Clinical Pharmacology Review

PRODUCT (Generic Name):	Perampanel
PRODUCT (Brand Name):	FYCOMPA®
NDA:	208-277
DOSAGE FORM:	Oral Suspension
DOSAGE STRENGTHS:	0.5 mg/mL
INDICATION:	Adjunctive therapy for partial-onset seizures or primary generalized tonic-clonic seizures in patients of 12 years old and above
SUBMISSION DATE:	06/30/2015
SPONSOR:	Eisai Co.
Clinical Pharmacology reviewer:	Xinning Yang, Ph.D.
TEAM LEADER:	Kevin Krudys, Ph.D. (Pharmacometrics) Angela Men, M.D., Ph.D.
OCP DIVISION:	DCP 1

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

Is the oral suspension formulation bioequivalent to the currently approved tablet formulation?

Yes. The suspension formulation was demonstrated to be bioequivalent to the tablet formulation under fasted condition and for AUC parameters of perampanel under fed state but not for C_{max} under fed state (on average 23% lower for the suspension formulation compared to tablet). However, based on population pharmacokinetic (popPK) simulated multiple-dosing scenario at steady state, the AUC and also C_{max} of perampanel were BE between treatments (i.e., before and after switching from one formulation/food intake status to another formulation/food intake status). Therefore, the difference in C_{max} observed in the single-dose evaluation is not considered to be clinically meaningful. In conclusion, the oral suspension formulation demonstrated comparable bioavailability as the tablet formulation and can be used interchangeably.

1.2 Recommendations

The Office of Clinical Pharmacology reviewers have reviewed the submission and find NDA 208-277 acceptable from Clinical Pharmacology's perspective provided that an agreement is reached between the Sponsor and the Agency regarding the recommended labeling language.

2 PERTINENT REGULATORY BACKGROUND

FYCOMPA® was approved as adjunctive therapy for treatment of partial-onset seizures (POS) with or without secondarily generalized seizures in patients aged 12 year and older under the original submission for NDA 202-834, and was later approved as adjunctive therapy for primary generalized tonic-clonic (PGTC) seizures in patients with epilepsy aged 12 years and older under an efficacy supplement submission (NDA 202-834/s005).

FYCOMPA® is currently available as film-coated tablets with multiple strengths - 2, 4, 6, 8, 10 and 12 mg. The sponsor also developed an oral suspension (OS) formulation as an alternative to the tablet formulation. The new formulation may address the needs of patients who are unable to or prefer not to swallow a solid oral dosage form. This submission does not contain a new efficacy or safety trial and the sponsor seeks OS approval solely relying on a pivotal bioequivalence (BE) study (Study E2007-A001-048) with supportive evidence from a popPK analysis. The sponsor pursues the same indications for OS formulation as those approved for tablet.

Study 048 was a randomized, open-label, 2-arm, single-dose, crossover study conducted in healthy subjects. Arm 1 compared the BE of a single 12-mg dose of perampanel OS to a single 12-mg dose of perampanel tablet under fasted conditions. Arm 2 compared the BE of a single 12-mg dose of perampanel OS to a single 12-mg dose of perampanel tablet when each was administered with a standard, high-fat meal.

In addition, results from a pilot relative bioavailability (BA) study (Study E2007-E044-028), a randomized, open-label, 2-period, 2-sequence crossover study comparing the PK of a single 4-mg dose of perampanel OS to a single 4-mg dose of perampanel tablet in healthy subjects, were provided. The OS formulation used in this pilot study was a 'prototype' suspension, different from the final formulation used in Study 048. Study 028 has been reviewed during the original NDA submission. The results are not included here since the relevance of this study to the current submission is remote.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Demonstration of Bioequivalence

The results from Study 048 demonstrated that both rate and extent of absorption (C_{max} and AUC) are BE between the OS and tablet formulations under fasted state (see Table 2 of Appendix 1). Under fed conditions, the extent of absorption (AUC) of the OS formulation was equivalent to the tablet formulation, whereas the rate of absorption from OS was slower with 23% lower C_{max} and 2-hours delay in T_{max} compared to tablet (see Table 4 of Appendix 1).. The clinical relevance of this reduction in C_{max} is further discussed in Section 3.3 and is deemed not clinically significant.

3.2 Food Effect

Based on cross-group comparisons, there was lack of significant food effect for the tablet formulation with a slight delay of 1 hour for the median T_{max} when given under fed state (see Table 5 of Appendix 1). As to the OS formulation, a high-fat meal reduced the $AUC_{(0-t)}$, $AUC_{(0-inf)}$, and C_{max} of perampanel by 10%, 13%, and 22%, respectively (see Table 6 of Appendix 1). The median T_{max} of perampanel was delayed by 2 hours.

In the original NDA submission (202-834) for the tablet formulation, the food effect was characterized in two studies which showed that the AUC of perampanel was not affected by a high-fat meal but the C_{max} was reduced by 40% (Study E2007-044-003) or 28% (E2007-044-009). The difference in the magnitude of C_{max} reduction observed from these studies (11% reduction in C_{max} from the current study) may be due to one or multiple factors of the followings: 1) nature of study design – cross-over (Study 003) vs. parallel groups (current study and Study 009); 2) number of subjects (n=24 in Study 003, n=8 for each group in Study 009, n = 36 - 49 for each group in the current study); 3) different tablet formulations used (formulation A in Study 003, formulation B in Study 009, and formulation D in the current study); 4) study variability. Nevertheless, the findings from the current study does not affect the dosing and administration recommended in the approved labeling, i.e., perampanel being taken regardless of food *at* bedtime, since 1) the extent of difference from this study is smaller compared to the previous results; 2) due to the long terminal half-life of perampanel (on average about 105 hours after single-dose administration), there is substantial accumulation of perampanel concentrations after multiple dosing. Thus, the difference in C_{max} observed in single-dose food effect study is anticipated to be smaller at steady state; 3) as a chronic treatment, the overall exposure (AUC) of perampanel may be more relevant to its efficacy than C_{max}.

For the OS formulation, although the food effect seemed to be larger than that for the tablet formulation, the OS formulation is expected to be BE in both C_{max} and AUC to the tablet at steady state, as indicated by the popPK analyses (see section 3.3). Therefore, it is acceptable to apply the dosing and administration recommended for tablet in the current labeling to the OS formulation.

3.3 Modeling and Simulation

PopPK analysis was conducted to simulate the PK profiles under multiple-dose, steady-state conditions. A population PK model was developed based on Study 048 data alone which captured the PK data reasonably well (see Table 7 and Figure 3 in Appendix 2). Simulations of concentration-time profiles were then performed using the popPK model for each scenario (suspension/tablet and fasted/fed) at steady-state (Day 27 after once daily dosing) and also on Day 28 (as a single-dose administration) following a "switch" in treatment as listed below.

- Tablet Fasted (Day 27) to Suspension Fasted (Day 28)
- Suspension Fasted (Day 27) to Tablet Fasted (Day 28)
- Tablet Fasted (Day 27) to Suspension Fed (Day 28)
- Suspension Fed (Day 27) to Tablet Fasted (Day 28)
- Tablet Fed (Day 27) to Suspension Fasted (Day 28)
- Suspension Fasted (Day 27) to Tablet Fed (Day 28)
- Tablet Fed (Day 27) to Suspension Fed (Day 28)
- Suspension Fed (Day 27) to Tablet Fed (Day 28)

One thousand (n=1000) concentration-time profiles were simulated for each treatment scenario in order to determine and compare the 90% prediction intervals on Day 27 (steady-state) and Day 28 (first day of change). For all scenarios (represented by switches between suspension under fed and tablet under fasted condition, see Figures 4 and 6 in Appendix 2), 90% prediction intervals on Day 27 and following the switch in treatment

on Day 28 were closely superimposed indicating that the steady-state exposure to perampanel was not affected by a change in either formulation or food with dosing at steady-state.

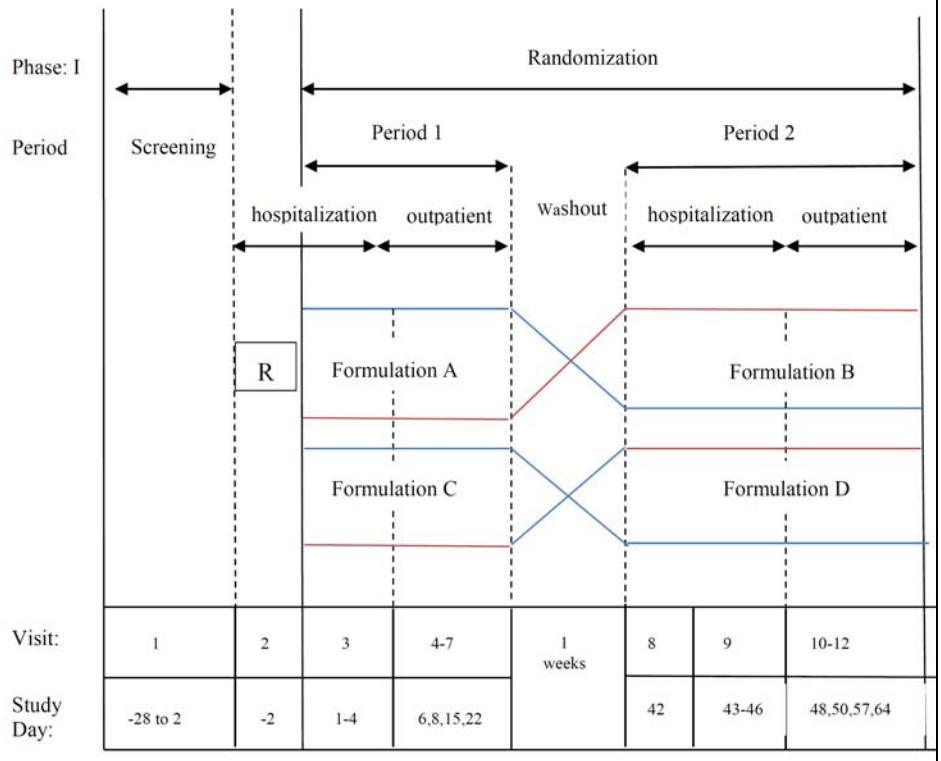
In addition, individual C_{min}, C_{max} and $AUC_{0\text{-}24hr}$ parameters were derived and a formal statistical analysis to evaluate BE following a switch in treatment at steady-state was performed. As represented by Forest plots (see Figures 7 and 8 in Appendix 2), the 90% confidence intervals (CI) of the geometric mean ratio (before and after the switch) for not only $AUC_{0\text{-}24hr}$ but also C_{max} are all falling within the 80% to 125% BE limit, indicating that the treatment on the first day after the switch (OS under fed state on Day 28) is equivalent to the treatment before the switch (tablet under fasted condition on Day 27). It is known that perampanel has a long half-life (on average ~105 hours) and there is substantial accumulation after multiple dosing, i.e., 4.3-fold accumulation for $AUC_{0\text{-}24hr}$, and 2.5-fold for C_{max} at steady state compared to single dose (please refer to the discussions in previous Clinical Pharmacology review for NDA 202-834). Thus, the ~23% difference in C_{max} observed between tablet and suspension formulations in the single dose BE evaluation under fed conditions becomes even smaller after multiple dosing.

Though not required for BE assessment, C_{min} was also evaluated, since it is often postulated to represent the exposure associated with efficacy. Compared to C_{max} and AUC, C_{min} showed larger variability. In all switching scenarios, the large majority of the 90% CI replicates for C_{min} were contained within BE limits. For the tablet (fasted) switching to suspension (fed) scenario, all the CIs substantially overlaid with the 0.8 to 1.25 BE limits; there were 3 CIs that were not completely contained within the equivalence limits. However, as shown in Figure 9 of Appendix 2, all 90% CIs of the 20 replicates substantially overlapped with the range limits. As to the other 7 scenarios, only 1 or 2 of the 20 replicates in each scenario were slightly outside the limit, also with substantial overlap with 0.8 to 1.25 limits (results not shown).

Though the sponsor performed simulation for all the scenarios as listed above, the current review only included the PK profiles and/or Forest plots for the scenarios switching from tablet administered under fasted state to the suspension given with food and *vice versa*. This pair of switches represents the 'worst' scenarios. As described in Section 3.1, after single-dose administration, the OS formulation resulted in lower C_{max} of perampanel compared to the tablet formulation (more obviously under fed state). As summarized in Section 3.2, a high-fat meal reduced exposure to perampanel for the tablet and more obviously for the OS formulation. Thus, the tablet formulation administered under fasted state and the OS formulation given under fed condition represent the boundary situations. The switches between these two reflect the largest change in PK parameters among all the scenarios.

Overall, the popPK analysis demonstrated that the small difference in C_{max} after single dose administration under fed conditions was not of clinical importance as evidenced by demonstration of BE for C_{max} and AUC_{ss} for various switching scenarios at the steady-state.

Appendix 1. Study E2007-A001-048: A Randomized, Open-Label, Crossover Study to Demonstrate Bioequivalence Between a 12-mg Dose of an Oral Suspension Formulation of Perampanel and a 12-mg Tablet Formulation of Perampanel Under Fasted and Fed Conditions in Healthy Subjects

Objective	*Primary:* To demonstrate bioequivalence (BE) between a single 12-mg dose of an oral suspension (OS) formulation of perampanel and a single 12-mg tablet formulation of perampanel when administered under fasted conditions. *Secondary:* • To evaluate bioequivalence between a single 12-mg dose of oral suspension formulation of perampanel and a single 12-mg tablet formulation of perampanel when both co-administered with a high-fat meal in healthy subjects • To evaluate and compare the PK profile, safety, and tolerability of a single 12-mg dose of an oral suspension formulation of perampanel with a single 12-mg tablet of perampanel under both fasted and fed conditions • To evaluate the effects of a high-fat meal on rate and extent of perampanel absorption following single dose administration of either a 12-mg dose of an oral suspension formulation of perampanel or a 12-mg tablet of perampanel
Study Design	This was an open-label, 2-arm, single-dose, randomized crossover study. In Arm 1, BE between the OS and tablet formulations of perampanel was evaluated under fasted conditions, whereas in Arm 2, BE between the two formulations was evaluated under fed conditions.  R = randomization Formulation A = Single oral dose of 1 x 12-mg perampanel tablet under fasted conditions. Formulation B = Single oral dose of 1 x 12-mg perampanel oral suspension under fasted conditions.

<table>
<tr><td></td><td>Formulation C = Single oral dose of 1 x 12-mg perampanel tablet under fed conditions.
Formulation D = Single oral dose of 1 x 12-mg perampanel oral suspension under fed conditions</td></tr>
<tr><td>Dosing & Administration</td><td>Arm 1: In both treatment periods, following an overnight fast of at least 10 hours, the subjects received a single oral dose of perampanel with 240 mL of water. No food was allowed for at least 4 hours after dosing. Water was allowed as desired except for 1 hour before and after drug administration.
Arm 2: In both treatment periods, following an overnight fast of at least 10 hours, subjects began the high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal 30 minutes before dosing; this test meal derived approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively. The meal was eaten in 30 minutes or less. All subjects were administered their assigned perampanel dose with 240 mL of water 30 minutes after the start of the meal, regardless of how much of the meal had been consumed at that point. If the meal had not been completed, the proportion not completed was recorded. No food was allowed for at least 4 hours after dosing. Water was allowed as desired except for 1 hour before and after dosing.</td></tr>
<tr><td>Study Population</td><td>Subjects were healthy adult males and females with a body mass index between 18 and 32 kg/m^2.</td></tr>
</table>

Category n (%)	Treatment Sequence AB (N=25)	Treatment Sequence BA (N=25)	Treatment Sequence CD (N=25)	Treatment Sequence DC (N=25)	Overall (N=100)
Age (year)[a]					
n	25	25	25	25	100
Mean (SD)	34.0 (11.13)	37.4 (11.33)	37.5 (10.08)	31.6 (8.62)	35.1 (10.48)
Median	30.0	35.0	38.0	32.0	33.5
Min, Max	19, 52	23, 55	20, 55	18, 49	18, 55
Sex, n (%)					
Female	14 (56.0)	13 (52.0)	12 (48.0)	10 (40.0)	49 (49.0)
Male	11 (44.0)	12 (48.0)	13 (52.0)	15 (60.0)	51 (51.0)
Ethnicity, n (%)					
Hispanic or Latino	13 (52.0)	15 (60.0)	12 (48.0)	14 (56.0)	54 (54.0)
Not Hispanic or Latino	12 (48.0)	10 (40.0)	13 (52.0)	11 (44.0)	46 (46.0)
Race, n (%)					
White	13 (52.0)	18 (72.0)	13 (52.0)	14 (56.0)	58 (58.0)
Black or African American	12 (48.0)	6 (24.0)	10 (40.0)	8 (32.0)	36 (36.0)
American Indian or Alaska Native				2 (8.0)	2 (8.0
Asian			2 (8.0)		2 (8.0)
Native Hawaiian or Other Pacific Islander		1 (4.0)			1 (1.0)
Multiple		1 (4.0)			1 (1.0)
Weight (kg)					
n	25	25	25	25	100
Mean (SD)	72.74 (11.991)	69.38 (10.993)	71.45 (11.274)	78.28 (14.155)	72.96 (12.431)
Median	73.70	69.10	71.00	81.80	71.55
Min, Max	55.3, 95.0	51.5, 98.0	52.8, 98.1	45.6, 95.7	45.6, 98.1

<table>
<tr><td>PK Assessments</td><td>Beginning on Day 1 of Treatment Period and Day 43 of Treatment Period 2, blood was 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, 336, and 504 hours post-dose.</td></tr>
<tr><td>Bioanalytical Methods</td><td>The bioanalytical method BTM-1076-R0 used to determine perampanel plasma concentrations was validated.
<table>
<tr><td>Analyte</td><td>Perampanel (ng/ml)</td></tr>
<tr><td>Method</td><td>LC-MS/MS</td></tr>
<tr><td>Internal Standard</td><td>ER-16761500</td></tr>
<tr><td>LLOQ</td><td>1</td></tr>
<tr><td>Calibration Range</td><td>1, 2, 5, 20, 100, 200, 400, 500</td></tr>
<tr><td>QC</td><td>3, 50, 380</td></tr>
<tr><td>Accuracy (%Actual)</td><td>97.6 – 101.3%</td></tr>
<tr><td>Precision (%CV)</td><td>3.6 – 4.1%</td></tr>
</table>
An ISR (Incurred Sample Reproducibility) evaluation was performed on a total of 252 study samples. All of the incurred samples met the acceptance criteria (i.e., at least 2/3 of all the analyzed ISR samples have no more than a ± 20.0% difference when compared to the original analysis results).</td></tr>
</table>

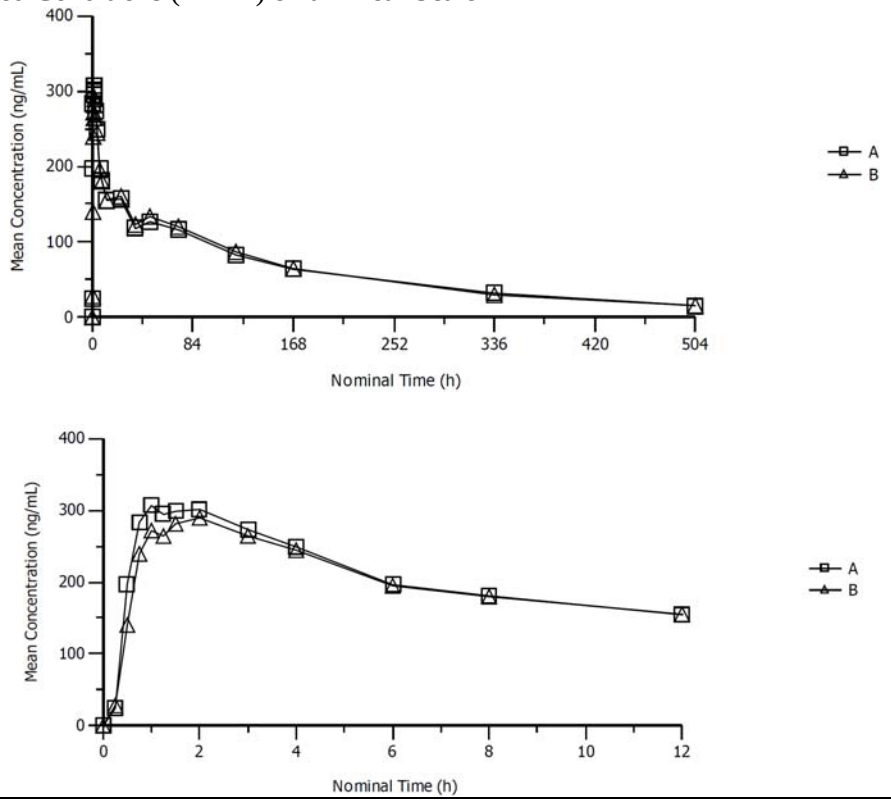
PK Results

All 100 randomized subjects were dosed in Period 1. Eleven subjects were not dosed in Period 2. The number of discontinuations was comparable across treatments.

1. BE under fasted condition

The OS formulation was demonstrated to be BE to the tablet formulation.

Figure 1. Perampanel Mean Plasma Concentration-Time Profiles after Treatments A and B under Fasted Conditions (Arm 1) on a Linear Scale



The OS formulation has similar or slightly larger variability (expressed as CV%) for the PK parameters under fasted condition.

Table 1. PK Parameters of Perampanel after Single Dose Administrations of Treatments A and B under Fasted Conditions (Arm 1)

Parameter	Treatment A: Perampanel 12-mg Tablet - Fasted				Treatment B: Perampanel 12-mg Oral Suspension - Fasted			
	n	Mean	SD	CV%	n	Mean	SD	CV%
t_{lag} (h)	49	0.00 (0.00-0.25)			48	0.00 (0.00-0.00)		
t_{max} (h)	49	1.00 (0.50-4.00)			48	2.00 (0.75-6.00)		
C_{max} (ng/mL)	49	376	115	30.6	48	348	137	39.5
$AUC_{(0-72)}$ (h*ng/mL)	49	10400	2420	23.3	48	10600	3130	29.5
$AUC_{(0-t)}$ (h*ng/mL)	49	29700	12300	41.4	48	30600	12700	41.6
$AUC_{(0-inf)}$ (h*ng/mL)	41	28900	11700	40.4	40	30000	14200	47.4
$\%AUC_{ex}$ (%)	44	7.61	5.94	78.1	45	8.06	7.54	93.6
λ_z (1/h)	44	0.00701	0.00372	53.1	45	0.00649	0.00360	55.4
$t_{1/2}$ (h)	44	122	50.5	41.6	45	134	63.6	47.3
t_{last} (h)	49	466.40	98.64	21.15	48	503.88	79.84	15.84
C_{last} (h)	49	17.1	16.3	95.4	48	15.7	15.5	98.6
CL/F (L/h)	41	0.498	0.229	46.1	40	0.477	0.191	40.0
V_z/F (L)	41	71.4	20.1	28.2	40	73.7	22.3	30.3

Median (range) reported for tlag and tmax.

Table 2. Statistical Analysis of the Natural Log-Transformed Plasma Exposure Parameters of Perampanel after Treatments A and B under Fasted Conditions (Arm 1)

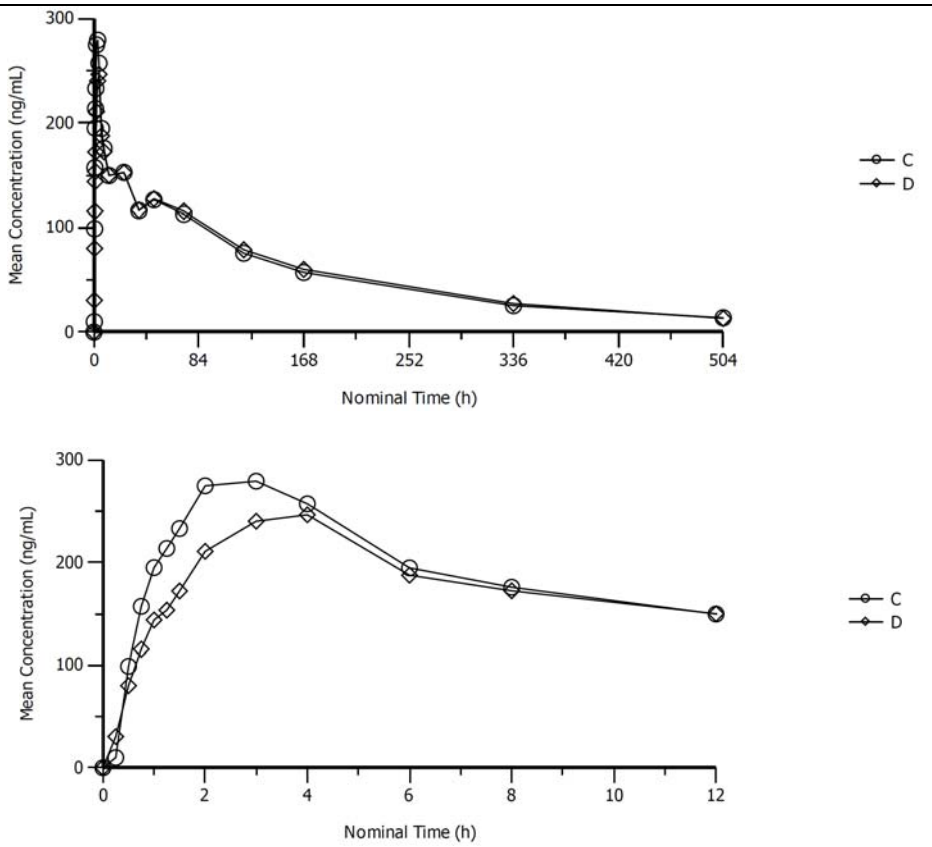
Dependent Variable	GeoMean [c] Test[a]	GeoMean [c] Ref[b]	Ratio (%)[d] (Test/Ref)	90% CI [e] Lower	90% CI [e] Upper
C_{max} (ng/mL)	329	365	90.01	84.28	96.12
$AUC_{(0-72)}$, (h*ng/mL)	10147	10100	100.47	96.77	104.31
$AUC_{(0-t)}$, (h*ng/mL)	27118	26765	101.32	97.01	105.82
$AUC_{(0-inf)}$, (h*ng/mL)	29565	29433	100.45	96.21	104.88

a: Test = 12-mg Perampanel Oral Suspension-Fasted
b: Ref = 12-mg Perampanel Tablet-Fasted
c: Geometric Mean for Test and Ref based on Least Squares Mean of log-transformed parameter values
d: Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
e: 90% Confidence Interval

2. BE under fed state

The OS formulation was BE to the tablet formulation in terms of AUC but not for C_{max}. On average, the OS formulation has about 23% lower C_{max} than the tablet formulation.

Figure 2. Perampanel Mean Plasma Concentration-Time Profiles after Single Dose Administration of Treatments C and D under Fed Conditions (Arm 2) on a Linear Scale



The OS formulation has similar or slightly larger variability (expressed as CV%) for the PK parameters under fed state.

Table 3. Pharmacokinetic Parameters of Perampanel after Single Dose Administration of Treatments C and D under Fed Conditions (Arm 2)

Parameter	Treatment C: Perampanel 12-mg Tablet - Fed				Treatment D: Perampanel 12-mg Oral Suspension - Fed			
	n	Mean	SD	CV%	n	Mean	SD	CV%
t_{lag} (h)	45	0.00 (0.00-0.50)			47	0.00 (0.00-0.00)		
t_{max} (h)	45	2.00 (0.75-6.00)			47	4.00 (2.00-12.00)		
C_{max} (ng/mL)	45	332	83.7	25.2	47	263	61.4	23.3
$AUC_{(0-72)}$ (h*ng/mL)	45	10100	1650	16.4	47	9930	2030	20.4
$AUC_{(0-t)}$ (h*ng/mL)	45	27300	9520	34.9	47	27800	12100	43.3
$AUC_{(0-inf)}$ (h*ng/mL)	36	26300	9040	34.4	40	27600	12900	46.8
$\%AUC_{ex}$ (%)	41	7.87	7.30	92.8	43	7.01	6.30	89.9
λ_z (1/h)	41	0.00729	0.00410	56.2	43	0.00776	0.00418	53.9
$t_{1/2}$ (h)	41	122	57.6	47.1	43	116	55.8	48.2
t_{last} (h)	45	462.97	88.88	19.20	47	454.06	98.44	21.68
C_{last} (h)	45	14.9	13.3	89.2	47	14.5	13.8	95.2
CL/F (L/h)	36	0.522	0.212	40.7	40	0.532	0.244	45.8
V_z/F (L)	36	70.5	15.2	21.6	40	69.5	19.5	28.1

Median (range) reported for tlag and tmax.

Table 4. Statistical Analysis of the Natural Log-Transformed Plasma Exposure Parameters of Perampanel after Treatments C and D under Fed Conditions (Arm 2)

Dependent Variable	GeoMean [c] Test[a]	GeoMean [c] Ref[b]	Ratio (%)[d] (Test/Ref)	90% CI [e] Lower	90% CI [e] Upper
C_{max} (ng/mL)	255	329	77.46	72.41	82.85
$AUC_{(0-72)}$, (h*ng/mL)	9754	9916	98.36	94.36	102.54
$AUC_{(0-t)}$, (h*ng/mL)	24734	24765	99.88	94.56	105.50
$AUC_{(0-inf)}$, (h*ng/mL)	26159	26309	99.43	93.64	105.59

a: Test = 12-mg Perampanel Oral Suspension-Fed
b: Ref = 12-mg Perampanel Tablet-Fed
c: Geometric Mean for Test and Ref based on Least Squares Mean of log-transformed parameter values
d: Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
e: 90% Confidence Interval

3. Food Effect

The food effect was evaluated based on cross-group comparisons. There was no significant food effect on the absorption of perampanel after administration of the tablet formulation. The absorption of perampanel was slightly delayed (by 1-hr in median T_{max}) under fed state.

As to the OS formulation, under fed state, there was an average reduction of approximately 10%, 13%, and 22% in $AUC_{(0-t)}$, $AUC_{(0-inf)}$, and C_{max}, respectively, relative to fasted condition. The median T_{max} was delayed by 2 hours under fed state.

Table 5. Statistical Analysis of the Natural Log-Transformed Plasma Exposure Parameters of Perampanel after 12-mg Perampanel Tablet Under Fed Conditions (Treatment C) and 12-mg Perampanel Tablet under Fasted Conditions (Treatment A)

Dependent Variable	GeoMean [c] Test[a]	GeoMean [c] Ref[b]	Ratio (%)[d] (Test/Ref)	90% CI [e] Lower	90% CI [e] Upper
C_{max} (ng/mL)	322	363	88.73	80.98	97.22
$AUC_{(0-72)}$, (h*ng/mL)	9932	10148	97.87	91.32	104.89
$AUC_{(0-t)}$, (h*ng/mL)	25613	27164	94.29	82.29	108.04
$AUC_{(0-inf)}$, (h*ng/mL)	26530	27998	94.76	81.50	110.17

Note: t1/2 and parameters based on extrapolation could not be calculated for all subjects; statistical analysis is based on n = 92 for C_{max}, $AUC_{(0-72)}$, $AUC_{(0-t)}$, and n = 84 for $AUC_{(0-inf)}$
a: Test = 12-mg Perampanel Tablet-Fed
b: Ref = 12-mg Perampanel Tablet-Fasted
c: Geometric Mean for Test and Ref based on Least Squares Mean of log-transformed parameter values
d: Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
e: 90% Confidence Interval

Table 6. Statistical Analysis of the Natural Log-Transformed Plasma Exposure Parameters of Perampanel after 12-mg Perampanel Oral Suspension Under Fed Conditions (Treatment D) and 12-mg Perampanel Oral Suspension under Fasted Conditions (Treatment B)

Dependent Variable	GeoMean [c] Test[a]	GeoMean [c] Ref[b]	Ratio (%)[d] (Test/Ref)	90% CI [e] Lower	90% CI [e] Upper
C_{max} (ng/mL)	257	330	77.92	70.40	86.23
$AUC_{(0-72)}$, (h*ng/mL)	9674	10237	94.51	87.26	102.36
$AUC_{(0-t)}$, (h*ng/mL)	24881	27701	89.82	77.65	103.90
$AUC_{(0-inf)}$, (h*ng/mL)	25933	29947	86.59	73.32	102.28

Note: t1/2 and parameters based on extrapolation could not be calculated for all subjects; statistical analysis is based on n = 91 for C_{max}, $AUC_{(0-72)}$, $AUC_{(0-t)}$, and n = 87 for $AUC_{(0-inf)}$

a: Test = 12-mg Perampanel Oral Suspension-Fed b: Ref = 12-mg Perampanel Oral Suspension-Fasted c: Geometric Mean for Test and Ref based on Least Squares Mean of log-transformed parameter values d: Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref) e: 90% Confidence Interval Reviewer's note: According to the reviewers from Office of Study Integrity and Surveillance who conducted the inspection at the bioanalytical site, the bioanalytical data of this study were found to be reliable.	
Conclusions	• The oral suspension formulation of perampanel is bioequivalent to the perampanel tablet formulation administered as single 12-mg doses under fasted conditions. • Under fed conditions, bioequivalence criteria were met for AUC parameters, but the Cmax for the perampanel suspension was approximately 23% lower than that for the tablet. • There was a slightly slower rate of absorption from the oral suspension formulation of perampanel relative to the perampanel tablet, as demonstrated by an approximately 1-hour delay in Tmax under fasted conditions and a 2-hour delay in Tmax when administered with a high-fat meal. • A high-fat meal has no significant effect on the absorption for the 12-mg perampanel tablet. • A high-fat meal resulted in slightly lower perampanel exposure for the 12-mg oral suspension of perampanel, relative to fasted conditions, as demonstrated by an approximately 22% and 13% decrease in mean Cmax and $AUC_{(0\text{-inf})}$ values of perampanel, respectively.

Appendix 2. Study Report CPMS-E2007-010R: Population Pharmacokinetics of Perampanel 12mg Oral Suspension & Tablet Formulation in Fed & Fasted Healthy Subjects

Objectives:

- To characterize the population pharmacokinetics (PK) of perampanel in fed and fasted subjects receiving single dose oral suspension and tablet formulations
- To simulate plasma perampanel concentration-time profiles for the purpose of assessing the impact of "switching" between the tablet and suspension formulation on steady-state exposure parameters (C_{max}, C_{min}, AUC) under both fasted and fed conditions.
- To evaluate bioequivalence (BE) at steady-state for C_{max}, C_{min}, AUC between suspension and tablet formulations under both fed and fasted conditions at steady-state.

Sponsor's Analyses:

Model based analysis consisted of a population PK model for perampanel using the data from Study 048 data alone, which was performed using NONMEM version 7.2 interfaced with PDxPop 5.0. This was a first-order absorption and 2-compartment disposition model with additional parameters included for rate of absorption (Ka) and relative extent of absorption ($F1_{rel}$) for suspension/tablet formulation in the presence or absence of food. The condition tablet/fasted was the reference treatment. No covariate analysis was performed for the purpose of this population PK analysis.

As previously shown and in line with the half-life of perampanel, once daily up to 27 days was adequate to reach steady-state. Based on the final population PK model for perampanel in subjects receiving single dose perampanel, steady-state profiles following perampanel 12 mg/day were simulated up to Day 27, and then on Day 28 following a switch in treatment. For purposes of completeness, all switch scenarios (suspension, tablet, fasted, fed) were simulated, as summarized below. For each scenario a sample of 1000 subjects were simulated, for the purposes of generating 20 replicates of 50 subjects each. The selection of replicates of 50 was based on the number of subjects planned for Study 048.

- Tablet Fasted (Day 27) to Suspension Fasted (Day 28)
- Suspension Fasted (Day 27) to Tablet Fasted (Day 28)
- Tablet Fasted (Day 27) to Suspension Fed (Day 28)
- Suspension Fed (Day 27) to Tablet Fasted (Day 28)
- Tablet Fed (Day 27) to Suspension Fasted (Day 28)
- Suspension Fasted (Day 27) to Tablet Fed (Day 28)
- Tablet Fed (Day 27) to Suspension Fed (Day 28)
- Suspension Fed (Day 27) to Tablet Fed (Day 28)

Simulated perampanel concentration-time profiles on Day 27 and Day 28 for each of the 1000 virtual subjects for each scenario were used to determine perampanel 90% prediction intervals on Days 27 and 28. In addition individual C_{min}, C_{max} and AUC

parameters were derived and a formal statistical analysis to evaluate BE following a switch in treatment at steady-state was performed.

Results:

1. Modeling

The population PK model reasonably well described perampanel concentration-time profiles following 12 mg single dose tablet or suspension formulation in either fed or fasted state. Model parameters are presented in Table 7. Goodness-of-fit-plots are presented in Figure 3.

Table 7. Final Model Population Pharmacokinetic Parameter Estimates of Perampanel

		NONMEM Estimates		
Parameter [Units]	**Point Estimate**	**%RSE**	**95% CI**	
CL [L/h] = Θ_{CL}				
Basal CL in L/h [Θ_{CL}]	0.437	5.74	0.388-0.486	
Vc [L] = Θ_{V1}				
Basal V1 in L [Θ_{V1}]	25.7	5.68	22.8-28.6	
Q [L/h] = Θ_{Q}				
Basal Q in L/h [Θ_{Q}]	7.41	5.10	6.67-8.15	
Vp [L] = Θ_{V2}				
Basal V2 in L [Θ_{V2}]	49.2	4.82	44.6-53.8	
Ka [1/h] = Θ_{Ka}				
$Ka_{Tablet/fasted}$ in 1/h [$\Theta_{Ka, Tablet/Fasted}$]	1.19	11.4	0.923-1.46	
$Ka_{Tablet/fed}$ in 1/h [$\Theta_{Ka, Tablet/Fed}$]	0.649	12.7	0.487-0.811	
$Ka_{Suspension/ fasted}$ in 1/h [$\Theta_{Ka, Suspension/ fasted}$]	0.807	8.43	0.674-0.940	
$Ka_{Suspension/fed}$ in 1/h [$\Theta_{Ka, Suspension/fed}$]	0.355	7.86	0.300-0.410	
F1rel = Θ_{F1rel}				
$F1rel_{Tablet/Fasted}$ [Θ F1rel, Tablet/Fasted]	1 (Reference)	--	--	
$F1rel_{Tablet/Fed}$ [Θ F1rel, Tablet/Fed]	1.04	4.20	0.954-1.13	
$F1rel_{Suspension/ fasted}$ [Θ F1rel, Suspension/ fasted]	1.01	2.07	0.969-1.05	
$F1rel_{Suspension/ fed}$ [Θ F1rel, Suspension/ fed]	1.04	4.54	0.947-1.13	
Inter-individual variability				CV%
CL	0.235	13.4		48.5
V1	0.120	20.3		34.6
V2	0.0987	25.0		31.4
Ka	0.215	21.9		46.4
F1rel	0.0149	32.8		12.2
Residual variability				CV%
Proportional	0.0857			29.3%

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CL = Clearance, Vc = volume of central compartment, Vp = volume of peripheral compartment, Q = inter-compartment clearance from Vc to Vp, Ka = Absorption rate, F1rel=Relative bioavailability

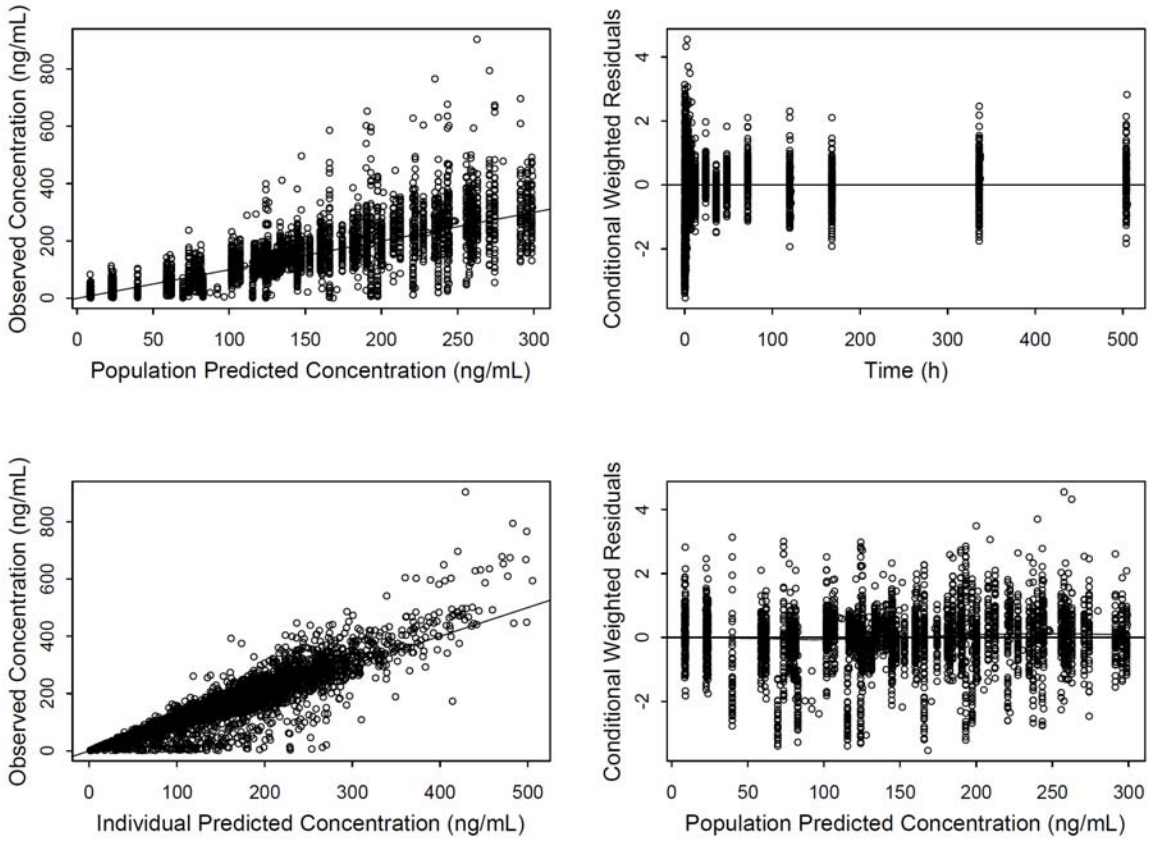
(from page 10 in Sponsor's Study Report CPMS-E2007-010R

The reviewer was able to reproduce the PK parameter estimations as shown in Table 7.)

As shown in the table, the rate of absorption was slower in the presence of a high fat meal and also slower for the suspension formulation compared to tablet, as evidenced also in the non-compartmental analysis (NCA) of Study 048 PK data.

With the reference formulation of tablet/fasted, $F1_{rel}$ was estimated to be 1.04 [95% CI: 0.954-1.13], 1.01 [95% CI: 0.969-1.05] and 1.04 [95% CI: 0.947-1.13] for tablet/fed, suspension/fasted and suspension/fed treatments, respectively. In all cases, 95% CI covered unity for $F1_{rel}$ and fall within the range of 0.8 to 1.25. Therefore, according to the model, the extent of perampanel absorption for all treatments was equivalent to that of the tablet/fasted treatment. This is in agreement with the results from the statistical analysis for AUC from the NCA.

Figure 3. Goodness-of-fit-plots for Perampanel Study 048 Final Population PK Model

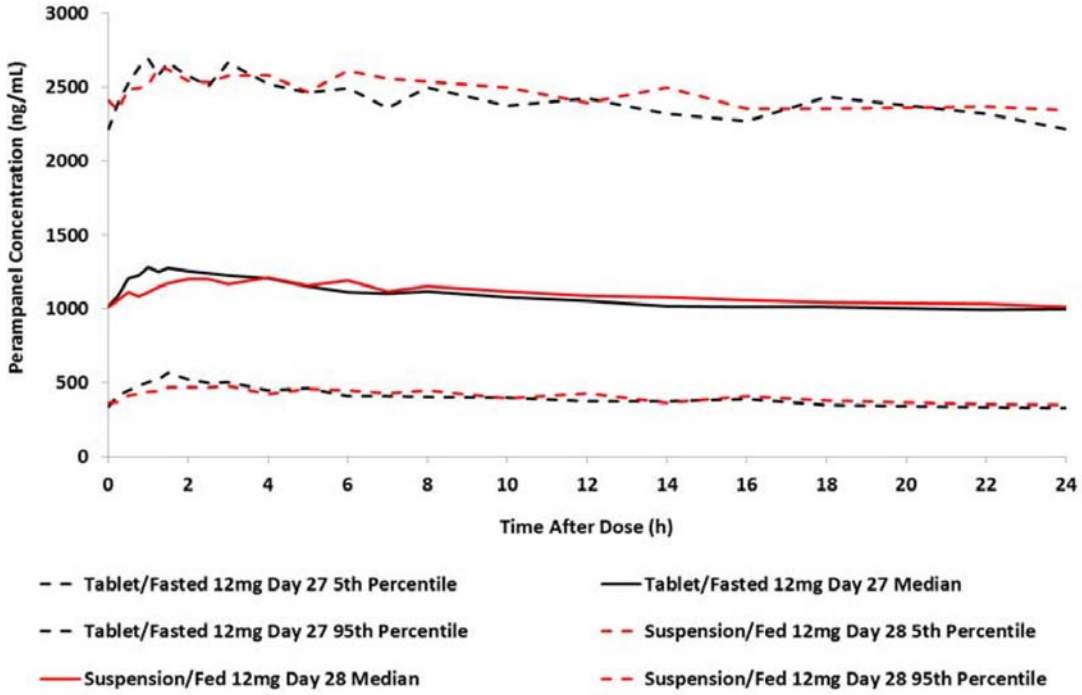


(from page 9 in Sponsor's Study Report CPMS-E2007-010R)

2. Simulation

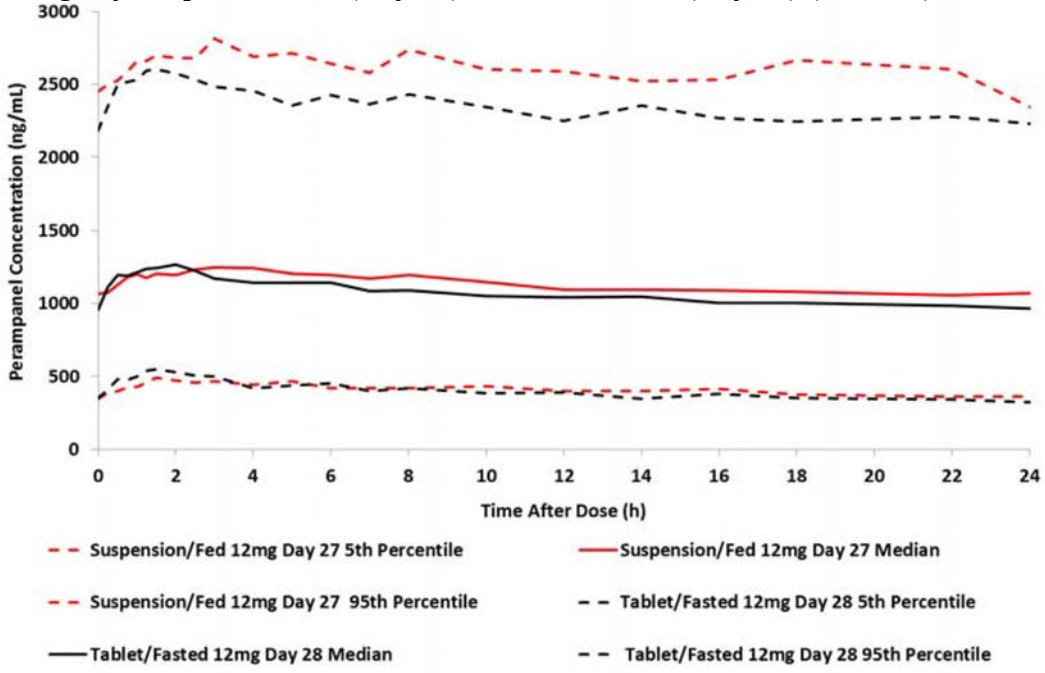
For each treatment condition on Day 27 following repeated dosing and on Day 28 following the switch in treatment, 90% prediction intervals for the concentration-time profiles (N=1000) were plotted. Herein, only the results for switching from tablet administered under fasted state to the suspension given with food and *vice versa* are included. This pair of switches represents the largest change among all the scenarios based on the NCA results and above popPK modeling analysis.

Figure 4. Perampanel Predicted Concentration-time Profile at Steady-State following 12mg/day Tablet/Fasted (Day 27) & Suspension/Fed (Day 28) (N=1000)



(from page 12 in Sponsor's Study Report CPMS-E2007-010R)

Figure 5. Perampanel Predicted Concentration-time Profile at Steady-State following 12mg/day Suspension/Fed (Day 27) & Tablet/Fasted (Day 28) (N=1000)



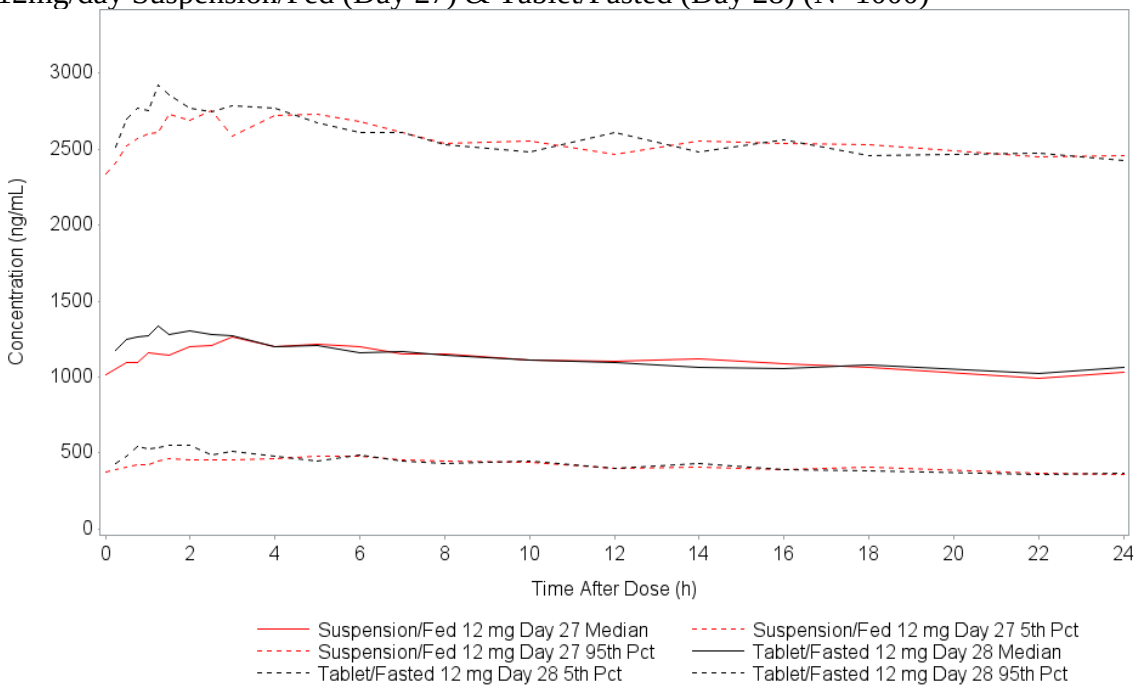
(from page 12 in Sponsor's Study Report CPMS-E2007-010R)

For all treatments (results only shown for switches between suspension under fed and tablet under fasted condition), 90% prediction intervals on Day 27 and following the switch in treatment on Day 28 were closely superimposed indicating that the steady-state exposure to perampanel was not affected by a change in either formulation or food with dosing at steady-state.

(*Reviewer's Comment:* Figure 5 (from the sponsor's study report) appears to be inconsistent with expectation. First, as shown by Study 048, formulation or food intake status had no or minimal impact on the AUC of perampanel. However, the predicted 95th of PK concentrations from suspension/fed, as shown above, are always higher than those from tablet/fasted. The PK profiles should have been close to those in Figure 4 with similar AUC between the two treatments. Secondly, the C_{max} of perampanel from tablet/fasted is expected to be slightly higher than that from suspension/fed (but still within the BE limit). Yet, we cannot see such difference in Figure 5 at all.

The reviewer ran the simulation independently using the same input data file and NONMEM code provided by the sponsor, and generated the following plot.

Figure 6. Perampanel Predicted Concentration-time Profile at Steady-State following 12mg/day Suspension/Fed (Day 27) & Tablet/Fasted (Day 28) (N=1000)



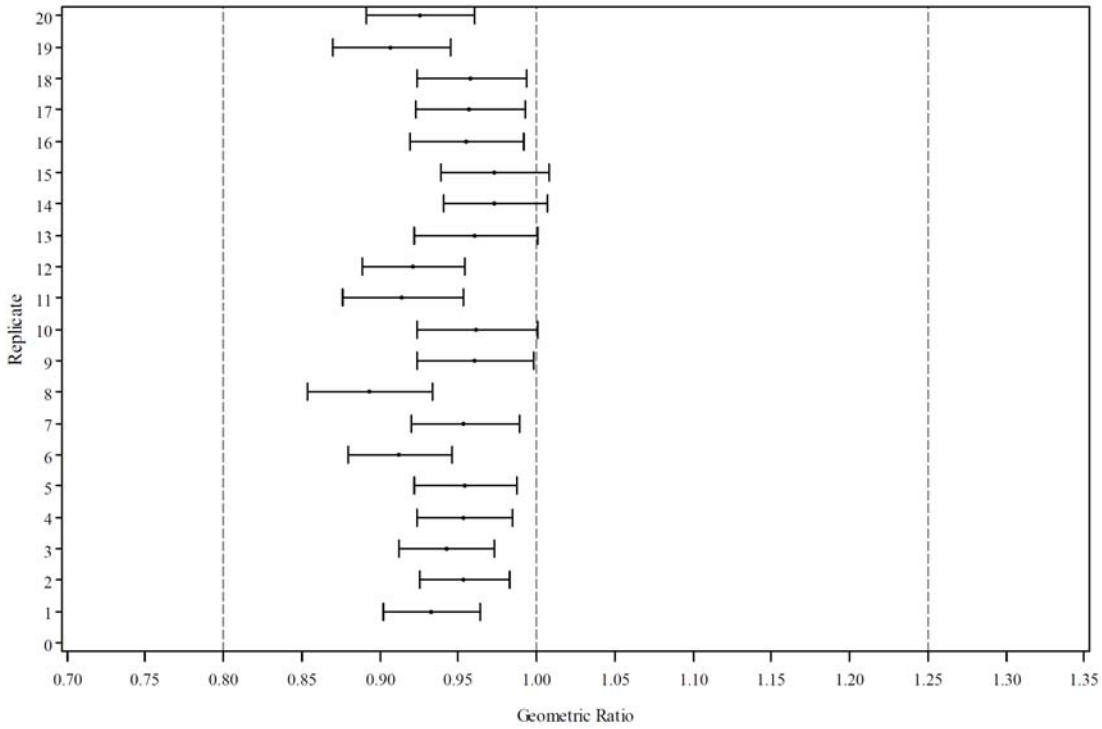
As shown in the above figure, the tablet/fasted treatment results in similar AUC as suspension/fed but with slightly higher C_{max} as anticipated. The reviewer also changed the seed number for simulation. The simulated concentrations of perampanel for individual/treatment become different, but, the concentration-time profiles are very similar to Figure 6. Nevertheless, the difference between Figures 5 and 6 does not affect the overall conclusion.)

3. Statistical Analyses

Ratios of geometric means and 90% CI are presented as Forest plots below. Only the results for switching from tablet administered under fasted state to the suspension given with food are included.

Though the C_{max} of perampanel on Day 28 after administration of suspension formulation under fed state is slightly lower than the C_{max} on Day 27 after repeated dosing of tablet formulation under fasted condition, the 90% CI falls within the equivalence limits 0.8 to 1.25, indicating that the treatment on the first day after the switch (Day 28) is equivalent to the treatment before the switch (Day 27). This is also true for all the other 7 scenarios.

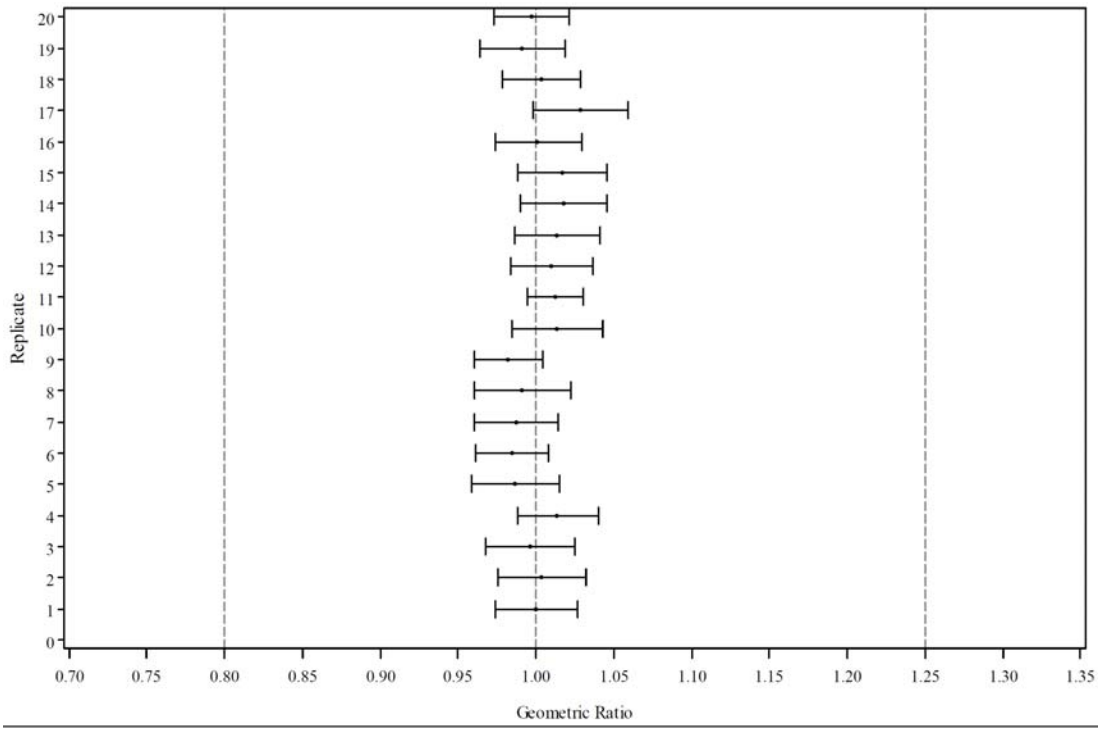
Figure 7. 90% CIs for the Comparison of Table Fasted (Day 27) to Suspension Fed (Day 28) C_{max}



(from page 23 in Sponsor's Study Report CPMS-E2007-010R)

The AUC of perampanel at steady state was also shown to be BE after switch.

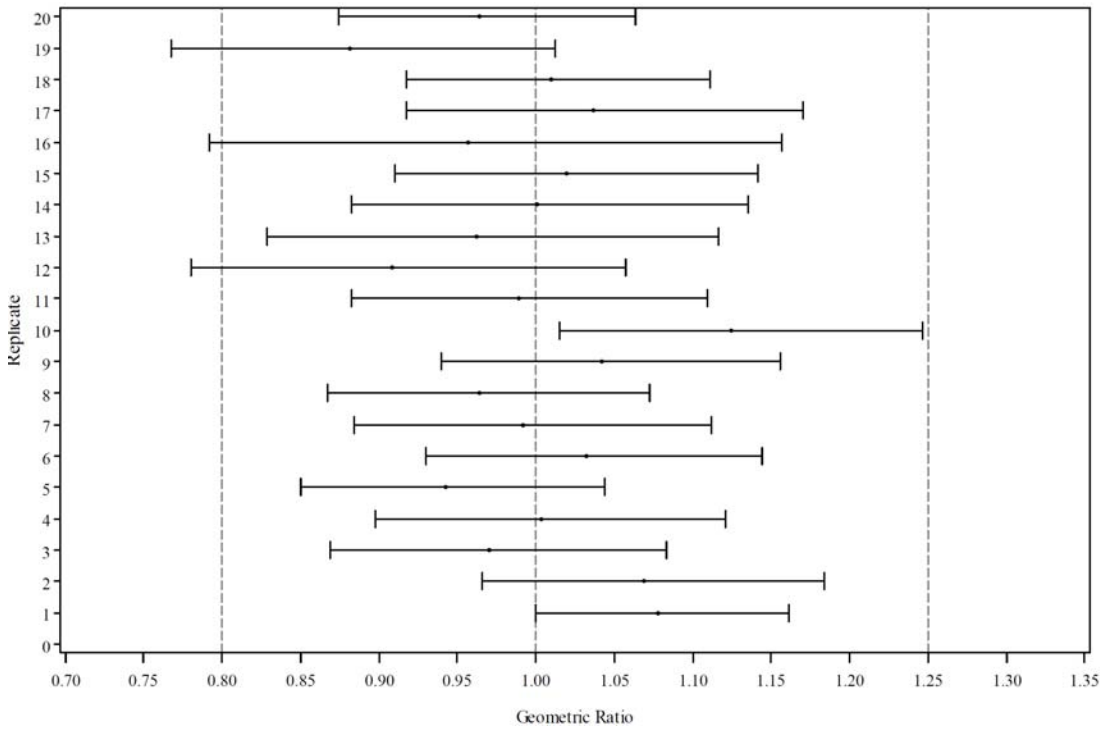
Figure 8. 90% Confidence Intervals for the Comparison of Tablet Fasted (Day 27) to Suspension Fed (Day 28) $AUC_{(0-24)}$



(from page 24 in Sponsor's Study Report CPMS-E2007-010R)

Though not required for BE assessment, C_{min} was also evaluated, since it is often postulated to represent the exposure associated with efficacy. Compared to C_{max} and AUC, C_{min} showed larger variability. In all switching scenarios, the large majority of the 90% CI replicates for C_{min} were contained within BE limits. For the tablet (fasted) switching to suspension (fed) scenario, all the CIs substantially overlapped the 0.8 to 1.25 BE limits; there were 3 CIs that were not completely contained within the equivalence limits. However, as shown in the figure below, all 90% CIs of the 20 replicates substantially overlapped with the range limits. It should be noted that each replicate CI estimate included data from N=50 subjects which was not selected based on consideration of the variability for each parameter, but rather based on the single dose study design used in Study 048, therefore, one of the possible explanations for the findings about C_{min} parameter might be associated with inadequate number of subjects included within each replicate, considering that the measurements for C_{min} are usually more variable. As to the other 7 scenarios, only 1 or 2 of the 20 replicates in each scenario were slightly outside the limit, also with substantial overlap with 0.8 to 1.25 limits.

Figure 9. 90% Confidence Intervals for the Comparison of Tablet Fasted (Day 27) to Suspension Fed (Day 28) C_{min}



(from page 23 in Sponsor's Study Report CPMS-E2007-010R)

Overall, the statistical analyses suggested that BE in exposure parameters is expected between the oral suspension and tablet formulation at steady state, either under fed or fasted conditions, and both formulations can be used interchangeably without any impact on maintaining therapeutic exposures.

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/s/

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04/25/2016

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04/26/2016

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04/26/2016

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