percent reduction in seizure frequency during DB phase and the probability of adverse events related to hostility and aggression (Table 13).

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).

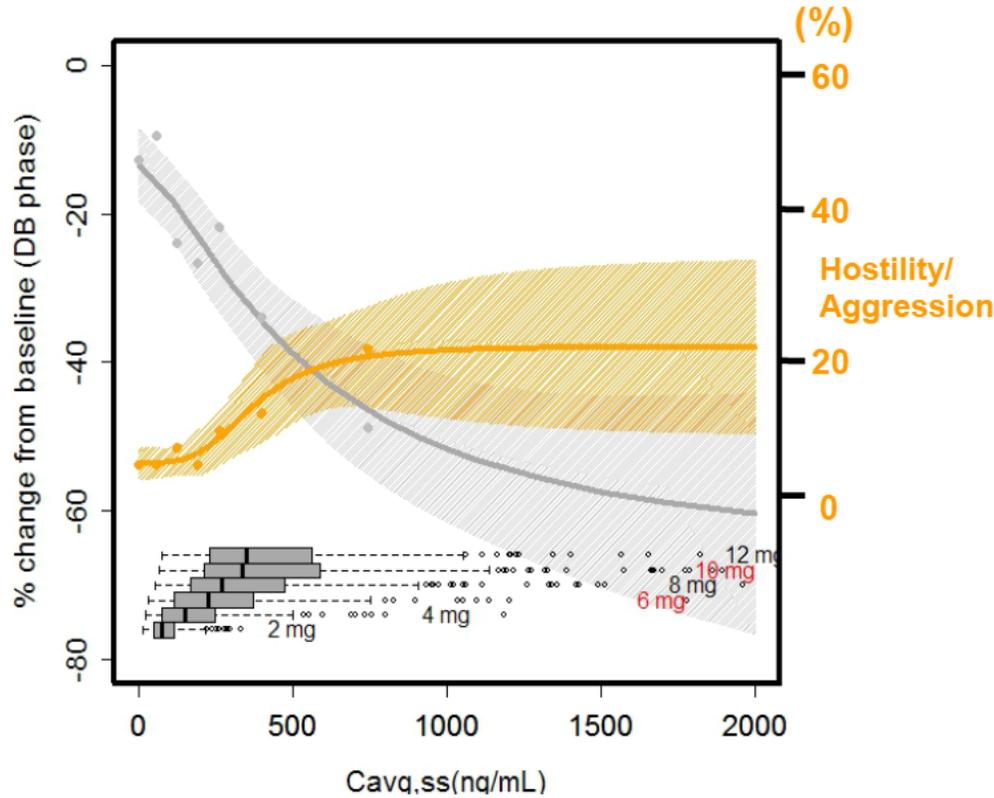


Table 13. Predicted % reduction in seizure frequency and %hostility/aggression-related adverse event based on the modeling results shown in Figure 9. The prediction was made at the median concentration at each dose. (6 mg and 10 mg were predicted based on the simulated exposure range).

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\pharma cometrics\
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

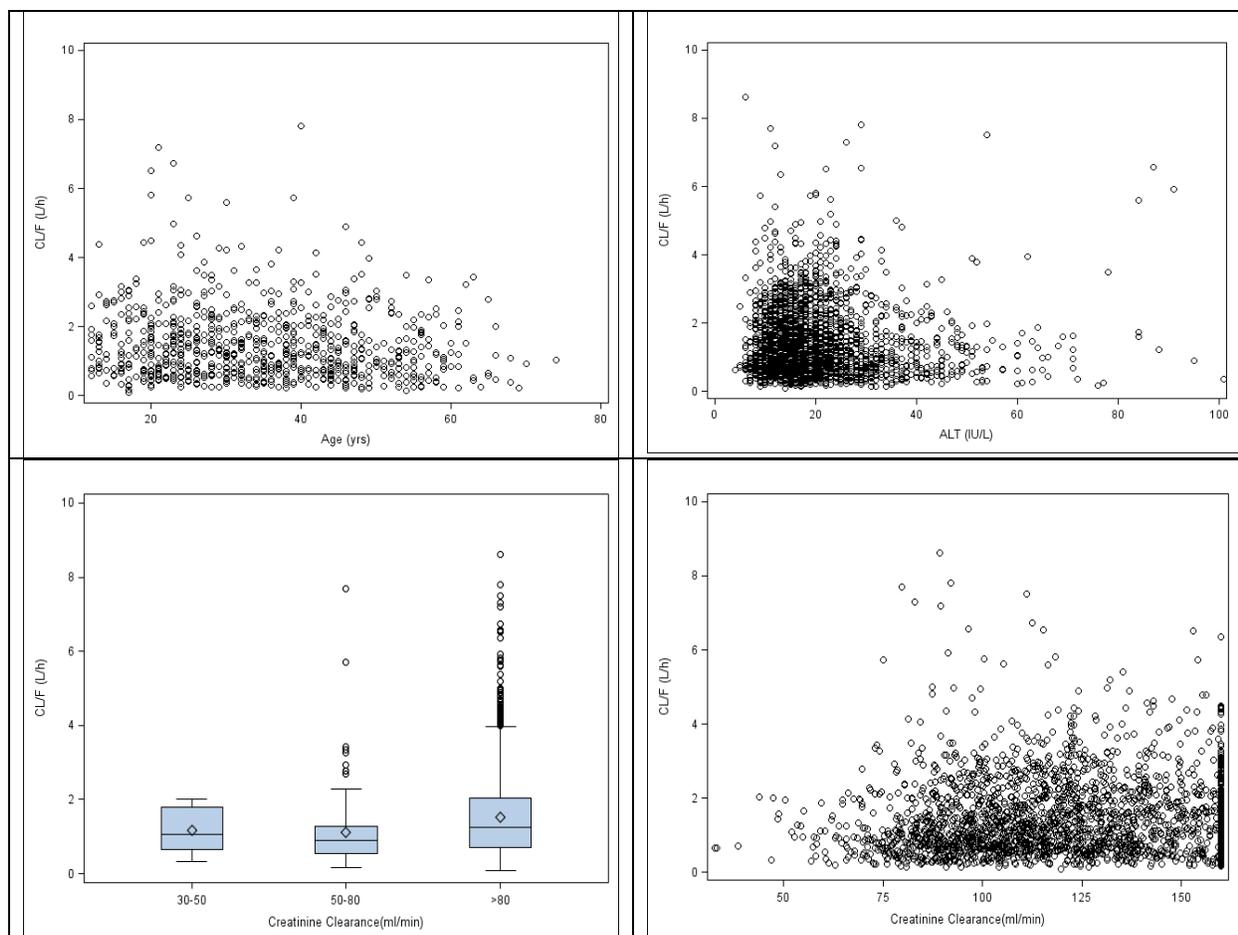
³⁾: Ratio to estimated value of subject whose FBM 17.1 kg

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			
<i>New Drug Application Filing and Review Form</i>			
<u>General Information About the Submission</u>			
	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. ¹⁴C-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. (b) (4) N=16 (b) (4) has similar AUC, but lower C_{max} and prolonged T_{max})
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 AUC_{0-t} and AUC_{0-inf}, but not C_{max} 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 C_{max} by 40% and prolonged T_{max} by ~2hr)
 - E2007-E044-009: SD 6 mg Formulation B, fasted vs. high fat, n=8 in each group (parallel design) (part 1) (No effect on AUC_{0-24hr}, reduced C_{max} by 28% and prolonged T_{max} 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: Time of Dosing (6mgx7d followed by 8 mgx7d then 10mgx7d, QD, morning or (part 2) evening dosing), n=8 in each group (C_{min} not affected by time of dosing)
 - E2007-E044-007: Mass Balance, SD 2 mg with ¹⁴C-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, peramp panel 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, C_{u,2 h} was 1.26-fold higher, t_{1/2} was 2.4-fold longer, and unbound AUC(0-inf) was 1.8-fold higher. For Child-Pugh B subjects, C_{u,2 h} was 1.18-fold higher, t_{1/2} 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 C_{max} of ethinylestradiol by <20%;
12 mg perampanel decreased levonorgestrel C_{max} 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		(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)		<ul style="list-style-type: none"> • 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	<p>Single oral doses:</p> <p><u>Perampanel tablets</u> (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)</p> <p><u>Placebo tablets</u> (N=13)</p>	55 healthy males age range, 18 – 45 y	<p>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.</p> <p>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.</p> <p>The safety, tolerability and pharmacokinetics of perampanel did not appear to be affected in poor metabolizers of CYP2D6 and CYP2C19.</p>
E2007-E044-003	Open-label, randomized, single-dose, two-way crossover study to evaluate the effect of food on PK and PD	<p>1 mg oral tablet (Formulation A); fasting</p> <p>1 mg oral tablet (Formulation A); fed</p>	24 healthy adults (12 males/12 females) age range, 19 – 41 y	<p>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.</p> <p>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.</p> <p>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.</p>
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	<p>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.</p>

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: <u>Perampanel tablets (N=56)</u> 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) <u>Placebo tablets (N=14)</u>	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	(b) (4)			

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 × 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: <u>Perampanel tablets</u> (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) <u>Placebo tablets</u> × 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-t) 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	<p><u>Single-dose phase: Part 1</u> Single-dose, randomized, active, and placebo-controlled parallel group, double-blind, double-dummy study to evaluate the impact of food on PK and PD</p> <p><u>Multiple-dose phase: Part 2</u> 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</p>	<p>6 mg perampanel (3 × 2 mg oral tablets, Formulation B); fasting</p> <p>6 mg perampanel (3 × 2 mg oral tablets, Formulation B); fed</p> <p>Oral placebo; fasting or fed</p> <p>Oral diazepam 5 mg</p> <p>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)</p> <p>Morning dosing (n=8)</p> <p>Evening dosing (n=8)</p> <p>Daily oral placebo (Days 1-21) (N=8)</p>	<p>8 healthy adults (7 males/1 female)</p> <p>8 healthy adults (7 males/1 female)</p> <p>8 healthy adults (6 males/2 females)</p> <p>7 healthy adults (6 males/1 female)</p> <p>8 healthy adults (4 males/4 females)</p> <p>8 healthy adults (4 males/4 females)</p> <p>4 healthy adults (2 males/2 females)</p>	<p>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 ($AUC_{(0-24h)}$) showed no noteworthy difference in the fed vs. fasted subjects.</p> <p>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.</p> <p>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.</p> <p>PSV parameters measured in the morning after evening dosing were less affected than after morning dosing of perampanel.</p> <p>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.</p>
E2007-J081-026	<p><u>Step 1:</u> QD dosing (Day1-14)</p> <p><u>Step 2:</u> QD dosing (Days 1-14)</p> <p>QD dosing (Days 15-28)</p>	<p><u>Formulation C:</u> Perampanel 2 mg QD Placebo 2 mg QD</p> <p>Perampanel 2 mg QD Placebo 2 mg QD Perampanel 4 mg QD Placebo 4 mg QD</p>	<p><u>healthy Japanese men:</u> n=9 n=3</p> <p>n=9 n=3</p> <p>(age range, 20 – 44 y)</p>	<p>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.</p> <p>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.</p> <p>At both the 2 mg and 4 mg doses, plasma perampanel concentrations showed an inverse correlation with PSV.</p>

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} , $AUC_{(0-t)}$, and $AUC_{(0-inf)}$ 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),s} 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 $AUC_{(0-inf)}$, C_{max} and $AUC_{(0-4)}$ 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 $t_{1/2}$ values were similar following perampanel plus levodopa and levodopa alone. The 90% CIs for both $AUC_{(0-inf)}$ 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) <u>Part A:</u> 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. <u>Part B:</u> 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 $AUC_{(0-24h)}$) 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 $AUC_{(0-24h)}$ 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 $AUC_{(0-24)}$ 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	<p>Perampanel 2 mg tablets (Formulation C)</p> <p><u>Part A:</u> single dose</p> <p>First treatment: Placebo, then alcohol Second treatment: Perampanel Cohort 1, 4 mg Cohort 2, 8 mg Cohort 3, 12 mg then alcohol (all cohorts)</p> <p><u>Part B:</u> QD dosing</p> <p>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</p>	<p>Healthy adults</p> <p>N=35 (22 males/13 females), (age range, 18 – 49 y)</p> <p>N=35</p> <p>N=12 N=12 N=11</p> <p>N=24 (18 males, 6 females), (age range, 20 – 47 y)</p> <p>N=18</p> <p>N=6</p>	<p>No formal PK analysis was performed.</p> <p>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.</p> <p>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.</p> <p>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</p>

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.	<p><u>Perampanel group:</u> 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)</p> <p><u>Placebo group:</u> Perampanel placebo QD (Days 1 – 16) Moxifloxacin placebo (Day 16)</p> <p><u>Moxifloxacin group:</u> Perampanel placebo QD (Days 1 - 16) Moxifloxacin 400 mg (Day 16)</p>	<p>257 healthy subjects, 129 males/128 females (age range, 18 – 55 y) N=107</p> <p>N=75</p> <p>N=75</p>	<p>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.</p> <p>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 $\Delta\Delta QTcF$ 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 $\Delta\Delta QTcF < 10$ msec). Similar results were observed with $\Delta\Delta QTcI$ and $\Delta\Delta QTcB$. Outlier analysis of absolute QTcF and $\Delta QTcF$ 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.</p>
E2007-E044-020	Randomized, placebo- and active-controlled, parallel group study to investigate the phototoxic potential of perampanel in healthy volunteers.	<p>Perampanel 2 mg tablets (Formulation C)</p> <p><u>10 days of treatment with:</u> Placebo QD</p> <p>Perampanel 6 mg QD</p> <p>Ciprofloxacin 500 mg BID (single evening dose on Day 1)</p>	<p>36 healthy subjects, 30 males/6 females (age range, 19 – 54 y)</p> <p>N=12</p> <p>N=12</p> <p>N=12</p>	<p>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.</p> <p>This study found no evidence that dosing healthy volunteers at 6 mg of perampanel induces skin phototoxicity to ultraviolet or visible light.</p>

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/s/

XINNING YANG
10/19/2012

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10/19/2012

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10/19/2012

TA-CHEN WU
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10/19/2012

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	202-834 (Resubmission/after refuse to file)
Submission Date:	12/22/11, 07/02/12, and 08/14/12
Brand Name:	Fycompa
Generic Name:	Perampanel
Formulation:	Oral immediately release (IR) tablet
Strength:	2, 4, 6, 8, 10, and 12 mg (six strengths)
Applicant:	Eisai Inc.
Type of submission:	Original/Standard
Reviewer:	Tien-Mien Chen, Ph.D.

SYNOPSIS

Background

Perampanel is an NME (new molecular entity) which is reported as a first-in-class, selective, non-competitive antagonist of the ionotropic α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor. Perampanel was identified and developed by Eisai, Inc.

Perampanel has been investigated for multiple indications including treatment of neuropathic pain, migraine prophylaxis, epilepsy, and Parkinson's disease. Development for the epilepsy indication was performed under IND 68,368.

Current Submission

On 5/25/11, Eisai submitted the Original NDA 202-384 for Fycompa (Perampanel) IR tablets for review, however, a refuse-to-file (RTF) letter was issued on 07/21/11. A RTF meeting was held on 09/26/11 to resolve the filing issues. The above NDA was resubmitted and the review clock started on 12/22/11.

Perampanel IR tablet is intended for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. The recommended target doses are between 4 mg/day and 12 mg/day. The product should be taken once daily before bedtime.

The resubmission of NDA 202-834 includes the Applicant's responses to the Biopharmaceutics issues raised in the RTF letter. On 07/02/12, additional information was provided to address the Biopharmaceutics comments included in an IR dated 06/07/12.

Biopharmaceutics Review

The Biopharmaceutics review is focused on the evaluation and acceptability of the information/data supporting; 1) the proposed dissolution method and acceptance criterion and 2) the biowaiver request for the 8 and 10 mg tablets.

Summary of Biopharmaceutics Findings and Conclusions:

The current NDA for perampanel IR tablet formulation proposed six strengths, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg. Tablet strengths 2 and 4 mg (Formulation C) (b) (4) and they had been tested clinically. The 6, 8, 10, and 12 mg tablet strengths (Formulation D) (b) (4) Formulations C and D are to same as the to-be-marketed ones. Tablet strengths 2, 4, 6, and 12 mg were employed in four *in vivo* Bioequivalence (BE) studies, but not the 8 and 10 mg tablet strengths. Upon request, a biowaiver request for 8 and 10 mg tablet strengths was submitted on 12/22/11.

Dissolution method and Acceptance Criteria:

The dissolution development report was provided in the NDA. It was reviewed and found acceptable. The proposed dissolution testing method and acceptance criterion for perampanel film-coated IR tablets of all six strengths are shown below.

Apparatus: USP 2 (Paddle) with 50 rpm
Dissolution Medium: 0.1 N HCl, 900 mL at 37°C
Analytical Method: UV detection at 320 nm and 640 nm
Acceptance Criterion: Q= (b) (4)

The dissolution is considered rapid, (b) (4) of perampanel dissolved in 15 min using the above proposed dissolution method. Additional dissolution data at 15 and 30 min from the primary stability batches were requested from the applicant, which still supported the dissolution acceptance criterion of Q (b) (4) at 15 min instead of the proposed (b) (4)

A teleconference was held on 08/09/12. At the end of the teleconference, the Applicant agreed 1). To revise the dissolution acceptance criterion from (b) (4) to Q (b) (4) at 15 min and 2). To update the specification section of the drug product, Module 32P51. The above updates were submitted to the FDA on 08/14/12.

Biowaiver:

All the proposed tablet strengths of perampanel dissolved (b) (4) in 15 min using the above proposed dissolution method. Therefore, the biowaiver request for the 8 and 10 mg tablets which were not tested clinically, is granted.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 202-834 for Fycompa IR Tablets is recommended for APPROVAL.

Tien-Mien Chen, Ph.D.
ONDQA Biopharmaceutics Reviewer

08/16/12

Date

Angelica Dorantes, Ph.D.
ONDQA Biopharmaceutics Team Leader

08/21/12

Date

CC: DARRTS/Resubmission NDA 202-834/RLostritto

PRODUCT QUALITY - BIOPHARMACEUTICS ASSESSMENT

BACKGROUND

Perampanel is an NME which is reported as a first-in-class, selective, non-competitive antagonist of the ionotropic α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor. It is also reported that activation of AMPA receptors by glutamate is responsible for most fast excitatory synaptic transmission in the brain. In *in-vitro* studies, perampanel inhibited AMPA-induced increase in intracellular calcium.

Perampanel was identified and developed by Eisai, Inc. It has been investigated for multiple indications including treatment of neuropathic pain, migraine prophylaxis, epilepsy, and Parkinson's disease. Development for the epilepsy indication was performed under IND 68,368.

CURRENT SUBMISSION

On 5/25/11, Eisai submitted NDA 202-384/N-000 for Fycompa (Perampanel) IR tablets for review, however, it was refused to file (RTF) initially on 07/21/11. An RTF meeting between the applicant and the Agency was held on 09/26/11 to resolve the issues. The above NDA was reactivated and the review clock started on 12/22/11.

The current NDA provides for perampanel IR tablet formulation to be available in six strengths, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg. Perampanel IR tablet is intended for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. The recommended target doses are between 4 mg/day and 12 mg/day. The product should be taken once daily before bedtime.

The NDA which was reactivated on 12/22/11 included the responses to Biopharmaceutics information request stated in the RTF letter, and further responses were submitted on 07/02/12 to respond to additional Biopharmaceutics information request dated 06/07/12. A teleconference was held on 08/09/12 with the applicant to discuss on setting a tighter dissolution acceptance criterion for Fycompa IR tablets. The Applicant agreed and submitted the revised Specifications to Module 3.2.P.5.1.

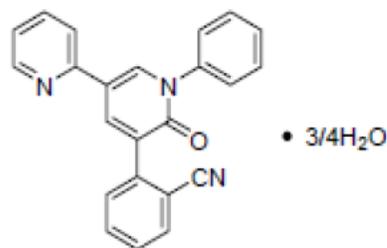
BIOPHARMACEUTICS REVIEW

This NDA and its responses to Biopharmaceutics information requests are reviewed here.

FORMULATION COMPARISONS

The molecular weight of perampanel is 362.90 (3/4 hydrate) and its chemical structure is shown below.

Figure 1. Chemical Structure of Perampanel



Perampanel is not chiral and its pKa is reported to be 3.24. The solubility of perampanel drug substance in aqueous solution is shown below.

Table 1. Solubility of Perampanel Drug Substance in Aqueous Solutions

Solvent	Value ($\mu\text{g/mL}$)
Aqueous Solutions at 25 °C (ionic strength (I)=0.3)	
pH 2 Britton-Robinson buffer	5.7×10
pH 3 Britton-Robinson buffer	7.2
pH 4 Britton-Robinson buffer	1.7
pH 5-7 Britton-Robinson buffer	1.3
pH 9-11 Britton-Robinson buffer	1.2
Aqueous Solutions at 37 °C^b	
0.1 mol/L HCl	4.7×10^2
pH 4.5 USP acetate buffer	2.2
pH 7.5 USP phosphate buffer	1.8

a: The saturated solubility was measured by HPLC.

b: The solubility at 37 °C was determined using the 15th batch (Lot 16091902).

The solubility of perampanel is higher in acidic conditions than neutral and basic conditions. Sink conditions using the highest strength (perampanel 12-mg film-coated tablet in 0.1 N HCl) were achieved at this dissolution medium proposed.

The dissolution profile was not improved

(b) (4)

Thus, the dissolution medium of 0.1 mol/L HCl was chosen (for all tablet strengths) because of the pH/solubility profile of perampanel and this medium mimics the gastric environment.

The proposed composition and formulations of Fycompa (perampanel) IR tablets (6 strengths) are shown below.

Table 2. Description of the Commercial Formulations of Perampanel IR Tablets

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

Source: 3.2.P.2.1.2.2, 3.2.P.2.2.1.1, and 3.2.P.2.2.1.1.5, Table 3.2.P.2.2-1

Fycompa formulations C and D are same as the to-be marketed (TBM) formulations. The composition/formulation of the Fycompa IR tablets are shown below.

Table 3. Composition of the Perampanel IR Tablet Formulations

Ingredient	Dosage Strength of Perampanel Film-coated Tablets						Function	Specification
	2 mg	4 mg	6 mg	8 mg	10 mg	12 mg		
Amount (mg)							(b) (4)	
								In-house (E2007)
								NF
								NF
								USP
								USP
								NF
								NF
								NF
								-
								In-house (03F43101)
								In-house (03F45059)
								In-house (03F44071)
								In-house (03F40008)
In-house (03F41127)								
In-house (03F40557)								
USP								
Total Weight (mg)	105	210	210	210	210	210	-	-

NF = National Formulary (U.S.), q.s. = quantum sufficit, USP = United States Pharmacopeia.

(b) (4)

b: Name as listed in European Pharmacopoeia.

c: (b) (4)

(b) (4)

Two and 4 mg IR tablets (Formulation C) (b) (4)

and were tested clinically. Four IR tablet strengths of Formulation D, i.e., 6, 8, 10, and 12 mg (b) (4)

and they have never been used in clinical trials. Four bioequivalence (BE) studies, however, were conducted;

BE study No. E2007-E044-016 comparing 1 x 4 mg and 2 x 2 mg
BE study No. E2007-E044-037 comparing 1 x 12 mg and 6 x 2 mg (Failed BE study)
BE study No. E2007-A001-039 comparing 1 x 6 mg and 3 x 2 mg
BE study No. E2007-A001-040 comparing 1 x 12 mg and 6 x 2 mg (Repeated BE study)

The BE studies are currently under review by the Office of Clinical Pharmacology (OCP). Strengths of 8 and 10 mg were not employed in clinical trial nor in the BE studies, therefore, a biowaiver for the above 8 and 10 mg strengths is needed, however, the biowaiver was not included in the original submission. An information request for the biowaiver and the comparative dissolution to support the biowaiver were included in the RTF letter dated 07/21/11. The applicant responded and the responses were included in the 12/22/11 resubmission.

DISSOLUTION METHODOLOGY AND ACCEPTANCE CRITERION

The dissolution development report was provided and reviewed. The proposed dissolution testing method and acceptance criterion for perampanel film-coated IR tablets of all six strengths are shown below.

Apparatus: USP 2 (Paddle) with 50 rpm
Dissolution Medium: 0.1 N HCl, 900 mL at 37°C
Analytical Method: UV detection at 320 nm and 640 nm
Timepoints: 5, 10, 15, 20, 30, and 45 minutes
Acceptance Criterion: Q= (b) (4)

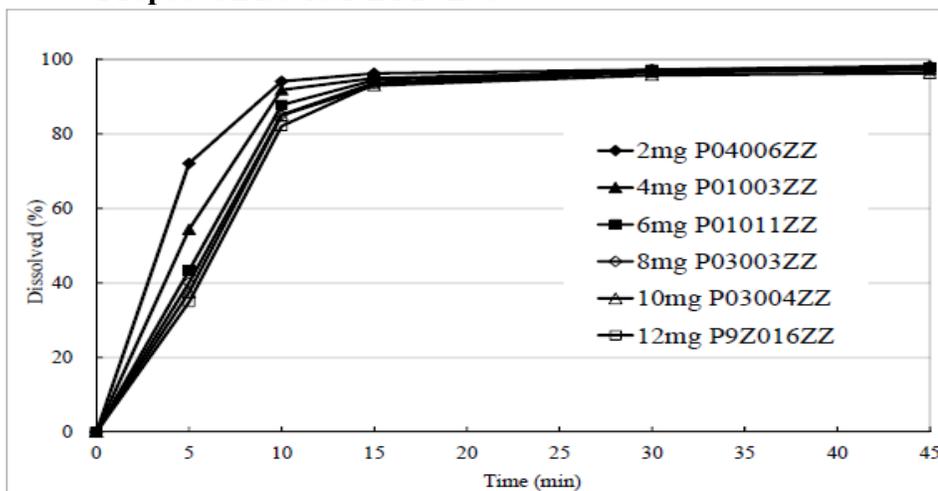
The dissolution profiles of perampanel 12 mg IR tablets in various dissolution media and rotation speeds are shown below.

Figure 2. Mean Dissolution Profiles of Perampanel 12 mg IR Tablets (lot No. P9Z016ZZ) in Various Dissolution Media and Rotation Speeds



Based on the above data, a paddle (USP Apparatus 2) with a rotational speed of 50 rpm and a dissolution medium of 900 ml of 0.1 N HCl at 37°C were selected. The mean comparative dissolution data/profiles for all the 6 strengths are summarized below.

Figure 3. Mean Comparative Dissolution Profiles of All 6 Strengths Using the Proposed Dissolution Method



Mean dissolution data of the 6 strengths are summarized below.

Table-4. Mean Dissolution Data of 2 mg Fycompa IR Tablets

Sampling Time (Min)	5	10	15	30	45
Mean (n=12)	72.0	94.1	96.2	97.2	98.2
SD	10.0	2.48	1.30	1.34	1.25
%CV	13.9	2.64	1.35	1.38	1.27

Table-5. Mean Dissolution Data of 4 mg Fycompa IR Tablets

Sampling Time (Min)	5	10	15	30	45
Mean	54.3	91.8	95.0	96.6	97.2
SD	7.45	1.98	1.24	0.95	1.01
%CV	13.7	2.16	1.30	0.98	1.04

Table-6. Mean Dissolution Data of 6 mg Fycompa IR Tablets

Sampling Time (Min)	5	10	15	30	45
Mean (n=12)	43.3	87.8	94.4	97.2	97.8
SD	4.37	3.30	1.80	1.16	1.10
%CV	10.1	3.76	1.91	1.20	1.12

Table-7. Mean Dissolution Data of 8 mg Fycompa IR Tablets

Sampling Time (Min)	5	10	15	30	45
Mean (n=12)	40.0	85.1	93.7	97.1	97.9
SD	3.26	3.49	1.70	1.03	0.96
%CV	8.15	4.10	1.82	1.06	0.98

Table-8. Mean Dissolution Data of 10 mg Fycompa IR Tablets

Sampling Time (Min)	5	10	15	30	45
Mean (n=12)	37.4	84.9	93.0	95.8	96.3
SD	3.68	3.90	1.69	0.63	0.54
%CV	9.84	4.59	1.82	0.65	0.56

Table-9. Mean Dissolution Data of 12 mg Fycompa IR Tablets

Sampling Time (Min)	5	10	15	30	45
Mean (n=12)	34.9	82.1	93.4	96.5	97.2
SD	3.54	5.86	1.88	0.83	0.88
%CV	10.1	7.13	2.02	0.86	0.90

All the tablet strengths dissolved ^{(b) (4)} in 15 min. Therefore, the biowaiver request for the 8 and 10 mg tablets which were not tested clinically, is granted.

Please see individual and mean dissolution data for the above 6 strengths in Appendix 2 for details. The batch information on the above 6 tablet strengths employed for comparative dissolution is summarized below.

Table 11. The Manufacturing Information on the Fycompa (Perampanel) IR Tablets of Six Strengths

Drug Product							
Dose Strength	Batch Number of Drug Product	Manufacture Date	Formulation Type	^{(b) (4)}	Batch Number of Drug Substance	Manufacturing Site	Remarks
2 mg	P04006ZZ	07 Apr 2010	C		19072201	Kawashima plant	Clinical Batch
4 mg	P01003ZZ	15 Jan 2010	C		19072201	Kawashima plant	Clinical Batch
6 mg	P01011ZZ	28 Jan 2010	D		19071501	Kawashima plant	Clinical + Stability Batch
8 mg	P03003ZZ	02 Mar 2010	D		19100503	Kawashima plant	Stability Batch
10 mg	P03004ZZ	02 Mar 2010	D		19100503	Kawashima plant	Stability Batch
12 mg	P9Z016ZZ	25 Dec 2009	D		19072901	Kawashima plant	Clinical Batch

The assay method employed in the dissolution testing was reviewed and found acceptable. Please see Appendix 1 for details.

Reviewer's Comments:

1. The dissolution is considered rapid. (b) (4) of perampanel dissolved in 15 min. Therefore, the proposed dissolution acceptance criterion of $Q = (b) (4)$ was not supported by the dissolution data submitted.

An information request was sent to the applicant on 06/07/12 requesting additional dissolution data at 15 min from the primary stability batches. The Applicant provided additional dissolution at both 15 and 30 min. The results showed that the submitted dissolution data (12 tablets/batch) on 07/02/12 supports $Q = (b) (4)$ at 15 min. However, the applicant still proposed (b) (4). Please see the dissolution data submitted on 07/02/12 for details.

A teleconference was held on 08/09/12 to discuss setting the dissolution acceptance criterion for Fycompa IR tablets. At the end of the teleconference, the Applicant agreed to revise the dissolution acceptance criterion (b) (4) to $Q = (b) (4)$ 15 min. On 08/14/12, the Applicant submitted the revised Specifications to update Module 3.2.P.5.1.

2. Since all tablet strengths of perampanel dissolved (b) (4) dissolved in 15 min, the biowaiver request for the 8 and 10 mg tablets which were not tested clinically, is granted.

**NDA 202-384/N-000 for Fycompa (Perampanel)
IR Capsules, 2, 4, 6, 8, 10, 12 mg**

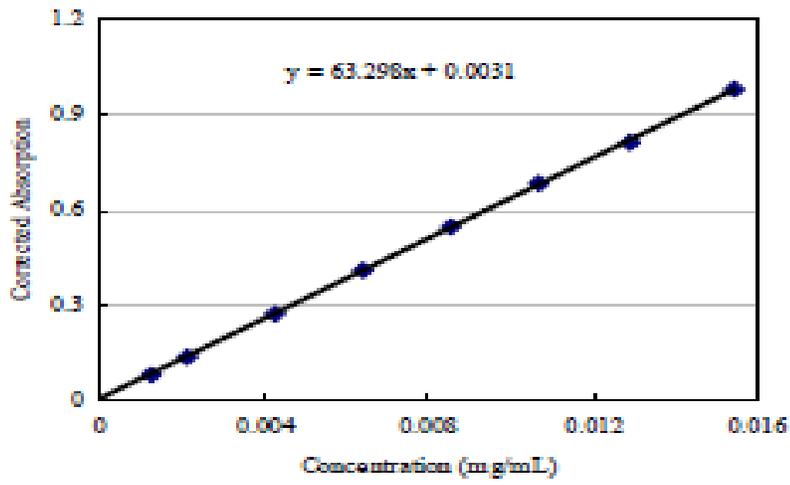
Appendix 1

**Validation of Analytical Method for
Dissolution Testing**

Table . Summary of Validation Results of Dissolution Testing

Validation Item	Acceptance Criteria (b) (4)	Results		
Specificity		2 mg matching placebo tablet: Met the criteria (1%)		
		4 mg matching placebo tablet: Met the criteria (1%)		
		6 mg matching placebo tablet: Met the criteria (0%)		
		8 mg matching placebo tablet: Met the criteria (0%)		
		10 mg matching placebo tablet: Met the criteria (0%)		
		12 mg matching placebo tablet: Met the criteria (0%)		
		Linearity	r=1.000	
Validation Item	Acceptance Criteria (b) (4)	Results		
Accuracy		2 mg tablet: 60%: 100.7% 80%: 99.3% 120%: 99.7%		
		4 mg tablet: 60%: 100.3% 80%: 99.7% 120%: 98.4%		
		6 mg tablet: 60%: 98.7% 80%: 98.6% 120%: 98.6%		
		8 mg tablet: 60%: 98.4% 80%: 98.5% 120%: 98.2%		
		10 mg tablet: 60%: 99.1% 80%: 99.4% 120%: 99.3%		
		12 mg tablet: 60%: 100.1% 80%: 98.8% 120%: 98.7%		
		Precision		2 mg tablet: 1) 0.86% 2) 1.15%
				4 mg tablet: 1) 0.43% 2) 1.09%
				6 mg tablet: 1) 0.39% 2) 0.64%
				8 mg tablet: 1) 0.50% 2) 0.86%
				10 mg tablet: 1) 0.38% 2) 0.63%
				12 mg tablet: 1) 0.45% 2) 0.79%
Range		Met the criteria within 60% to 120% of the nominal concentration level		
Stability of solutions		The time that met the acceptance criteria was at least 7 days.		

RSD = relative standard direction.



**NDA 202-384/N-000 for Fycompa (Perampanel)
IR Capsules, 2, 4, 6, 8, 10, 12 mg**

Appendix 2

**Individual and Mean Dissolution Data (n=12
tablets/batch, Mean Profile, and Batch
Information**

Figure 1 Super-imposed Dissolution Profiles of Perampanel 2, 4, 6, 8, 10 and 12 mg Tablets

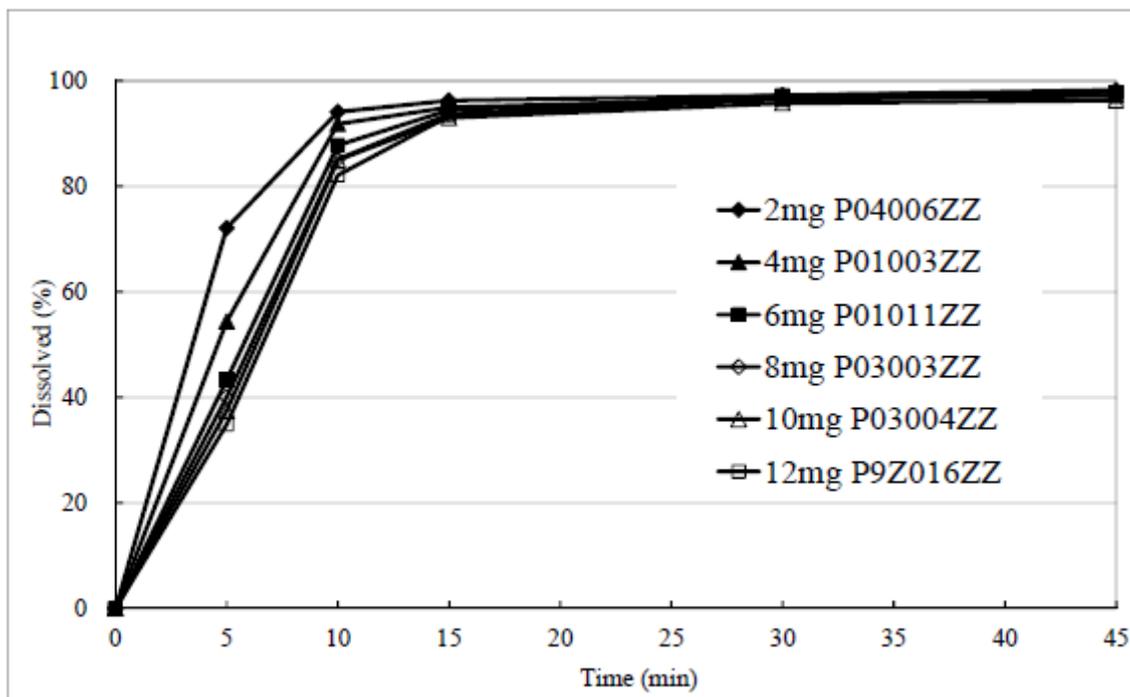


Table 1 Summary of f_1 and f_2 Calculations

Reference sample	Test sample	f_1 value	f_2 value
2 mg P04006ZZ	4mg: P01003ZZ	1	87
	6mg: P01011ZZ	3	70
	8mg: P03003ZZ	4	63
	10mg: P03004ZZ	5	62
	12mg: P9Z016ZZ	5	57

Please note: The dissolved percent at 10, 15 and 30 minutes was used for calculation.

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/s/

TIEN MIEN CHEN
08/22/2012

ANGELICA DORANTES
08/22/2012

Clinical Pharmacology Review

NDA:	202,834 (Sn 0008)
TYPE:	Type A
PRODUCT NAME:	Perampanel (E2007, FYCOMPA [®])
INDICATION:	Adjunct therapy for partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy (aged 12 and older)
DOSAGE FORM:	Tablet
DOSE STRENGTH:	2, 4, 6, 8, 10 and 12 mg
ROUTE of ADMINISTRATION:	Oral
SUBMISSION DATE:	08/05/2011
INTERNAL MEETING:	09/19/2011
SPONSOR MEETING:	09/26/2011
SPONSOR:	Eisai Inc.
REVIEWER:	Xinning Yang, Ph.D.
TEAM LEADER:	Angela Y. Men. M.D., Ph.D.

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INTRODUCTION:

Perampanel was recently submitted by the sponsor on May 25, 2011 under NDA 202,834, as adjunctive therapy for the treatment of partial-onset seizure in patients aged 12 years and older. A Refusal to File (RTF) letter was issued on July 21, 2011, citing issues regarding the content, format and organization of the NDA. Herein, the sponsor requests this Type A meeting to clarify the requests outlined in the RTF letter and to confirm with the Division that Eisai's proposals would adequately resolve all the RTF issues, both for content and timing, and will result in a successful resubmission of the NDA.

BACKGROUND:

Perampanel is a noncompetitive and highly selective 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. The dosing regimen proposed in labeling is a starting dose of 2 mg/day, increased based on clinical response and tolerability by 2 mg/day increments at weekly intervals to a dose of 4 mg to 12 mg/day.

The efficacy of perampanel was demonstrated by three Phase 3 pivotal trials. There were 27 Phase 1 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 were four Phase 2 trials and three open-label extension studies, with two Phase 2 studies having PK information. In addition, there were 4 population PK/PD reports, 16 bioanalytical validation reports and 20 *in vitro* studies. Please refer to the Clinical Pharmacology filing review archived by Dr. Xinning Yang in DARRTS under NDA 202-834 for the details about the Clinical Pharmacology studies.

Prior to filing NDA 202834, the sponsor ever submitted two formal pre-NDA meeting requests (October 2009 and September 2010) and a General Correspondence with pre-NDA type questions (May 2010) for written feedback. The Division declined both meeting requests and declined to respond to their written questions until data from at least two positive pivotal trials would be available.

QUESTIONS:

None of the questions are addressed to Clinical Pharmacology.

COMMENTS:

1 In study report for the relative BA study E2007-E044-028, you mentioned that the details on the analytical methodology, the method of validation, and the analytical within-study quality control procedures are included in Appendix 16.1.13. However, the appendix is not included. You should submit the sample analysis report for this study.

2. You need to submit the Bioanalytical Data Report (b) (4) Project Number (b) (4) 105673/1) for study E2007-E044-037. You also need to submit the bioanalytical reports for study E2007-E044-030, E2007-E044-023 and E2007-A001-024.

3. In your previous pre-NDA meeting request, you mentioned that the datasets from two Phase 1 studies (010 and 026) in Japanese healthy volunteers would not be translated or submitted. You should translate and submit the PK concentrations raw datasets in .xpt format, as well as the bioanalytical reports, in resubmission. In addition, you should submit the raw dataset of PK concentrations and bioanalytical report for the Phase 2 study (E2007-J081-231) that was conducted in Japanese patients.

4. There was no raw dataset of PK concentrations for these Clinical Pharmacology studies (001, 002 and 003). Please provide the datasets in .xpt format.

5. For bioequivalence studies (008 and 037), please provide dataset in .xpt format for PK parameters.

Meeting Discussion

The sponsor acknowledged the comments and confirmed that the requested reports and data will be included in the resubmission.

Xinning Yang, Ph.D.
Division of Clinical Pharmacology I

Team Leader: Angela Y. Men, M.D., Ph.D. _____

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/s/

XINNING YANG
12/29/2011

YUXIN MEN
12/30/2011

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology			
<i>New Drug Application Filing and Review Form</i>			
<u>General Information About the Submission</u>			
	Information		Information
NDA/BLA Number	N 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	5/25/2011	Route of Administration	Oral
Estimated Due Date of OCP Review	4/19/2012	Sponsor	Eisai Co.
Medical Division Due Date	4/26/2012	Priority Classification	Regular
PDUFA Due Date	3/25/2012		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

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.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

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. ¹⁴C-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. (b) (4), N=16 (b) (4) has similar AUC, but lower C_{max} and prolonged T_{max})
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 AUC_{0-t} and AUC_{0-inf}, but not C_{max} 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 C_{max} by 40% and prolonged T_{max} by ~2hr)
 - E2007-E044-009: SD 6 mg Formulation B, fasted vs. high fat, n=8 in each group (parallel design) (part 1) (No effect on AUC_{0-24hr}, reduced C_{max} by 28% and prolonged T_{max} 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: Time of Dosing (6mgx7d followed by 8 mgx7d then 10mgx7d, QD, morning or evening dosing), n=8 in each group (C_{min} not affected by time of dosing) (part 2)
 - E2007-E044-007: Mass Balance, SD 2 mg with ¹⁴C-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, C_{u,2 h} was 1.26-fold higher, t_{1/2} was 2.4-fold longer, and unbound AUC(0-inf) was 1.8-fold higher. For Child-Pugh B subjects, C_{u,2 h} was 1.18-fold higher, t_{1/2} was 2.1-fold longer, and the unbound AUC(0-inf) was 3.3-fold higher.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

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 C_{max} of ethinylestradiol by <20%;
12 mg perampanel decreased levonorgestrel C_{max} 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)

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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<i>Clin. Pharm. and Biopharm. Information</i>				
	“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		(b) (4) to Tablet
solution as reference:				
alternate formulation as reference:				

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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			
Filability and QBR comments				
	“X” if yes	Comments		
Application filable?	X			
Comments sent to firm?				
QBR questions (key issues to be considered)		<ul style="list-style-type: none"> • 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			

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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			

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	
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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.

Xinning Yang	July 12nd, 2011
Reviewing Clinical Pharmacologist	Date
Angela Y. Men	July 12nd, 2011
Team Leader/Supervisor	Date

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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	<p>Single oral doses:</p> <p>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)</p> <p>Placebo tablets (N=13)</p>	55 healthy males age range, 18 – 45 y	<p>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.</p> <p>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.</p> <p>The safety, tolerability and pharmacokinetics of perampanel did not appear to be affected in poor metabolizers of CYP2D6 and CYP2C19.</p>
E2007-E044-003	Open-label, randomized, single-dose, two-way crossover study to evaluate the effect of food on PK and PD	<p>1 mg oral tablet (Formulation A); fasting</p> <p>1 mg oral tablet (Formulation A); fed</p>	24 healthy adults (12 males/12 females) age range, 19 – 41 y	<p>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.</p> <p>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.</p> <p>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.</p>
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	<p>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.</p>

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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: <u>Perampanel tablets</u> (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) <u>Placebo tablets</u> (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	(b) (4)			

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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 × 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: <u>Perampanel tablets</u> (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) <u>Placebo tablets</u> × 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 ₍₀₋₁₂₎ 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.

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Study No.	Study Design and Objective	Treatments	Subjects	Key PK/PD Results/Conclusions
E2007-E044-009	<p><u>Single-dose phase: Part 1</u> Single-dose, randomized, active, and placebo-controlled parallel group, double-blind, double-dummy study to evaluate the impact of food on PK and PD</p> <p><u>Multiple-dose phase: Part 2</u> 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</p>	<p>6 mg perampanel (3 × 2 mg oral tablets, Formulation B); fasting</p> <p>6 mg perampanel (3 × 2 mg oral tablets, Formulation B); fed</p> <p>Oral placebo; fasting or fed</p> <p>Oral diazepam 5 mg</p> <p>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)</p> <p>Morning dosing (n=8)</p> <p>Evening dosing (n=8)</p> <p>Daily oral placebo (Days 1-21) (N=8)</p>	<p>8 healthy adults (7 males/1 female)</p> <p>8 healthy adults (7 males/1 female)</p> <p>8 healthy adults (6 males/2 females)</p> <p>7 healthy adults (6 males/1 female)</p> <p>8 healthy adults (4 males/4 females)</p> <p>8 healthy adults (4 males/4 females)</p> <p>4 healthy adults (2 males/2 females)</p>	<p>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 ($AUC_{(0-24h)}$) showed no noteworthy difference in the fed vs. fasted subjects.</p> <p>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.</p> <p>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.</p> <p>PSV parameters measured in the morning after evening dosing were less affected than after morning dosing of perampanel.</p> <p>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.</p>
E2007-J081-026	<p><u>Step 1:</u> QD dosing (Day1-14)</p> <p><u>Step 2:</u> QD dosing (Days 1-14)</p> <p>QD dosing (Days 15-28)</p>	<p><u>Formulation C:</u> Perampanel 2 mg QD Placebo 2 mg QD</p> <p>Perampanel 2 mg QD Placebo 2 mg QD Perampanel 4 mg QD Placebo 4 mg QD</p>	<p><u>healthy Japanese men:</u> n=9 n=3</p> <p>n=9 n=3</p> <p>(age range, 20 – 44 y)</p>	<p>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.</p> <p>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.</p> <p>At both the 2 mg and 4 mg doses, plasma perampanel concentrations showed an inverse correlation with PSV.</p>

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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-t) , and AUC _(0-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.

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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),s} 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.

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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 $AUC_{(0-inf)}$, C_{max} and $AUC_{(0-4)}$ 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 $t_{1/2}$ values were similar following perampanel plus levodopa and levodopa alone. The 90% CIs for both $AUC_{(0-inf)}$ 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) <u>Part A:</u> 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. <u>Part B:</u> 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 $AUC_{(0-24h)}$) 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 $AUC_{(0-24h)}$ 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 $AUC_{(0-24)}$ 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.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

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	<p>Perampanel 2 mg tablets (Formulation C)</p> <p><u>Part A:</u> single dose</p> <p>First treatment: Placebo, then alcohol Second treatment: Perampanel Cohort 1, 4 mg Cohort 2, 8 mg Cohort 3, 12 mg then alcohol (all cohorts)</p> <p><u>Part B:</u> QD dosing</p> <p>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</p>	<p>Healthy adults</p> <p>N=35 (22 males/13 females), (age range, 18 – 49 y)</p> <p>N=35</p> <p>N=12 N=12 N=11</p> <p>N=24 (18 males, 6 females), (age range, 20 – 47 y)</p> <p>N=18</p> <p>N=6</p>	<p>No formal PK analysis was performed.</p> <p>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.</p> <p>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.</p> <p>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</p>

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Study No.	Study Design and Objective	Treatments	Subjects	Key PK/PD Results/Conclusions
E2007-A001-023	Double-blind, ascending single-dose study designed to identify the MTD of perampanel in healthy recreational polydrug users with a history of psychedelic drug use	Perampanel 2 mg tablets (Formulation C) <u>Single doses of:</u> <u>Perampanel</u> 8 mg 12 mg 16 mg 20 mg 24 mg 28 mg 32 mg 36 mg Placebo	56 healthy polydrug users, 38 males/18 females, (age range 21 – 50 y) N=8 N=6 N=8 N=8 N=8 N=8 N=7 N=8 N=31	Mean perampanel plasma concentrations increased rapidly, with maximum concentrations occurring within 1 and 2 h postdose. Perampanel plasma concentrations declined in an apparently biphasic manner, and were still detectable in plasma at 72 h postdose for all doses. C _{max} and AUC _(0-∞) increased with increasing perampanel dose up to 28 mg. At 32 and 36 mg, C _{max} values were similar to that at 28 mg but the AUC _(0-∞) continued to increase. Median t _{max} values were 1 to 2 hours at most dose levels, but increased in some subjects to 4 h at some higher doses, indicative of slower absorption. Perampanel showed subjective effects distinguishable from placebo for Drug Liking, Good Drug Effects, Any Drug Effect, and Bad Drug Effects. Only Bad Drug Effects showed an apparent dose response, i.e., were more prominent at higher doses. A high degree of variability was observed in the PD responses.
E2007-A001-024	Randomized, double-blind, placebo- and active-controlled crossover study to evaluate the abuse potential of perampanel in healthy recreational polydrug users	<u>Phase 1, single oral doses:</u> Ketamine 100 mg Alprazolam 1.5 mg Placebo <u>Phase 2, single oral doses:</u> Perampanel 8 mg Perampanel 24 mg Perampanel 36 mg Alprazolam 1.5 mg Alprazolam 3 mg Ketamine 100 mg Placebo	40 healthy polydrug users (age range, 19 – 54 y) n=39 (PK data) n=34 (PD data)	Study validity was demonstrated by the statistically significant effects of alprazolam and ketamine compared to placebo on relevant abuse potential measures. Perampanel was also associated with statistically significant differences compared to placebo on the majority of primary and secondary measures, especially at the two higher doses. While 8 mg perampanel showed statistically lower effects compared to alprazolam and ketamine on most measures, the abuse potential profile of perampanel at the 24 mg and 36 mg doses was not statistically different from alprazolam on the primary measures or the majority of secondary measures. At the 24 mg and 36 mg doses, perampanel had statistically greater negative effects compared to alprazolam, and particularly at 24 mg and 36 mg, perampanel also had statistically greater other effects compared to alprazolam, such as floating, spaced out, visual clarity, and attention span. Perampanel also had statistically greater negative and sedative effects compared to 100 mg ketamine and demonstrated a different timecourse profile.

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/s/

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