CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208277Orig1s000

MEDICAL REVIEW(S)

Medical Team Leader Review

Date	04/26/2016
From	Eisai Co.
Subject	Clinical Team Leader
NDA/BLA # Supplement#	208-277
Applicant	Eisai Inc.
Date of Submission	06/30/2015
PDUFA Goal Date	04/30/2016
Proprietary Name / Established (USAN) names	Fycompa Perampanel
Dosage forms / Strength	Fycompa oral suspension 0.5 mg/mL
Proposed Indication(s)	1. Adjunctive Treatment of with Partial Onset Seizures(POS) in Patients (b)(4) 12 years of age 2. Adjunctive Treatment of with Primary Generalized Tonic Clonic (PGTC) Seizures in Patients (b)(4) 12 years of age
Recommended:	Approval

1. Introduction/Background

Perampanel is a non-competitive AMPA receptor antagonist developed by Eisai. Based upon prior adequately controlled trials Fycompa tablets was approved on 10/22/12 for adjunctive treatment of partial onset seizures (POS) and later on 6/19/15 for adjunctive treatment of primary generalized tonic clinic (PGTC) seizures, both in patients 12 years of age and older. The present application provides a request for the approval of a Fycompa oral suspension (0.5 mg/ml) formulation for the same indications and at the same dosages as is presently labeled for the tablets based upon a pharmacokinetic comparison of this new formulation to the presently marketed tablet. Because clinical pharmacology is the predominate data relied on for approval the Clinical Pharmacology Team Leader, Angela Men, is serving as the CDTL.

2. CMC/Device

The quality review was performed by S. McLamore, K. Janoria, P Krieger, R. Xu, O. Anand, D. Woody, and M. Heiman. They note that "from a quality perspective, NDA 208277 for Fycompa® (perampanel) oral suspension is recommended for approval." They do not recommend any postmarketing commitments or requirements.

Also noted in this review is that because the manufacturing process is a low risk process and the firm provided sufficient in-process controls, no PAI is necessary. Thus the site was found acceptable based on the inspection history.

3. Nonclinical Pharmacology/Toxicology

No new data and none required.

4. Clinical Pharmacology/Biopharmaceutics

The OCP reviewer was Dr. X. Yang. Drs. K. Krudys and A. Men were the Team Leaders from this division. Dr. Men, as noted above, served as the CDTL. OCP noted that in fasting state a single dose of the presently marketed tablet and the study suspension where bioequivalent with regard to the Cmax and AUC based upon standard criteria. This was also true for the AUC in the fed state as well. However, the Cmax did not meet bioequivalence standards in the fed state, with a 23% mean reduction in the Cmax of the suspension as compared to the tablet. Based on population pharmacokinetic simulated multiple-dosing scenario analysis at steady state, the AUC and Cmax of perampanel were determined to be bioequivalent when the tablet under fasting conditions was compared to the suspension under the fed state. Because the maintenance therapy at study state is the pertinent issue regarding fed to fasting states OCP concluded that "the oral suspension formulation demonstrated comparable bioavailability as the tablet formulation and can be used interchangeably." This will be noted in the label.

As per the OCP review, the Office of Study Integrity and Surveillance determined that based upon inspection the bioanalytical site, the bioanalytical data of this study are reliable.

OCP recommends approval (see Dr. A. Men's review) and has no additional post marketing commitments or requirements.

5. Clinical Microbiology

P. Krieger performed the microbiology review. She recommended that this submission be approved from the standpoint of microbiology product quality.

6. Clinical/Statistical- Efficacy

Clinical efficacy is concluded and is based upon the prior demonstration of the efficacy of the tablet formulation and the bridging pharmacokinetic studies comparing the tablet and suspension formulations provided in this application.

7. Safety

Safety is concluded and is based upon the prior demonstration of the safety of the tablet formulation and the bridging pharmacokinetic studies comparing the tablet and suspension formulations provided in this application. Safety data, from the pharmacokinetic studies, was reviewed in this application as well.

Exposures and numbers of patients examined in the present pharmacokinetic studies are substantially less than those that led to approval of the tablets. The new safety data submitted in these pharmacokinetic studies, however, were reviewed by Dr. Getzoff, DNP Clinical Review.

Safety data from the following two studies were reviewed:

- Study E2007-E044-028 (Study 028): a randomized, open-label, 2-period, 2-sequence crossover study that compared the relative bioavailability of a single 4 mg dose of perampanel oral suspension to a single 4 mg dose of perampanel tablet (reference formulation) in healthy adult subjects (n=16) under fasted conditions.

- Study E2007-A001-048 (Study 048): an open-label, 2 arm (tablet and oral suspension), single-dose, randomized crossover bioequivalence study that compared a single 12 mg dose of the tablet to the suspension formulation under fasted (Arm 1, n=50) and a single 12 mg dose of the tablet and suspension formulation under fed (high-fat meal) conditions (Arm 2, n=50) in healthy adult subjects.

Subjects in the above studies received two single doses of formulations separated by a wash out period. In study 48, 94 received the tablet formulation, and 95 received the oral suspension. In study 28, 15 received both formulations.

No Deaths were observed.

Dr. Getzoff notes that a single serious adverse event (SAE) occurred in Study 048 that was described as a spontaneous abortion. The subject was a 23-year-old female, who was noted to have a positive pregnancy test at the check-in visit for Treatment Period 2 (b) (4) and was not administered the second dose of perampanel (OS). On (b) (4) the subject presented to the ER with vaginal bleeding. She had "low" beta-human chorionic gonadotropin levels, and an ultrasound was performed in the ER, which detected no pregnancy. The investigator was unable to rule out the possibility that the event was related to the study drug. Little can be concluded from this single case of a single dose exposure. Chronic exposures in animals, however, have been associated with fetal death. (b) (4) as (b) (4) (b) (4)

Dr. Getzoff notes that there were no adverse events resulting in treatment withdrawal, discontinuation of the study drug, or study drug adjustment in either study. However, it should be noted that the above adverse SAE resulted in exclusion from receiving a second dose. This was discussed with Dr. Getzoff who agrees that this represents a single case of withdrawal because of an adverse event

Dr. Getzoff notes that there were no incidences of adverse events from allergic reaction (including rash and hypersensitivity), suicidality, or drug induced liver injury.

Although, the predominant determination of safety is based upon prior studies bridged through the present PK studies, a brief summary of common adverse events are discussed below.

Of the 16 patients studied in Study 28, 13 subjects reported 26 TEAEs during the conduct of the study. This study was too small to provide any new information regarding the difference between tablet and liquid formulation. Nonetheless, no new obvious adverse event suggested a definitive new signal. Of note there was a high incidence of the reporting of gastroenteritis during for both the tablet and suspension, with 4 of15 and 3 of 16 cases noted for the suspension and tablet, respectively. It is difficult to conclude anything from this because of the limited number of subjects and the fact that this study was performed at a single site. Headache and dizziness was also common. These two adverse events are labeled as common adverse events.

Seventy-four subjects (74%) of the 100 patients studied experienced a treatment emergent adverse event in Study 048 at the studied dose of 12 mg. All adverse events observed in this study are presented in the table below (transcribed from Dr. Getzoff's review). This was a relatively short study, with relatively short exposures. But, in general it does not appear that tablet and solution differed with regard to occurrence of common adverse events. The events presented here are similar to that described in the label and with similar relative rates; e.g., dizziness, somnolence, headache and nausea were observed at high rates compared to other adverse events. Euphoric Mood was also observed and is noted in the label.

Table 6: TEAEs in ≥ 5% of Subjects in Any Treatment Group During the Treatment Phase by SOC and PT (Safety Analysis Set, Study 048)

MedDRA System Organ Class Preferred Term	Treatment A (Tablet/fasted) (N=49)	Treatment B (OS/fasted) (N=48)	Treatment C (Tablet/fed) (N=45)	Treatment D (OS/fed) (N=47)	Overall (N=100)
Subjects with any TEAE	**36 (73.5)**	**31 (64.6)**	**26 (57.8)**	**24 (51.1)**	**74 (74.0)**
Ear and labyrinth disorders	**3 (6.1)**	**2 (4.2)**	**2 (4.4)**	**0 (0)**	**7 (7.0)**
Vertigo	3 (6.1)	2 (4.2)	2 (4.4)	0 (0)	7 (7.0)
Gastrointestinal disorders	**14 (28.6)**	**6 (12.5)**	**4 (8.9)**	**2 (4.3)**	**22 (22.0)**
Dry mouth	3 (6.1)	0 (0)	0 (0)	0 (0)	3 (3.0)
Nausea	5 (10.2)	4 (8.3)	2 (4.4)	0 (0)	9 (9.0)
Paraesthesia oral	6 (12.2)	2 (4.2)	0 (0)	0 (0)	6 (6.0)
General disorders and administration site conditions	**4 (8.2)**	**2 (4.2)**	**1 (2.2)**	**4 (8.5)**	**11 (11.0)**
Infections and infestations	**2 (4.1)**	**1 (2.1)**	**1 (2.2)**	**1 (2.1)**	**5 (5.0)**
Nervous system disorders	**31 (63.3)**	**28 (58.3)**	**24 (53.3)**	**18 (38.3)**	**63 (63.0)**
Dizziness	22 (44.9)	19 (39.6)	14 (31.1)	7 (14.9)	41 (41.0)
Headaches	5 (10.2)	7 (14.6)	1 (2.2)	1 (2.1)	12 (12.0)
Somnolence	12 (24.5)	10 (20.8)	16 (35.6)	14 (29.8)	39 (39.0)
Psychiatric disorders	**3 (6.1)**	**3 (6.3)**	**0 (0)**	**1 (2.1)**	**4 (4.0)**

Source: Study 048, CSR, Table 17 (verified using JMP)
(Highlighted ≥5%)

As this is a new formulation CSS was requested to review the application. As per my opinion no new pertinent dependence or addiction data appear to be included in this application. Dr.

Alicja Lerner performed the review. She recommended that the label provides information in section 5.5 and section 9 that "during the post-marketing period withdrawal convulsions and drug dependence were reported." This recommendation was based upon postmarketing reports of seizures upon withdraw of Fycompa in epilepsy patients, Upon questioning Dr. Lerner she clarified that the description of a drug dependence syndrome is based upon her interpretation that seizures represent withdrawal seizures. Of note, section 5.5 of the label, entitled Withdrawal of Antiepileptic Drugs, presently states "there is the potential of increased seizure frequency in patients with seizure disorders when antiepileptic drugs are withdrawn abruptly," and further states "a gradual withdrawal is generally recommended with antiepileptic drugs, but if withdrawal is a response to adverse events, prompt withdrawal can be considered." It is noteworthy that drug withdrawal in pivotal studies, which were provided in the previously reviewed applications, was performed abruptly; likely because of the very long half-life of this drug (105 hours). In these studies there was insufficient evidence of a seizure withdrawal syndrome. Dr. Lerner requested specific post-marketing information on seizures associated with withdrawal in a 3/9/16 request to the sponsor. Fourteen cases were provided by the sponsor. Dr. Lerner expressed the opinion in a follow-up review that these demonstrated the possibility of the existence of a withdrawal seizure withdrawal syndrome. In her second review she notes that section 9 should provide information describing the "potential for Fycompa to produce withdrawal symptoms," in other parts of this section noting withdrawal convulsions. Neither I nor Dr. Getzoff, after examining the postmarketing cases, believes this data provide proof that such convulsions were a part of a withdrawal syndrome. Seizures upon removal of therapeutic agent may occur simply as a result of reduced treatment. While many of the cases states seizures were increased, it does not note that they necessarily increased over a pre-Fycompa treatment period. Moreover, I do not believe the postmarketing data trumps those from the pivotal controlled trials, which notes that a definitive seizure withdrawal syndrome was not identified in the examination of the phase 3 studies. Lastly, the Sponsor does have a PMR that will more carefully study this issue. While in some respects the PMR study may flawed, as expressed in discussions with Dr. Lerner, as it is examining seizure patients, I believe with careful observation, it has the potential to answer the question of wither there is a seizure withdrawal syndrome. Also, as noted above, the present label suggests care when withdrawing Fycompa, by its reference to the antiepileptic class of drugs. Following review of the postmarketing cases Dr. Getzoff and I had a teleconference with Dr. Lerner, but we were unable to come to a consensus on this issue. The two Divisions and the Division Directors will meet again, post action, to discuss this issue so as to come to a mutually agreed upon conclusion.

Dr. Lerner has requested that additional information on an animal dependence study[1] be included in the label; this information was provided in prior approval packages. I would concur to this. Dr. Lerner also notes that the Sponsor did not submit to CSS animal studies previously requested (study in rats # ES06156 and juvenile toxicity studies). This action is not part of this submission and CSS should provide a separate inquiry.

[1] "Pre-clinical dependence study in rats showed significant withdrawal symptoms including hyper-reactivity to handling, muscle rigidity, decreases in food consumption and body weights."

No significant EKG or vital sigh change was noted in patients in the two reviewed studies. One case of low neutrophil count was noted following the last dose of drug. This was thought to be potentially a result of a viral illness and not believed to be drug related. A single case as this, against the already large clinical database, is unrevealing.

I agree with Dr. Getzoff that, "there are no clinical safety issues impeding the approval of the proposed product."

One additional safety matter should be noted that is requiring a labeling change. In section 5.1, Serious Psychiatric and Behavioral Reactions, the label presently notes that "in the non-epilepsy trials, psychiatric events that occurred in perampanel-treated patients more often than placebo-treated patients included disorientation, delusion, and paranoia." Because delusions are most notably associated with psychosis, and a potential signal for psychosis was identified in a pediatric review by DPV, Dr. K. Long of DPV, performed a postmarketing review of the FAERS database and literature for neuropsychiatric adverse events. She identified 32 cases of psychosis or delirium that suggest a causal association with perampanel. She notes

> All 32 cases reported a temporal relationship with a median time to onset of 30 days, and 25 cases reported a positive dechallenge. Twenty-nine cases reported a serious outcome, including 16 hospitalizations. More than half of the cases (17 of 32) required treatment in a medical facility, with 9 cases reporting the use of an antipsychotic or benzodiazepine.

She also further notes:

> Both the perampanel-treated groups and the phase 3 placebo groups reported neuropsychiatric adverse events related to psychosis or delirium, however, some events were reported only in the perampanel-treated group (i.e., psychotic disorder, delirium, hallucination auditory, paranoia, and acute psychosis). The phase 2 placebo groups did not report neuropsychiatric adverse events related to psychosis or delirium. Lastly, the disproportionality analysis for perampanel with events related to psychosis or delirium (psychotic disorder, acute psychosis, hallucinations, psychotic behavior, and confusional state) revealed an EB05 score of ≥ 2, suggesting a potential association.

Moreover, Dr. Long further notes that:

> Non-epilepsy doubleblind pooled studies reported the following adverse events in perampanel-treated groups that were not reported in the placebo groups: paranoia, hallucination auditory, acute psychosis.

This led Dr. Long to believe that causality was likely and severity was sufficient to require the adding of this information to section 5.1.

She recommends that the following be added:

> In the postmarketing setting, there have been reports of psychosis (acute psychosis, hallucinations, delusions, paranoia) and delirium (delirium, confusional state, disorientation, memory impairment) in patients treated with perampanel.

I agree with this. In particular, I believe that the combination of the very clear signal for delusions in normal subjects from the clinical trial, knowing the association of delusional behavior and psychosis, and the strong post marketing signal for psychosis requires our recommended labeling.

8. Advisory Committee Meeting

None necessary.

9. Pediatrics

Dr. Getzoff notes a number of PREA PMRs in her review. Except for one (see below), these represent old PMRs for the tablets. Because of a change in policy regarding pediatric extrapolation the division is no longer requesting a controlled efficacy/safety trial for (b) (4) partial onset seizures in patients 4 years to 12 years old, but allows extrapolation from adults with adequate PK data. We, however, continue to request open-label safety data in this population. We will therefore specify in a new PMR for this safety data as follows:

> A long-term, open-label, safety study of adjunctive therapy in patients 1 month to < 12 years with epilepsy: The purpose of this study is to evaluate the long-term safety of perampanel as adjunctive therapy in the treatment of partial-onset seizures (ages 1 month to < 12 years) or primary generalized tonic-clonic seizures in pediatric patients (ages 2 to < 12 years). Doses for this study must be at or above those doses determined to be efficacious by Study 1932-4 (patients 1 month to < 4 years old with partial-onset seizures), Study 2922-1 (patients 2 to < 12 years with primary generalized tonic-clonic seizures), and the pharmacokinetic analyses used for the extrapolation of efficacy in pediatric patients 4 to < 12 years with partial-onset seizures. This study may include subjects enrolled in the extension phases of Studies 1932-1, 1932-2, 1932-4, and 2922-1, and may be supplemented as necessary. A minimum of 100 patients must be exposed to study drug for one year at or above the dose or doses identified as effective. Subjects should be balanced among age cohorts to allow for adequate conclusions to be drawn.

This PMR was agreed upon by PeRC. (b) (4)

10. Other Relevant Regulatory Issues

- Financial disclosures: Dr. Getzoff examined the financial disclosure information for study E2007-A001-048 and notes that there were no financial disclosable arrangement, and concludes there that no financial arrangements "introduced significant bias into the results of this trial."

11. Labeling

See above and final agreed upon label.

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval.
- Risk Benefit Assessment: No new safety issues for this formulation were identified. OCP determined that this formulation can be interchangeably used with that of the tablet.
- Recommendation for Postmarketing Risk Evaluation and Management Strategies: None required.
- Recommendation for other Postmarketing Requirements and Commitments: The only postmarketing issue identified by the team was the PREA PMR, noted above.
- Recommended Comments to Applicant: The Clinical Team has none.

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/s/

NORMAN HERSHKOWITZ
04/28/2016

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA-208277

Submission Date(s): 6/30/2015

Applicant: Eisai, Inc

Product: Fycompa (perampanel) oral suspension

Reviewer: Natalie Getzoff, MD

Date of Review: 3/29/2016

Covered Clinical Study (Name and/or Number): 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)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 9		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation

		from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- N/A. All clinical investigators had no disclosable financial arrangements, as per Form 3454.

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

N/A. All clinical investigators had no disclosable financial arrangements

[1] See [web address].

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

/s/

NATALIE B GETZOFF
03/30/2016
Clinical Investigator Financial Disclosure Review

NORMAN HERSHKOWITZ
03/31/2016

CLINICAL REVIEW

Application Type	NDA, 505(b)(1)
Application Number(s)	208277
Priority or Standard	Standard
Submit Date(s)	6/30/2015
Received Date(s)	6/30/2015
PDUFA Goal Date	4/30/2016
Division / Office	DNP
Reviewer Name(s)	Natalie Getzoff
Review Completion Date	3/25/2016
Established Name	Perampanel
Trade Name	Fycompa
Therapeutic Class	Anticonvulsant
Applicant	Eisai, Inc
Formulation(s)	Oral suspension
Dosing Regimen	8-12 mg once daily
Indication(s)	Adjunctive treatment of partial onset or primary generalized tonic-clonic seizures
Intended Population(s)	Patients with epilepsy ≥ 12 years old

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The applicant has developed an oral suspension formulation of perampanel for the treatment of partial onset seizures (POS) or primary generalized tonic clonic (PGTC) seizures in patients ≥ 12 years of age. The product has the same active ingredient) as the approved tablet formulation and will be marketed in 0.5 mg/mL dosage strength.

There are no clinical safety issues impeding the approval of the proposed product. It is therefore recommended that the product be approved.

1.2 Risk Benefit Assessment

The overall risk to benefit analysis of Fycompa OS is therapeutically acceptable. Perampanel, marketed in the United States for adult and adolescent patients with epilepsy since 2014, has a fairly well characterized safety profile. According to the Clinical Pharmacology reviewer for this application, Fycompa OS has been shown to be bioequivalent when compared to Fycompa tablets. No new or unexpected adverse events were discovered in the course of the development program of Fycompa OS in healthy adults.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

- PMR1: Pediatric Pharmacokinetic and Tolerability Study(ies) to explore the range of tolerated doses in patients 1 month to < 12 years old with epilepsy. Sufficient PK and tolerability data must be generated from this study before conducting efficacy and safety studies, to inform the dose selection for those studies. Sampling must be optimized to ensure adequate characterization of perampanel PK. The study must provide sufficient data to determine a dosing regimen that provides a similar drug exposure in pediatric patients 4 years of age with POS as the levels demonstrated to be effective in adults and adolescents with POS. The pharmacokinetic analysis will also be used to inform dose selection in PMR 2 and PMR 3.
- PMR 2: Randomized, double-blind, placebo-controlled, parallel group, efficacy

and short-term safety study in pediatric patients 2 to < 12 years of age with primary generalized tonic-clonic seizures using a diary-based primary endpoint. The duration for the study should have a titration period followed by 12 weeks fixed dose evaluation period.

- PMR 3: Pediatric Efficacy and Safety study in patients 1 month to < 4 years with refractory POS: Randomized, double blind, placebo-controlled, parallel group, efficacy and short-term safety study. The trial must maximize the opportunity to detect a treatment effect of the drug, if there is one in this population. The objective is to establish the efficacy and short-term safety of perampanel as adjunctive therapy in refractory partial onset seizures in pediatric patients ages 1 month to < 4 years with partial onset seizures, using a video/EEG based primary endpoint.
- PMR 4: Long-term (1 year) Safety study: An open-label safety study of adjunctive therapy in patients 1 month to < 12 years. This study could be an extension to the efficacy studies above (PMR 2 and PMR 3). The long-term safety data must be at or above the dose or doses identified as effective.

Safety PMRs: Continue current PMRs and routine postmarket surveillance.

2 Introduction and Regulatory Background

2.1 Product Information

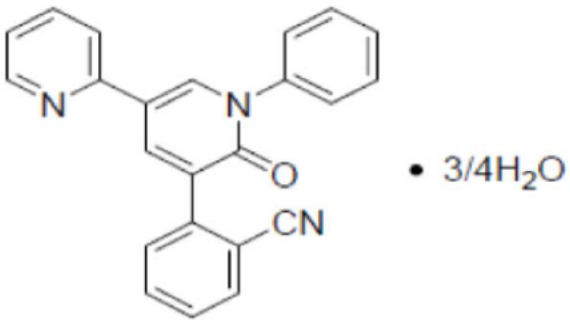
Perampanel is a noncompetitive and selective α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) receptor antagonist. AMPA receptors can mediate glutaminergic activity in the cortex, and an AMPA-antagonist may reduce excitatory activity. Reduction of excitatory activity may lead to an antconvulsant effect, and, as noted by the sponsor, there are some animal data (reduction of seizures in rat models) to support this hypothesis.

The applicant seeks approval for Fycompa (perampanel), oral suspension for the same indication for which the tablet formulation is approved (adjunctive therapy for treatment of POS or PGTC seizures in patients with epilepsy ≥ 12 years of age), based on a bioequivalence study. Fycompa was originally approved by the FDA (NDA 202834) as an adjunctive treatment of POS in patients with epilepsy ≥ 12 years of age on October 22, 2012. On June 19, 2015, Fycompa was approved for adjunctive treatment of PGTC seizures in patients with epilepsy ≥ 12 years of age. Currently, Fycompa is commercially available as 2, 4, 6, 8, 10, and 12 mg tablets. The new formulation is an oral suspension of 0.5 mg/ml.

The clinical program that forms the basis of this application consists of one “definitive”

bioequivalence study conducted in 100 healthy male and female volunteers. The study compared the rate and extent of absorption of a single 12 mg dose of perampanel oral suspension compared with a single dose of perampanel 12 mg tablet in the fed and fasted state. Safety information from a second smaller single dose bioequivalence study is also reviewed. The pharmacokinetic and clinical safety findings for this pivotal study are presented in this review.

Figure 1: Perampanel Molecule



Molecular formula: $C_{23}H_{15}N_3O \cdot 3/4H_2O$
Chemical name: 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3yl)benzonitrile hydrate (4:3) (IUPA)

Composition	Components (mg/mL)	Function	Specification
Perampanel (anhydrous basis)	(b) (4)		In-house
Sorbitol (b) (4)			USP, Ph. Eur.
Microcrystalline cellulose and carboxymethylcellulose sodium			NF, Ph. Eur.
Poloxamer (b) (4)			NF, Ph. Eur.
Simethicone (b) (4)			USP
(b) (4) citric acid			USP, Ph. Eur.
Sodium benzoate			NF, Ph. Eur.
Purified water[d]			USP, Ph. Eur.

(b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, four antiepileptic drugs (AEDs) (topiramate, levetiracetam, lamotrigine and perampanel) have demonstrated efficacy in controlled clinical trials and have been approved by the Agency for the adjunctive treatment of PGTC seizures. Additionally,

valproate is approved for "multiple seizure types which include absence seizures" and is widely used in clinical practice for the treatment of PGTC seizures. There are a multitude of drugs approved for adjunctive treatment of POS, and several drugs which are used for this purpose, though the language in the labeling is general.

Table 1: AEDs Currently Available for Adjunctive therapy in POS and/or PGTCS

AED	Adjunctive therapy in POS	Adjunctive therapy in PGTCs
Lamotrigine (XR)	Yes	Yes
Levetiracetam	Yes	Yes
Topiramate	Yes	Yes
Valproic Acid	Yes	No, (b) (4)
Carbamazepine	Yes, though language is general	No
Ezogabine	Yes	No
Felbamate	Yes, but not first line use due to safety issues	No
Gabapentin	Yes	No
Lacosamide	Yes	No
Oxcarbazepine	Yes	No
Phenobarbital	Not NDA approved; seizure type not specified in label	No
Phenytoin	Yes	No
Pregabalin	Yes	No
Primidone	Yes, generally	No
Tiagabine	Yes	No
Vigabatrin	Yes, but not first line use due to safety issues	No
Zonisamide	Yes	No

2.3 Availability of Proposed Active Ingredient in the United States

Perampanel was approved as FYCOMPA for marketing in the US on October 22, 2012 for adjunctive therapy of partial-onset seizures (POS) in patients with epilepsy aged 12 years and older. It was approved on June 19, 2015 for adjunctive therapy of PGTC seizures in patients with epilepsy ≥ 12 years of age.

2.4 Important Safety Issues With Consideration to Related Drugs

Several AMPA antagonists are currently in either preclinical or clinical development in various therapeutic areas. However, no other selective AMPA antagonists are currently FDA approved for any indication.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

As noted above, FYCOMPA was originally approved for adjunctive treatment of POS in

patients ≥ 12 years of age on October 22, 2012 and for adjunctive treatment of PGTC seizures in patients ≥ 12 years of age on June 19, 2015.

The sponsor requested a Type C meeting on bioequivalence parameters and study design of Study E2007-A001-048 on March 17, 2014, and preliminary comments were sent out on May 27, 2014. The sponsor requested Type B Written Advice on the format and content of the PMA on February 25, 2015 and comments were sent on April 21, 2015.

With respect to the regulatory history, the sponsor notes *Concerning BE, both FDA and EMA provided feedback supporting the 4-phase single dose BE study utilized in Study E2007-A001-048. It was recommended that the BE/food-effect study be performed with a to-be-marketed formulation of the oral suspension (using planned manufacturing method for the marketed formulation), which was followed. Should this study result in significant differences concerning the BA of the tablet and the oral suspension formulation, it was remarked that simulation methods could either be helpful in order to decide whether a multiple dose BE study or a clinical study in patients would be expedient…, and that simulations could be used both to assess for potential differences in C_{min} of perampanel at steady-state under fasted and fed condition, and to simulate scenarios where patients on maintenance doses of perampanel switch from the tablet formulation to the oral suspension formulation and vice versa. It was also remarked that comparability of C_{max}, C_{min}, and AUC of perampanel should be demonstrated before and after switching.*

2.6 Other Relevant Background Information

None submitted and none required

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the submission was acceptable. The NDA was submitted in eCTD format and conformed to CDISC SDTM standards. The information required for the review of the NDA was well-organized, easy to navigate, and complete.

3.2 Compliance with Good Clinical Practices

At DNP's request, the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the analytical portion of the bioequivalence study a (b) (4) . According to Dr. Zhang's review, *"no deficiencies were observed and no Form FDA 483 was issued. The final classification for this inspection is No Action Indicated (NAI). We recommend that the data from the analytical portion of Study*

E2007-A001-048 be accepted for further agency review."

3.3 Financial Disclosures

The sponsor provided required information regarding financial disclosure and there was no evidence that any study investigators had financial arrangements that may have introduced significant bias into the results of this trial.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The complete review is not submitted at the time of this writing. No CMC issues have been identified at this point.

4.2 Clinical Microbiology

No Clinical Microbiology studies were performed

4.3 Preclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology studies were performed in support of this supplement. The sponsor referenced NDA-202834 for pharmacology/toxicology.

4.4 Clinical Pharmacology

Please refer to Section 5.3 of this review for a discussion of the submitted bioequivalence study.

4.4.1 Mechanism of Action

Perampanel is a noncompetitive and selective AMPA receptor antagonist. AMPA receptors can mediate glutaminergic activity in the cortex, and an AMPA-antagonist may reduce excitatory activity. Reduction of excitatory activity may lead to an antconvulsant effect, and, as noted by the sponsor, there are some animal data (reduction of seizures in rat models) to support this hypothesis.

4.4.2 Pharmacodynamics

No new pharmacodynamics studies were performed for this formulation.

4.4.3 Pharmacokinetics

Pharmacokinetics of perampanel are similar in healthy subjects, and in patients with POS or PGTC seizures. The half-life of perampanel is about 105 hours, so steady state is reached in about 2-3 weeks. AUC of perampanel increased in a dose-proportional manner after single-dose administration of 0.2-12 mg tablets and after multiple-dose administration of 1-12 mg tablets once daily.

FYCOMPA oral suspension has comparable bioavailability to FYCOMPA tablets under steady state, and both formulations may be used interchangeably.

5 Sources of Clinical Data

The data files are located in the following directories:
\\Cdsesub1\evsprod\NDA208277\0000\m5\datasets\e2007-a001-248
\\Cdsesub1\evsprod\NDA208277\0000\m5\datasets\e2007-a001-048

The study reports are located in the following directories:
\\Cdsesub1\NDA022416\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\e2007-a001-048
\\Cdsesub1\NDA022416\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\e2007-a001-048

5.1 Tables of Studies/Clinical Trials

The following table provides an overview of the two clinical studies (Studies 028 and 048) submitted with the application. The bioequivalence assessments are derived from Study 048, and the safety data are derived from both studies. The table below is reproduced from the sponsor's submission.

Table 2: Overview of Clinical Studies

Study ID	Design; Control Type	Number of Study Centers (Locations)	# Subjects by Arm; Entered/ Completed	Indication Studied	Gender M/F Mean age (Range) Race	Duration	Study and Control Drugs Dose, Route, Regimen
Study 028	Randomized, open-label, crossover study to compare relative bioavailability	1 (UK)	16/15	Healthy male and female subjects	9/7 38.4 years (20 to 53 years)	Single dose of each study drug separated	Single dose of Perampanel 4-mg oral suspension, administered as 8

Study ID	Design; Control Type	Number of Study Centers (Locations)	# Subjects by Arm; Entered/ Completed	Indication Studied	Gender M/F Mean age (Range) Race	Duration	Study and Control Drugs Dose, Route, Regimen
	between perampanel 4-mg oral suspension to perampanel 4-mg tablet in healthy subjects				15 white, 1 black	by a 6 week washout period	mL of 0.5 mg/mL suspension Single dose of perampanel 4-mg tablet
Study 048	Randomized, open-label, crossover study to demonstrate bioequivalence between perampanel 12-mg oral suspension to perampanel 12-mg tablet formulation under fasted and fed conditions in healthy subjects	1 (US)	Arm 1: 47 A: 24 B: 23 Arm 2: 42 C: 20 D: 22 Total: 100/89	Healthy male and female subjects	51/49 35.1 years (18 to 55 years) white 58, black 36, American Indian or Alaska 2, Asian 2, Native Hawaiian or other Pacific Islander 1, Multiple 1	Single dose of each study drug separated by a 6 week washout period (up to 84 days)	Single dose of perampanel 12-mg oral suspension, (ad-ministered with approximately 240 ml of water 30 min before a meal) Single dose of perampanel 12-mg tablet Administered under fasted (Arm 1) and fed (Arm 2) conditions

5.2 Review Strategy

Since the only study conducted for this application was a bioequivalence study, it is reviewed in the subsequent section, Section 5.3. Discussion of the study is presented in the following categories:

- Overview of study design
- Subject disposition, demographic and baseline characteristics
- Pharmacokinetic results

There was no review of efficacy as the study under review is a bioequivalence study. Therefore, Section 6 of this review not applicable.

Safety findings in the study are presented in Section 7..

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study Design

5.3.1.1 Study E2007-001-048

This was a randomized, crossover study comparing a single 12 mg perampanel tablet to a 12 mg dose of the perampanel oral suspension in healthy adults in fed and fasted conditions. The purpose of the study was to demonstrate bioequivalence between the two perampanel formulations.

Objectives

Primary objective**:** *To demonstrate bioequivalence between a single 12-mg dose of oral suspension formulation of perampanel and a single 12-mg tablet formulation of perampanel when administered under fasted conditions*

Secondary objectives**:**

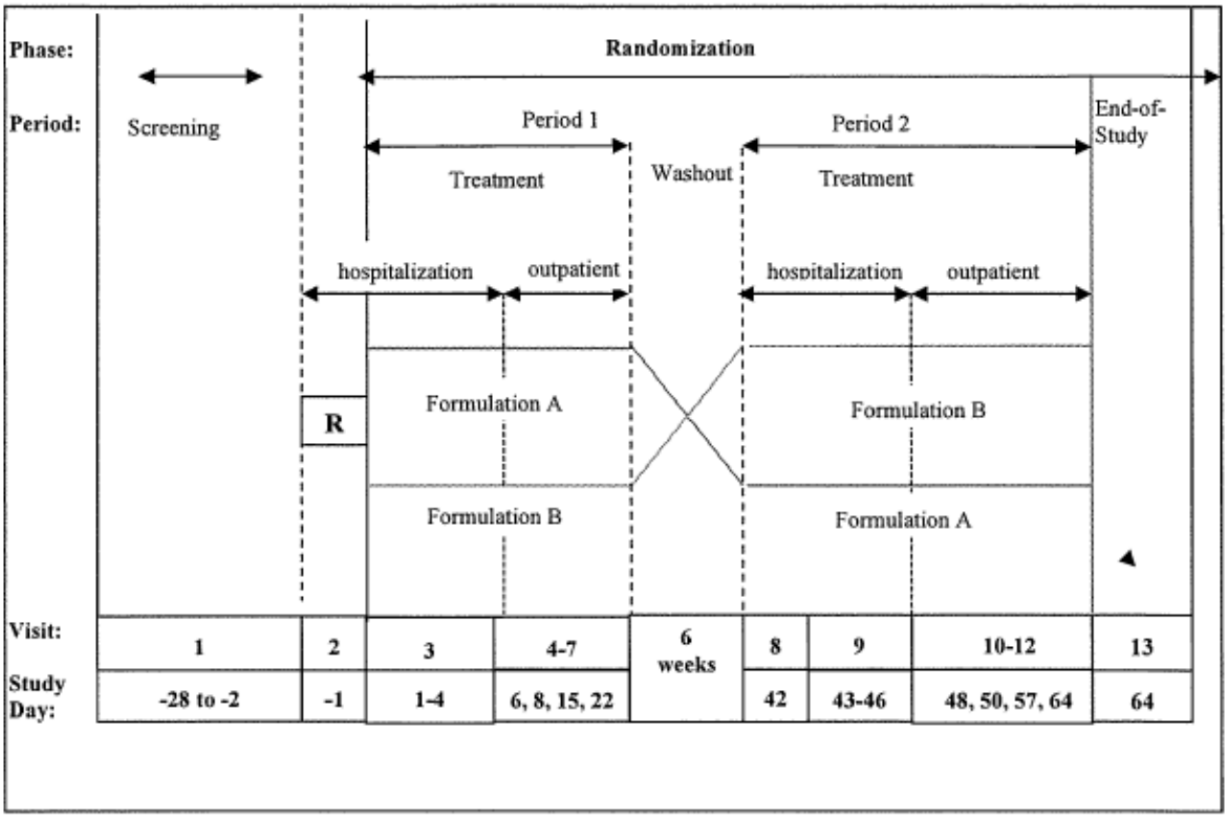
- *To evaluate bioequivalence between a single 12-mg dose of oral suspension formulation of perampanel and a single 12-mg tablet formulation of perampanel when both co-administered with a high-fat meal in healthy subjects*
- *To evaluate and compare the safety and tolerability of a single 12-mg dose 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 with a planned sample size of 100 subjects (50 each arm). Arm 1 evaluated the oral suspension and tablet forms of perampanel in fasted subjects. Fed subjects were evaluated in Arm 2. In both arms, subjects would be randomized to either receive a 12 mg perampanel tablet or 12 mg in the oral suspension formulation. Subjects were to return on day 43 for dosing of the other formulation (6 week washout). Subjects were randomized to 1 of 4 treatment allocations (AB, BA, CD, or DC), as defined below:

- Fasted (Arm 1):
    - Treatment A: Single oral dose of a 12-mg perampanel tablet
    - Treatment B: Single 12 mg dose of perampanel oral suspension.
- Co-administered with a high fat meal (Arm 2)
    - Treatment C: Single oral dose of a 12-mg perampanel tablet.
    - Treatment D: Single 12 mg dose of perampanel oral suspension.

Figure 2: Study Schematic (Study 048)



Screening and Baseline Periods

Obtain informed consent, establish eligibility

Treatment Phase

The treatment phase consisted of 2 identical study periods. The only difference between periods was the treatment administered (either single 12 mg tablet or single 12 mg dose of oral suspension).

- Fasted Treatment: Subjects fasted overnight (10 hours), and then were given a single 12 mg dose of perampanel with 240 mL of water. No food was allowed for at least 4 hours after dosing.
- Fed Treatment: Subjects fasted overnight (≥ 10 hours) then consumed a high fat (~50% of caloric content) and high calorie (800-1000 calories) meal 30 minutes before dosing. The meal was to be eaten within 30 minutes. No food was allowed for 4 hours after dosing.

Study Population

Healthy males or females, ages 18 to 55 years with BMI of 18 to 32 kg/m^2 were

included. Subjects were in good health as determined by a medical history, physical examination (including vital signs), electrocardiogram (ECG) and the usual clinical laboratory tests as well as negative screening of cotinine, ethanol and drugs of abuse in urine and negative pregnancy test (for female subjects). Please see Section 9.4 for key exclusion criteria.

The study included the following restrictions on prior and concomitant medications, food and beverages:

- No prescription drugs (including hormonal forms of birth control) within 4 weeks of dosing and OTC drugs within 2 weeks before dosing or throughout the Treatment Phase
- No smoking or use of tobacco or nicotine-containing products within 4 weeks before dosing and throughout the Treatment Phase
- No intake of caffeinated beverages or food from 72 hours before dosing to 72 hours post-dose
- No intake of nutritional supplements, juice, and herbal preparations or other foods or beverages that may affect CYP3A4 enzyme or transporters within 2 weeks before dosing and throughout the Treatment Phase
- No intake of St. John's Wort within 4 weeks before dosing and throughout the Treatment Phase

The schedule of assessments is summarized in Table 8 in Section 9.5 (which is reproduced from the submission).

Assessments

Pharmacokinetic Assessments:

Blood samples for PK assessments were collected from pre-dose to 504 hours post-dose in all subjects. *Plasma concentrations of perampanel in sodium heparin were quantified by liquid chromatography with tandem mass spectrometry (LC-MS/MS) methodology using a previously validated assay by* (b) (4)*. The lower limit of quantitation was 1.00 ng/mL with a dynamic range 1.00 – 500 ng/mL.*

Safety Assessments

All AEs and SAEs, lab values (hematology, blood chemistry, and urine values), vital signs, ECGs, and physical exams.

5.3.1.2 Study E2007-001-028

Study Design

This was a randomized, open-label crossover study comparing a single 4 mg perampanel tablet to a 4 mg dose of the perampanel oral suspension in 16 healthy adults. The primary purpose of the study was to compare relative bioavailability

between the two perampanel formulations at the 4 mg doses. Other objectives includes evaluate and compare PK profile, safety and tolerability of the two formulations. Subjects were administered both formulations, separated by a 6 week washout period. Subjects were randomly assigned to one of two treatment sequences (tablet then OS or OS then tablet).

Screening and Baseline Periods

Obtain informed consent, establish eligibility

Treatment Phase

Subjects were randomized to either treatment group AB or treatment group BA. Treatment A was a single dose of 4 mg perampanel in tablet form (reference) and Treatment B a single 12 mg dose of oral suspension.

Study Population

Key inclusion criteria:

- Healthy males or females, ages 18 to 55 years, inclusive
- Body mass index (BMI) of 18 to 32 kg/m^2 inclusive

The study included the following restrictions on prior and concomitant medications, food and beverages:

- Poppy seeds or food containing poppy seeds for at least 48 hours before attending the study center and Days 6, 8 and 29
- No prescribed or OTC drugs (other than oral contraceptives and paracetamol [up to 4 g per day]), or herbal remedies from screening until the follow-up visit
- Abstain from alcohol for 48 hours before they check in to the study unit for each study period and for the duration of their sample collection for that study period
- Methylxanthine-containing products, grapefruit and grapefruit juice-containing products, OTC medications, nutritional supplements, vitamins and herbal preparations are not permitted during the study

The schedule of assessments is summarized in Table 9, which is reproduced from the submission and is in Section 9.5.

Assessments

Pharmacokinetic Assessments/Analyses:

Blood samples for PK assessments were collected from pre-dose to 168 hours post-dose in all subjects. The following PK parameters were determined:

- Primary PK parameters: C_{max}, AUC_{0-72}, and tmax

- Secondary PK parameters: tlag,, AUC_{last} , Kel, and $t_{½}$

Relative bioavailability of the 4 mg oral suspension of perampanel (test) versus the 4 mg tablet will be estimated by analysis of variance (ANOVA) on the log transformed $AUC_{0\text{-}inf}$ using PROC MIXED in SAS. The model will include terms for formulation, period and subject. A 95% confidence interval will be presented for the ratio of the mean $AUC_{0\text{-}inf}$ for the 2 formulations.

Safety Assessments/Analyses:

The safety analysis dataset will consist of all subjects who received at least one dose of perampanel and had on post-dose safety assessment.

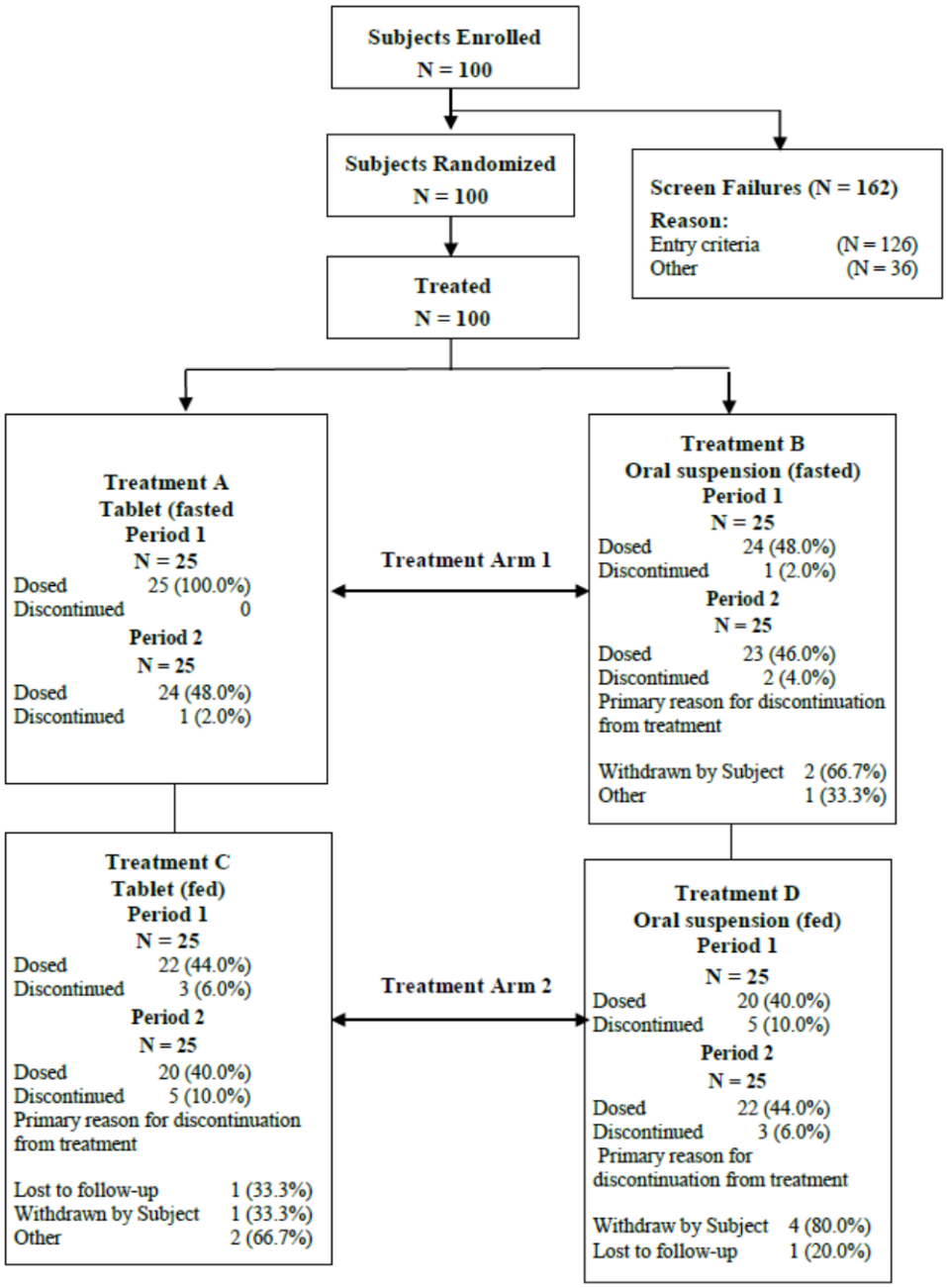
Safety data will include all AEs and SAEs, lab values (hematology, blood chemistry, and urine values), vital signs, and ECGs and will be evaluated using descriptive statistics. AEs will be coded to System Organ Class and preferred term as defined in MedDRA.

5.3.2 Subject disposition, demographic and baseline characteristics (Study 048)

Study 048 was conducted at a single site in the US between 11 SEP 2014 and 12 DEC 2014. A total of 263 subjects were screened, and 162 were considered screen failures. One hundred (100) subjects were enrolled and randomized, and 89 completed the study (47 in Treatment Arm 1 and 42 in Treatment Arm 2). All 100 randomized subjects were dosed in Period 1; 11 subjects were not dosed in Period 2. Disposition is summarized in Figure 3 below and Table 10 in Section 9.5.

During Treatment Arm 1 (fasted), all 50 subjects received at least one dose of perampanel. One subject received only the 12 mg perampanel oral suspension (Period 1). Two subjects received only the 12 mg perampanel tablet and were withdrawn prior to check-in at Period 2. During Treatment Arm 2 (fed), all 50 subjects received at least one dose of perampanel; however, 3 subjects received only the 12 mg perampanel tablet and 5 subjects received only the 12 mg perampanel oral suspension.

Figure 3: Subject Disposition and Primary Reason for Discontinuation From Study Treatment, Study 048



Source: Study 048 CSR, Figure 2

Demographics

There were no significant differences between the fasted (Treatment Arm 1) and fed (Treatment Arm 2) groups. There were slightly more male (51.0%) and white (58.0%)

subjects. Subjects in the Treatment DC group had slightly greater body weight (mean 78.28 kg) as compared to the overall mean weight (72.96 kg) and the other treatment groups, but BMI was similar in all groups.

There were no reported prior medications in violation of the eligibility criteria. One subject (10011048) took a single dose of a concomitant drug during the study (800 mg ibuprofen).

5.3.3 Subject disposition, demographic and baseline characteristics (Study 028)

Study 028 was conducted at a single site in the US. A total of 29 subjects were screened, 9 of whom did not meet the eligibility criteria, 2 of whom withdrew consent, and the other 2 subjects were "not required for dosing". Sixteen (16) subjects were enrolled and randomized, and 15 completed both treatment periods. All 16 randomized subjects were dosed in Period 1; a single subject (#10011013) did not receive drug (oral suspension) during period 2 due to a positive drug screen.

Demographics

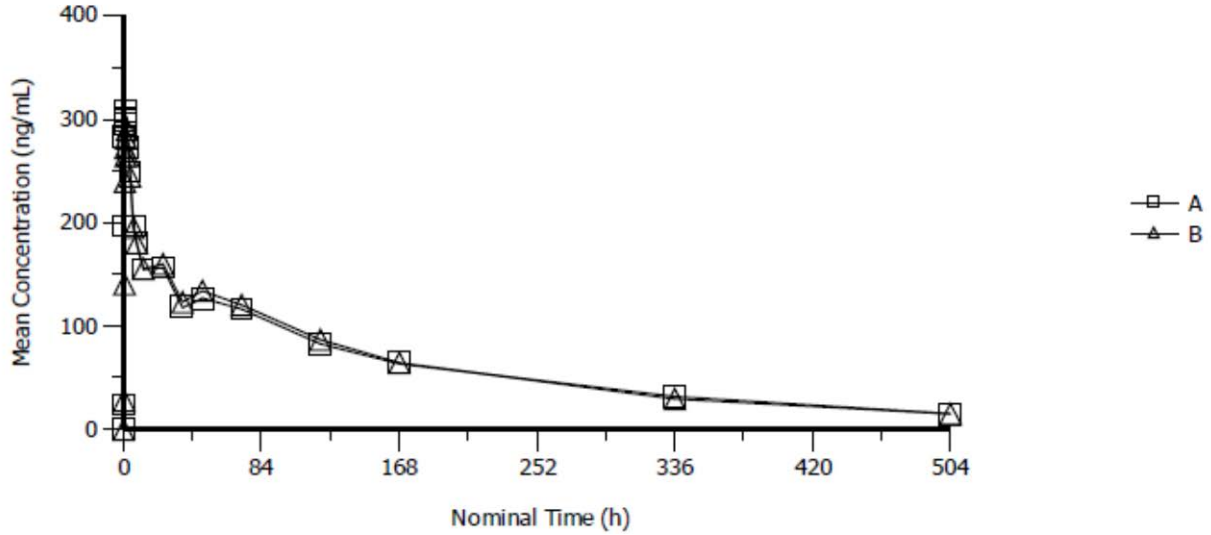
There were no significant differences in mean demographics between the two groups. Nine male and seven female subjects with a mean age of 38.4 years (range 20-53 years) were enrolled. Fifteen subjects were white and 1 subject was African American. Please see Table 12 in Section 9.5 below for specifics.

5.3.4 Pharmacokinetic results

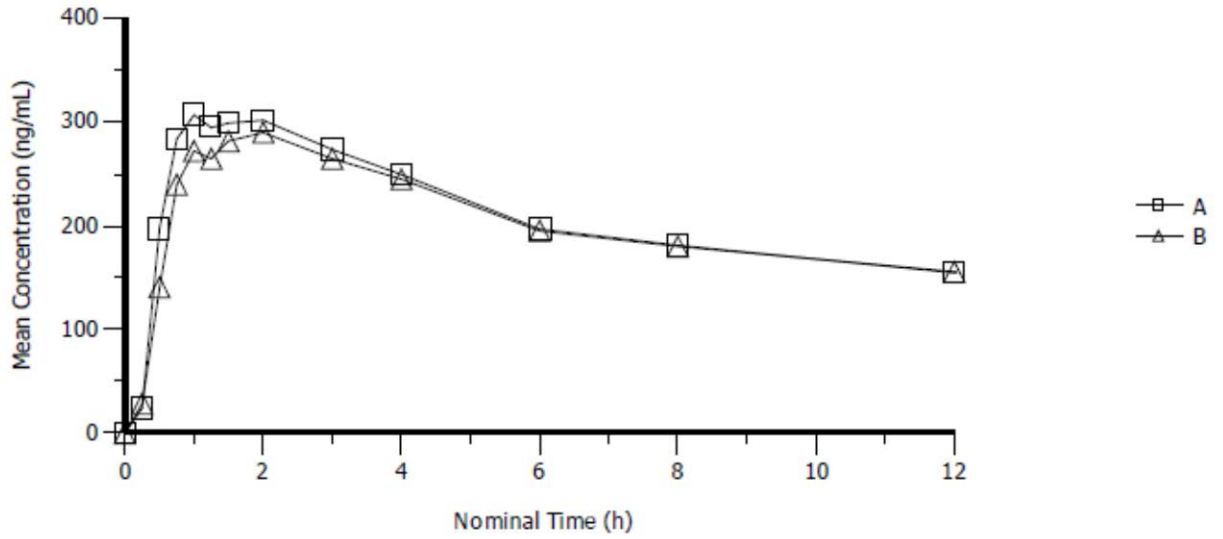
Bioequivalence results from Study 048 are summarized in this section, as they are the basis of this NDA.

In the Clinical Overview, the sponsor states *The PK profile for the 12-mg perampanel oral suspension administered under fasted conditions was essentially super-imposable with that for the 12-mg perampanel tablet under fasted conditions (Study 048 CSR, Table 14.2.3.1 and Study 048 CSR Table 14.2.3.2). There was no lag in absorption for either formulation; the time at which the highest drug concentration occurs (tmax) for the tablet was 1 hour and that for the suspension was 2 hours.* The mean apparent $T_{1/2}$ was 122 hours for the tablet in the fasted group and 134 hours for the suspension in fasted subjects. The mean plasma concentration-time profiles for single dose administrations of perampanel 12 mg tablet and 12 mg oral suspension were very similar after long-term testing and when truncated to 12 hours. (See Figure 4 below)

Figure 4: Perampanel Mean Plasma Concentration-Time Profiles (fasted)



After Single Dose Administrations of 12-mg Perampanel Tablet (Treatment A) and 12-mg Perampanel Oral Suspension (Treatment B) under Fasted Conditions (Arm 1) on a Linear Scale



After Single Dose Administrations of 12-mg Perampanel Tablet (Treatment A) and 12-mg Perampanel Oral Suspension (Treatment B) under Fasted Conditions (Arm 1) Truncated to 12 hours on a Linear Scale

BE criteria were met for all primary endpoints ($AUC_{(0-t)}$, $AUC_{(0-inf)}$, and C_{max}) under fasted conditions) as shown in Table 3 below.

Table 3: Plasma Exposure Parameters after 12 mg Perampanel Oral Suspension (Treatment B) and 12-mg Perampanel Tablet (Treatment A) 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
$AUC_{(0-72h)}$, (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

$AUC_{(0-t)}$ = area under the concentration-time-curve from 0 time to time of last measurable concentration, $AUC_{(0-inf)}$ = area under the concentration-time-curve from 0 time extrapolated to infinite time, $AUC_{(0-72h)}$ = area under concentration-time-curve from 0 time to 72 hours postdose, C_{max} = maximum observed concentration, CI = confidence interval.
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
Source: Study 048 CSR, Table 14.2.3.5

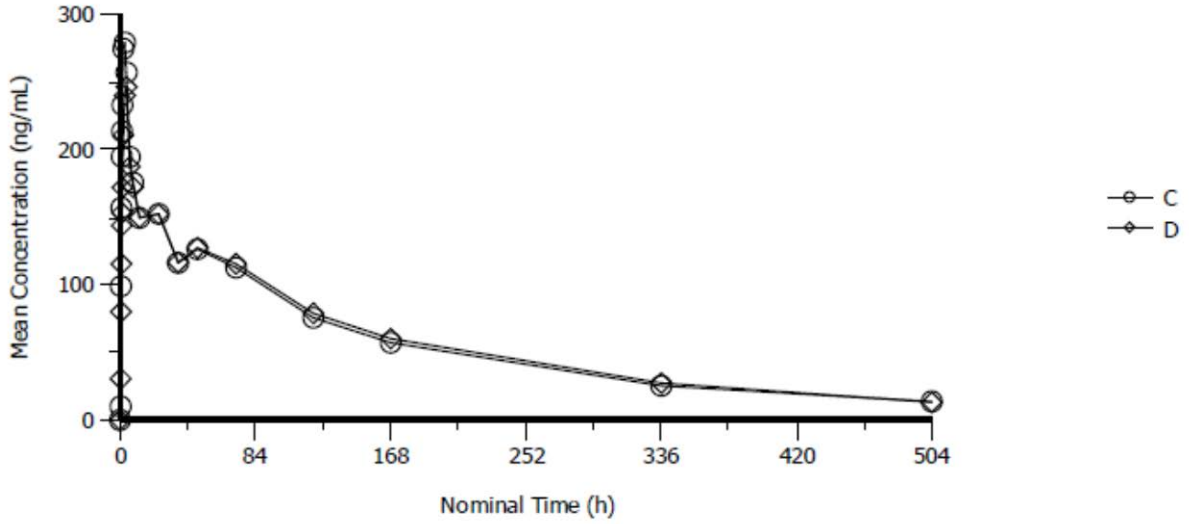
Study 048 also evaluated the pharmacokinetics of perampanel tablet (12 mg) vs. oral suspension (12 mg) in the fed state. The BE criteria for the AUC parameters ($AUC_{(0-t)}$, $AUC_{(0-inf)}$, and $AUC_{(0-72h)}$) were met in this population, suggesting (as per the sponsor) that a high-fat meal did not have an effect on the perampanel absorption from tablet compared to oral suspension. However, there was an ~23% reduction in C_{max} (ratio test/ref = 77.46% [72.41, 82.85]) and a median 2 hour delay in t_{max} after a single 12 mg dose of oral suspension formulation, relative to the tablet formulation. Please see Table 4 and Figure 5 below for specifics.

Table 4: Plasma Exposure Parameters after 12 mg Perampanel Oral Suspension (Treatment D) and 12-mg Perampanel Tablet (Treatment C) under Fed Conditions (Arm 2)

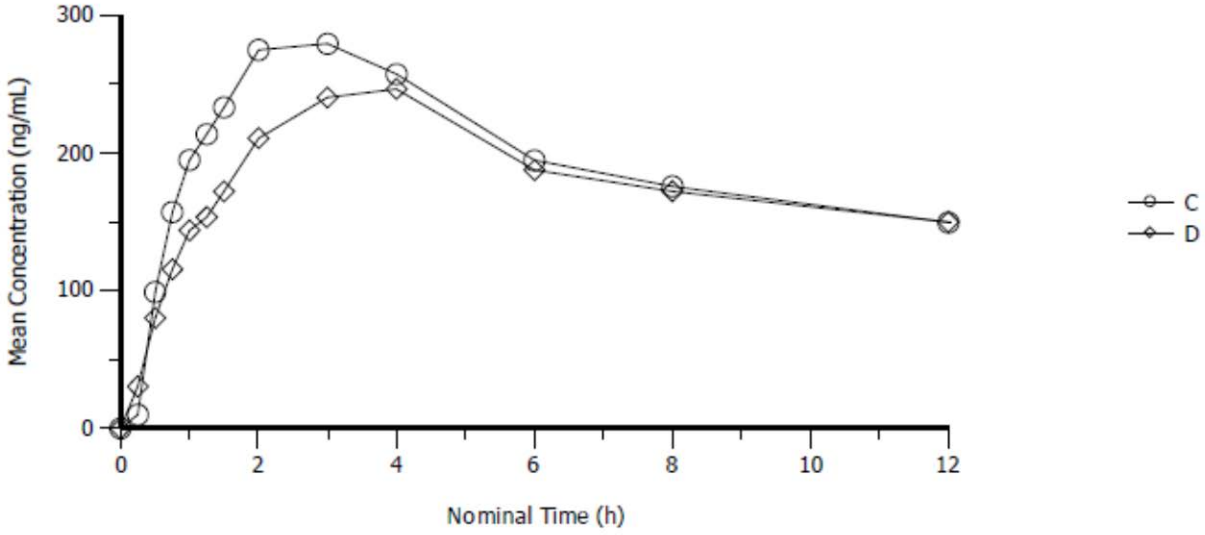
Dependent Variable	GeoMean[c] Test[a]	GeoMean[c] Ref[b]	Ratio (%)[d] (Test/Ref)	90% CI[e] Lower	90% CI[e] Upper
C_{max} (ng/mL)	255	329	77.46	72.41	82.85
$AUC_{(0-72h)}$, (h*ng/mL)	9754	9916	98.36	94.36	102.54
$AUC_{(0-t)}$, (h*ng/mL)	24734	24765	99.88	94.56	105.50
$AUC_{(0-inf)}$, (h*ng/mL)	26159	26309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

$AUC_{(0-t)}$ = area under the concentration-time-curve from 0 time to time of last measurable concentration, $AUC_{(0-inf)}$ = area under the concentration-time-curve from 0 time extrapolated to infinite time, $AUC_{(0-72h)}$ = area under concentration-time-curve from 0 time to 72 hours postdose, C_{max} = maximum observed concentration, CI = confidence interval.
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
Source: Study 048 CSR, Table 14.2.3.6

Figure 5: Perampanel Mean Plasma Concentration-Time Profiles (fed)



After Single Dose Administrations of 12-mg Perampanel Tablet (Treatment C) and 12-mg Perampanel Oral Suspension (Treatment D) under Fed Conditions (Arm 1) on a Linear Scale



After Single Dose Administrations of 12-mg Perampanel Tablet (Treatment C) and 12-mg Perampanel Oral Suspension (Treatment D) under Fed Conditions (Arm 1) Truncated to 12 hours on a Linear Scale

The sponsor performed population PK modeling to further investigate this issue. Please see Dr. Xinning Yang's review for assessment of the pop-PK analysis.

Reviewer's Comments: At the time that this review was completed, the Clinical Pharmacology review was not completed. Brief discussion with Dr. Yang identified no significant issue with the PK data in the NDA submission.

6 Review of Efficacy

Not applicable, as there was no efficacy trial conducted for the FYCOMPA (perampanel) oral suspension.

7 Review of Safety

Safety Summary

This perampanel sNDA submission summarizes the safety data of 116 subjects exposed to perampanel oral suspension in two bioequivalence trials. The clinical safety tests conducted in the trial were appropriate and capable of identifying major safety signals. Overall, the safety findings from this submission are consistent with data from the original NDA submission for partial-onset seizures and the efficacy supplement for primary generalized tonic clonic seizures. No new safety signals were identified in either Study 048 or Study 028.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The sponsor provided data from two bioequivalence trials to support safety of Fycompa oral suspension. Please also see Table 2 for more information on the following studies.

- Study E2007-A001-048 (Study 048): an open-label, 2 arm, single-dose, randomized crossover study that demonstrated bioequivalence between a single dose of perampanel 12 mg oral suspension and a single dose of perampanel 12 mg tablet when administered under fasted and fed (high-fat meal) conditions in healthy subjects.
- Study E2007-E044-028 (Study 028): a randomized, open-label, 2-period, 2-sequence crossover study that compared the relative bioavailability of a single dose of perampanel 4 mg oral suspension to a single dose of perampanel 4 mg tablet (reference formulation) in healthy subjects.

Reviewer's Comments: The studies are limited by lack of a concurrent placebo control arm against which to compare known (and previously unknown) safety concerns. The safety profile of perampanel for US and EU approvals of POS was based on a total of 1639 patients with epilepsy who received perampanel in double-blind Phase 2 and 3 studies

and open-label extensions.

7.1.2 Categorization of Adverse Events

Adverse events were defined in the protocols of Studies 028 and 048 as *"Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product."*

For the purpose of the safety analysis, a treatment emergent adverse events (TEAEs) were defined *as AEs that emerge during treatment, having been absent at pre-treatment (Baseline) or:*

- *Re-emerge during treatment, having been present at Baseline but stopped prior to treatment; or*
- *Worsen in severity during treatment relative to the pre-treatment state, when the adverse event is continuous.*

A serious adverse event was defined in the protocols for Studies 028 and 048 as *any untoward medical occurrence that at any dose:*

- *Results in death;*
- *Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death.);*
- *Requires in-patient hospitalization or prolongation of existing hospitalization;*
- *Results in persistent or significant disability/incapacity; or*
- *Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug).*

AEs were collected from the date of informed consent for both trials and until the last follow-up visit. AEs were followed until resolution or 30 days after the last follow-up visit, whichever came first. For each study, AEs were originally coded or were recoded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In both studies exposure was similar between the tablet and OS formulations.

Of the 100 subjects enrolled in Study 048, 94 received the tablet formulation, and 95

received the oral suspension, and 89 subjects completed both arms of the study, as seen in Table 5 below.

Table 5: Exposure per Period (Safety Analysis Set), Study 048

	Treatment Arm 1 (Fasted)		Treatment Arm 2 (Fed)		
Parameter	Perampanel 12-mg Tablet (N=50)	Perampanel 12-mg OS (N=50)	Perampanel 12-mg Tablet (N=50)	Perampanel 12-mg OS (N=50)	Overall (N=100)
Period 1	25 (50.0)	25 (50.0)	25 (50.0)	25 (50.0)	100 (100.0)
Period 2	24 (48.0)	23 (46.0)	20 (40.0)	22 (44.0)	89 (89.0)

Source: Study 048 CSR, Table 14.3.1.1.

Of the 16 subjects enrolled in Study 028, 15 completed both treatment periods. The one subject (Subject 10011013) who received only one dose was not dosed in Treatment Period 2 due to a positive drug screen at baseline for Period 2. He received perampanel tablet in Treatment Period 1.

Demographics of Studies 028 and 048 are discussed in Sections 5.3.2 and 5.3.3 above.

7.2.3 Special Animal and/or In Vitro Testing

None in this supplement

7.2.4 Routine Clinical Testing

In Study 028, all laboratory tests were not collected at the same visit, and safety laboratory tests were collected at screening, baseline (day -1), and days 2 and 8 of each treatment period and day 29 postdose in Treatment Period 2 (final visit). In Study 048, clinical lab data were collected at screening at baseline (days -1 and 42) and days 2, 22, 44, and 64.

Clinical laboratory tests in both studies consisted of serum chemistry, hematology, cholesterol (screen only), liver function tests (ALT, AST, alkaline phosphatase, bilirubin, GGT), renal function testing, and urinalysis. Virology testing (Study 048 only) included Hepatitis B surface antigen, hepatitis C antibody, and HIV.

Vital signs, ECGs, and examinations were performed/collected during both studies.

7.2.5 Metabolic, Clearance, and Interaction Workup

The reader is referred to the Clinical Pharmacology Review.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in either Study 028 or Study 048.

7.3.2 Nonfatal Serious Adverse Events

A single SAE occurred in Study 048: spontaneous abortion in subject 10011217. The subject, a 23-year-old female, had a positive pregnancy test at the check-in visit for Treatment Period 2 (Day 42) and was not administered the second dose of perampanel (OS). On Day 52, the subject presented to the ER with vaginal bleeding. She had "low" beta-human chorionic gonadotropin levels, and an ultrasound was performed in the ER, which detected no pregnancy. When she followed up with her physician 1 or 2 weeks later, as recommended, a follow-up US showed no fetus or sac. The investigator was unable to rule out the possibility that the event was related to the study drug.

There were no SAEs in Study 028.

7.3.3 Dropouts and/or Discontinuations

There were no TEAEs resulting in treatment withdrawal, discontinuation of the study drug, or study drug adjustment in either study.

7.3.4 Significant Adverse Events

There were no reported cases of allergic reaction (including rash and hypersensitivity), suicidality, or drug induced liver injury.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

7.4.1.1 Common AEs in Study 048

As shown in Table 6 below, 74 subjects (74%) experienced a TEAE in Study 048. None of the AEs were adjudicated as severe and there was a single SAE (see Section 7.3.2 above). Overall, there were no significant differences in AEs between the study arms or between formulations.

As expected, the most common AEs overall were dizziness and somnolence. Twenty-two subjects (44.9%) in Treatment A (tablet/fasted) experienced at least 1 AE of dizziness, while dizziness was reported in 19 subjects (39.6%) in the OS/fasted group (Treatment B). Sixteen subjects (31.1%) reported at least 1 AE of somnolence in the Treatment C group (tablet/fed), while 7 (14.9%) subjects reported at least 1 AE of somnolence when receiving Treatment D (OS/fed). Overall, vertigo, nausea, oral paresthesia, dizziness, headache, and somnolence occurred at a frequency of ≥5% during the study (Table 6). Most of the reported AEs were of short duration.

Table 6: TEAEs in ≥ 5% of Subjects in Any Treatment Group During the Treatment Phase by SOC and PT (Safety Analysis Set, Study 048)

MedDRA System Organ Class Preferred Term	Treatment A (Tablet/fasted) (N=49)	Treatment B (OS/fasted) (N=48)	Treatment C (Tablet/fed) (N=45)	Treatment D (OS/fed) (N=47)	Overall (N=100)
Subjects with any TEAE	**36 (73.5)**	**31 (64.6)**	**26 (57.8)**	**24 (51.1)**	**74 (74.0)**
Ear and labyrinth disorders	**3 (6.1)**	**2 (4.2)**	**2 (4.4)**	**0 (0)**	**7 (7.0)**
Vertigo	3 (6.1)	2 (4.2)	2 (4.4)	0 (0)	7 (7.0)
Gastrointestinal disorders	**14 (28.6)**	**6 (12.5)**	**4 (8.9)**	**2 (4.3)**	**22 (22.0)**
Dry mouth	3 (6.1)	0 (0)	0 (0)	0 (0)	3 (3.0)
Nausea	5 (10.2)	4 (8.3)	2 (4.4)	0 (0)	9 (9.0)
Paraesthesia oral	6 (12.2)	2 (4.2)	0 (0)	0 (0)	6 (6.0)
General disorders and administration site conditions	**4 (8.2)**	**2 (4.2)**	**1 (2.2)**	**4 (8.5)**	**11 (11.0)**
Infections and infestations	**2 (4.1)**	**1 (2.1)**	**1 (2.2)**	**1 (2.1)**	**5 (5.0)**
Nervous system disorders	**31 (63.3)**	**28 (58.3)**	**24 (53.3)**	**18 (38.3)**	**63 (63.0)**
Dizziness	22 (44.9)	19 (39.6)	14 (31.1)	7 (14.9)	41 (41.0)
Headaches	5 (10.2)	7 (14.6)	1 (2.2)	1 (2.1)	12 (12.0)
Somnolence	12 (24.5)	10 (20.8)	16 (35.6)	14 (29.8)	39 (39.0)
Psychiatric disorders	**3 (6.1)**	**3 (6.3)**	**0 (0)**	**1 (2.1)**	**4 (4.0)**

Source: Study 048, CSR, Table 17 (verified using JMP)
(Highlighted ≥5%)

Psychiatric AEs are of special interest, given the significant psychiatric AEs observed in the placebo controlled epilepsy trials. There were 5 AEs categorized by the PT Euphoric Mood in 5 subjects, all of which were mild and of short duration. Two subjects experienced abnormal dreams. There were no reported episodes of suicidal thought or behavior, delusions, psychosis, delirium, or violent of aggressive behavior.

Reviewer's Comments: There were no concerning psychiatric AEs in Study 048.

7.4.1.2 Common AEs in Study 028

Overall, 13 subjects reported 26 TEAEs during the conduct of the study. There was no notable difference in the number of subjects reporting TEAEs after dosing with the suspension (9 subjects) or the tablet (11 subjects). There were no reported severe

TEAEs. The most common TEAEs were upper respiratory tract infection (6 subjects), headache (3 subjects), gastroenteritis (2 subjects) and dizziness (2 subjects). All other TEAEs were reported by 1 subject during the study. Four subjects reported 6 TEAEs that were considered possibly or probably related to study drug; 3 events (headache, dizziness and vaginal bleeding) were reported by 3 subjects after receiving the suspension and 3 events (headache, dizziness and postural dizziness) were reported by 2 subjects after receiving the tablet. Most AEs occurred within 48 hours of drug administration.

Table 7: TEAEs in by SOC and PT (Safety Analysis Set, Study 028)

System Organ Class Preferred Term	Perampanel 4 mg		
	Suspension (N=15) n (%)	Tablet (N=16) n (%)	Combined Total (N=16) n (%)
Any TEAE	9 (60.0)	11 (68.8)	13 (81.3)
Infections and Infestations	5 (33.3)	4 (25.0)	7 (43.8)
Upper respiratory tract infection	4 (26.7)	3 (18.8)	6 (37.5)
Gastroenteritis	0	2 (12.5)	2 (12.5)
Hordeolum	1 (6.7)	0	1 (6.3)
Oral herpes	1 (6.7)	0	1 (6.3)
Nervous system disorders	2 (13.3)	4 (25.0)	5 (31.3)
Headache	1 (6.7)	3 (18.8)	3 (18.8)
Dizziness	1 (6.7)	1 (6.3)	2 (12.5)
Dizziness postural	0	1 (6.3)	1 (6.3)
General disorders and administration site conditions	0	2 (12.5)	2 (12.5)
Catheter site inflammation	0	1 (6.3)	1 (6.3)
Vessel puncture site hematoma	0	1 (6.3)	1 (6.3)
Reproductive system and breast disorders	2 (13.3)	1 (6.3)	2 (12.5)
Dysmenorrhea	1 (6.7)	1 (6.3)	1 (6.3)
Vaginal hemorrhage	1 (6.7)	0	1 (6.3)
Musculoskeletal and connective tissue disorders	0	1 (6.3)	1 (6.3)
Musculoskeletal pain	0	1 (6.3)	1 (6.3)
Neoplasms benign, malignant and unspecified (inc cysts and polyps)	0	1 (6.3)	1 (6.3)
Melanocytic nevus	0	1 (6.3)	1 (6.3)

Source: Study 028, CSR, Table 14.3.1.2, verified with JMP

There were three AEs in Two subjects that were considered moderate in severity, both of which were deemed not related to the study drug. Subject 10011012 had moderate gastroenteritis (tablet) and Subject 10011007 had moderate oral herpes and moderate upper respiratory tract infection (oral suspension).

A total of 9 subjects received treatment for their AEs. Six of these occurred after receiving the tablet (4 subjects took paracetamol for headaches, 1 subject took paracetamol for dysmenorrhea, and 1 subject took co-codamol for an upper respiratory tract infection). Three subjects received treatment for AEs after the oral suspension (2 subjects took paracetamol for upper respiratory tract infections and 1 subject took

paracetamol for dysmenorrhea).

7.4.2 Laboratory Findings

7.4.2.1 Measures of Central Tendency and Shift Changes

In study 048, the mean values for all laboratory parameters were generally unchanged for the suspension and tablet formulations and between fed and fasted states. While there were some parameters in which subjects experienced a shift from within the normal reference range at baseline to outside the reference range after receiving perampanel, the majority of subjects had values within the normal reference range before and after dosing. Any shifts were transient and only just outside the normal reference range. There were no notable differences between the four treatment arms in shift data for any laboratory parameter.

In Study 028, the mean values for all laboratory parameters were generally unchanged for both the suspension and tablet formulations, with the exception of creatine kinase. After dosing with suspension and tablet, mean creatine kinase values were notably lower on Day 2 (63.8 IU/L and 64.8 IU/L, respectively) than at Baseline (107.4 IU/L and 117.4 IU/L, respectively). Creatine kinase values returned to Baseline by Day 8. There was no notable difference between formulations in the mean values for any laboratory parameter. The majority of subjects had values within the normal reference range at pre- and post-dose. There were some parameters in which subjects experienced a shift from within the normal reference range at Baseline to outside the reference range after dosing. These shifts were transient and only just outside the normal reference range. There were no notable differences between formulations in shift data for any laboratory parameter.

Reviewer's Comments: The only notable mean change in lab values was a decrease in mean CK on day 2 in comparison to baseline. A similar reduction in CK was not noted in the placebo controlled epilepsy trials. This finding is of unclear significance.

7.4.2.2 Potentially Clinically Significant Laboratory Data

There was a single subject in Study 048 with an AE related to a lab value. Subject 10011003 had a low neutrophil count (1.0) on study day 64 (last dose on day 43). He was reported to be recovering from a viral illness at the time of the lab work on day 64. His screening neutrophil count was 2.3 (day -1) and his second baseline neutrophil count was 3.3, (day 42). Follow-up neutrophil count on day 91 was 3.7. The AE was considered not related to the drug by the investigator.

There were no clinically significant abnormalities in any individual laboratory

assessment during Study 028.

Reviewer's Comments: It is unlikely that the low neutrophil count was related to the drug, based on the presence of a concurrent viral illness. Additionally, the RCTs of perampanel did not demonstrate any difference in incidence of neutropenia between drug and placebo.

7.4.3 Vital Signs

7.4.3.1 Clinically or Potentially Clinically Significant Vital Signs

There were no reported changes of clinical significance in mean vital signs in Study 048. There were no vital signs results after dosing that were considered markedly abnormal. There were no differences between the treatment groups in vital signs results.

In study 028, the mean values for vital signs after dosing were unchanged compared with baseline values. There were no notable differences in mean values or changes from baseline between the tablet and oral suspension formulations.

7.4.4 Electrocardiograms (ECGs)

In Study 048, 12 lead ECGs were collected at screening, baseline period 1, days 1, 4, 22, 42 (baseline period 2), 43, 46, and 64. There were no changes from baseline of clinical importance in mean ECG parameters over time and no post-baseline ECG results were identified as markedly abnormal values.

In Study 028, 12-lead ECGs were collected at screening, day 1 (predose and postdose) and day 8. No clinically significant abnormalities were reported.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies performed in this supplement.

7.5 Other Safety Explorations

Safety explorations such as dose dependency for adverse events, time dependency for adverse events, or drug-disease interactions were not conducted for this application.

7.6 Additional Safety Evaluations

Please refer to the Fycompa Package Insert for information related to the following special groups and situations:

Human carcinogenicity
Human reproduction and pregnancy data
Pediatrics and assessment of effects on growth

7.6.3 Pediatrics and Assessment of Effects on Growth

N/A, studies done in adults.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

7.6.4.1 Overdose

There were no subjects with overdose during either study.

The reader is referred to the Controlled Substance Staff review for further details regarding drug abuse potential and withdrawal. CSS reviewer recommends changes to the labeling based on reported "withdrawal seizures" reported in some patients during post market usage of the tablet formulation. Further information was provided by the sponsor in response to an Information Request dated March 9, 2016. As part of this submission, the sponsor provided summary information on 14 patients in whom seizures occurred in the setting of abrupt discontinuation of FYCOMPA. Of these 14 patients, 13 were being treated with FYCOMPA tablets for a diagnosis of epilepsy, and one patient was receiving the drug for an unknown reason. Many of these patients were on other AEDs, thus confounding the situation. Additionally, withdrawal seizures were not deemed a safety concern on review of the randomized, placebo controlled efficacy trials in patients with POS (n=706) or PGTC seizures (n=162), when there was no drug taper specified.

At this time of the completion of this review, CSS had not commented on the information included in the IR.

Reviewer's Comments: Patients with poorly controlled (or even well-controlled) epilepsy may have seizures on withdrawal of an anticonvulsant drug, even if the drug is gradually tapered, because the drug may have been effective in reducing seizures. In most of the 14 cases identified by the sponsor, it is difficult to identify withdrawal as the cause of seizures, as opposed to discontinuation of a potentially effective drug. Based on this information and the lack of a signal for withdrawal seizures in the controlled studies in which there was no taper of the drug, this reviewer does not recommend any changes to

the label warning of withdrawal seizures.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

Fycompa OS is not approved for use and therefore there are no available postmarketing data. Postmarketing information related to perampanel orally disintegrating tablet can be found in the Fycompa® Package Insert.

9 Appendices

9.1 Literature Review/References

None

9.2 Labeling Recommendations

Labeling is currently under review.

9.3 Advisory Committee Meeting

N/A

9.4 Eligibility Criteria

Study 048 Key Exclusion Criteria:

- Clinically significant illness within 8 weeks or a clinically significant infection within 4 weeks of dosing
- Evidence of disease that may influence the outcome of the study within 4 weeks of dosing, or subjects who have a congenital abnormality in metabolism
- Any history of gastrointestinal surgery that may affect PK profiles of perampanel or slow gastric emptying.
- Any clinically abnormal symptom or organ impairment found at Screening or any physical examinations, vital signs, electrocardiogram (ECG) finding, or laboratory test results that require medical treatment at Screening or Baseline

- Any laboratory abnormalities considered clinically significant by the investigator
- A prolonged QT/QTc interval (QTc >450 msec) as demonstrated upon repeat ECG at Screening or Baseline
- Cardiac history: prolonged QT/QTc interval; ischemic heart disease; risk factors for torsade de pointes
- Sitting heart rate <40 or >100 bpm and sitting SBP > 140 mmHg or <90 mmHg or DBP >90 mmHg or <60 mmHg at Screening or Baseline
- Hemoglobin <11.5 g/dL for females and <12.5 g/dL for males
- Weight loss or gain of >10% between Screening and before dosing
- Hypersensitivity to the study drug or any of its excipients
- HIV positive or Active viral hepatitis (B or C) at Screening
- History of use of illegal (or legalized) recreational drugs in the past year
- History of drug or alcohol dependency or abuse within the last 2 years or positive urine drug test or breath alcohol test at Screening or Baseline
- Engagement in strenuous exercise within 2 weeks before dosing

Study 028 Key Exclusion Criteria:

- Currently taking or have taken any prescribed or OTC drug (except paracetamol [max 4 g per day]) or herbal remedies in the 4 weeks prior to the start of study
- On special diets or dietary aids that are known to modulate drug metabolizing enzymes (e.g., St John's Wort)
- Do not agree to avoid consumption of grapefruit or grapefruit-containing products during the study
- Have received any experimental drug within the 12 weeks leading up to the start of study drug treatment or are enrolled in another clinical trial
- History of alcohol abuse (within the past 6 months) or who drink more than the maximum recommended number of units of alcohol per week (21 units for men, 14 units for women) or who are unwilling to abstain from consumption of alcohol during in-patient confinement
- Consume more than 5 caffeinated beverages per day or who are unwilling to abstain from consumption of caffeine-containing food and beverages during in-patient stay
- Smoke more than 5 cigarettes (or equivalent amount of tobacco) per day or who are unwilling to abstain from the use of nicotine-containing products during in-patient stay
- History of drug abuse or dependence or a positive urine drug screening test
- Women of child-bearing potential who do not agree to use 2 methods of adequate contraception throughout the study.

9.5 Summary Tables

Table 8: Study 048 – Schedule of Assessments

Phase	Pre-randomization		Randomization																
Period	Screening	Baseline Period 1	Treatment Period 1								Baseline Period 2	Treatment Period 2							
Visit	1	2	3			4	5	6	7	8	9				10	11	12	13'	
Day	Day-28 to-2	-1	1	2	3	4	6	8	15	22	42	43	44	45	46	48	50	57	64
Assessment																			
Informed consent	X																		
Demographics	X																		
Inclusion/exclusion criteria	X	X																	
Medical history	X	X																	
Prior/Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X										X								X
Vital signs"	X	X	X			X				X	X	X			X				X
Height and weight	X																		
12-lead ECG'	X	X	X			X				X	X	X			X				X
Virology tests"	X																		
Serum pregnancy test'	X																		X
Urine pregnancy test'		X									X								
Clinical laboratory tests'	X	X		X						X	X		X						X
Urine drug screen"	X	X									X								
Study drug administration"			X									X							
High fat meal (Arm 2 only)'			X									X							
Blood sample for PK'			X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization			X																
Admission to clinic		X'									X'								
Discharge from clinic						X									X				
Outpatient visit	X						X	X	X	X						X	X	X	X
Discharge from Study																			X

Table 9: Schedule of Procedures and Assessments for Study E2007-E044-028

Phase	Pre-Randomization		Randomization												
Period	Screening	Baseline 1	Treatment Period 1					Baseline 2	Treatment Period 2						
Visit	1	2	3					4	5	6				7	8a
Day	Days -21 to -2	-1	1	2	3	4	6	8-41b	-1	1	2	3	4	6	8	29
Assessments																
Informed consent	X															
Demographics	X															
Inclusion/exclusion criteria	X	X														
Medical history	X															
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X								X						X	X
Vital signsc	X	X	X				X	X	X	X				X	X	X
Height, Weight, BMI	X															
12-lead ECG	X	X	X						X	X					X	X
Serum pregnancy test	X															
Urine pregnancy test		X							X							
Laboratory safety tests	X	X		X				X	X		X				X	X
Urine drug screen	X	X							X							
Breath alcohol test	X	X							X							
Admission to clinic		Xi							Xi							
Discharge from unit/study						X	X	X					X	X	X	X
Randomization		X														
Study drug administration			X							X						
PK sampling pharmacokinetics[k]			X	X	X	X	X	X		X	X	X	X	X	X	X
Standardized meals		X	X	X	X				X	X	X	X				
Outpatient visit	X						X	X						X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Virology tests	X															

Source: Table 2, Study 028 Protocol

Table 10: Subject Disposition and Primary Reason for Discontinuation From Study Treatment – All Randomized Subjects, Study 048

	Treatment A	Treatment B	Treatment C	Treatment D	Overall
Randomized, n	50	50	50	50	100
Period 1	25	25	25	25	100
Dosed study treatment, n (%)	25 (50.0)	24 (48.0)	22 (44.0)	20 (40.0)	91 (91.0)
Discontinued study treatment, n (%)	0	1 (2.0)	3 (6.0)	5 (10.0)	9 (9.0)
Period 2	25	25	25	25	100
Dosed study treatment, n (%)	24 (48.0)	23 (46.0)	20 (40.0)	22 (44.0)	89 (89.0)
Discontinued study treatment, n (%)	1 (2.0)	2 (4.0)	5 (10.0)	3 (6.0)	11 (11.0)
Period 1 or 2					
Primary reason for discontinuation, n (%)					
Lost to follow-up	0	0	1 (33.3)	1 (20.00	2 (18.2)
Physician decision	0	0	1 (33.3)		1 (9.1)
Withdrawal by subject	0	2 (66.7)	1 (33.3)	4 (80.0)	7 (63.6)
Other	0	1 (33.3)	0	0	1 (9.1)

Source: Study 048, CSR, Table 7

Table 11: Baseline Demographics – Safety Analysis Dataset, Study 048

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)					
Mean (SD)	34.0 (11.13)	37.4 (11.33)	37.5 (10.08)	31.6 (8.62)	35.1 (10.48)
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)
Race, n (%)					
White	13 (52.0)	18 (72.0)	13 (52.0)	14 (56.0)	58 (58.0)
Black	12 (48.0)	6 (24.0)	10 (40.0)	8 (32.0)	36 (36.0)
Other		2 (8.0)	2 (8.0)	2 (8.0)	6 (6.0)
Weight (kg)					
Mean (SD)	72.74 (11.991)	69.38 (10.993)	71.45 (11.274)	78.28 (14.155)	72.96 (12.431)
Min, Max	55.3, 95.0	51.5, 98.0	52.8, 98.1	45.6, 95.7	45.6, 98.1
BMI (kg/m^2)					
Mean (SD)	26.6 (3.09)	25.6 (2.98)	25.9 (3.27)	26.8 (3.83)	26.2 (3.30)
Min, Max	19.7, 21.1	21.1, 29.8	21.0, 31.8	18.9, 31.7	18.9, 31.9

Source: CSR Study 048

Table 12: Summary of Demographic and Baseline Characteristics

	Group 1 N=8	Group 2 N=8	Combined N=16
Mean ± SD Age (years)	39.9 ± 12.18	37.0 ± 12.47	38.4 ± 12.00
Mean ± SD Height (cm)	171.6 ± 11.16	171.6 ± 10.72	171.6 ± 10.57
Mean ± SD Weight (kg)	75.56 ± 17.232	77.03 ± 13.565	76.29 ± 15.000
Mean ± SD BMI (kg/m2)	25.39 ± 3.824	25.99 ± 2.585	25.69 ± 3.169
Race			
White n (%)	7 (87.5)	8 (100)	15 (93.8)
Black or African American n (%)	1 (12.5)	0 (0)	1 (6.3)
Sex			
Male n (%)	4 (50.0)	5 (62.5)	9 (56.3)
Female n (%)	4 (50.0)	3 (37.5)	7 (43.8)

Source: CSR Study 028, Table 14.1.4

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