CLINICAL REVIEW

Application Type	Supplemental NDA
Application Number(s)	Efficacy Supplement, S-005 Seq 0089 to NDA 202-834
Priority or Standard	Standard
Submit Date(s)	August 19, 2014
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Division / Office	Division of Neurology Products Office of New Drugs
Reviewer Name(s)	Mary Doi, M.D., M.S.
Review Completion Date	May 11, 2015
Established Name	Perampanel
(Proposed) Trade Name	FYCOMPA
Therapeutic Class	Anticonvulsant
Applicant	Eisai Inc.
Formulation(s)	Oral tablet
Dosing Regimen	4mg – 12 mg daily
Indication(s)	Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in epilepsy patients
Intended Population(s)	12 years of age and above

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This is the safety review of sNDA 202-834 (perampanel) as of March 30, 2015. The efficacy of perampanel in the adjunctive therapy of primary generalized tonic-clonic seizures (PGTC) in epilepsy patients is being reviewed by Dr. Philip Sheridan. Final recommendations on approval of this application will be provided by Drs. Sheridan (primary reviewer) and Hershkowitz (CDTL).

1.2 Risk Benefit Assessment

Please refer to the review of clinical efficacy by Dr. Philip Sheridan.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

I recommend enhanced pharmacovigilance of postmarket safety for the following adverse events of special interest: acute pancreatitis, drug reaction with eosinophilia and systemic symptoms, and ligament/tendon rupture.

1.4 Recommendations for Postmarket Requirements and Commitments

I recommend a postmarket requirement for further evaluation of the safety signal of weight gain and other metabolic changes.

2 Introduction and Regulatory Background

2.1 Product Information

The chemical name of perampanel is 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzonitrile. The Applicant reports that perampanel is a selective non-competitive antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor, inhibiting binding of the excitatory neurotransmitter, glutamate. The precise mechanism by which perampanel exerts its antiepileptic effects has not yet been fully established.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are many currently available drugs approved for the adjunctive therapy of primary generalized tonic-clonic seizures. Please see the list provided in the efficacy review performed by Dr. Sheridan.

2.3 Availability of Proposed Active Ingredient in the United States

Perampanel was approved as Fycompa for marketing in the U.S. on October 22, 2012 for adjunctive therapy of partial-onset seizures (POS) in patients with epilepsy aged 12 years and older.

2.4 Important Safety Issues With Consideration to Related Drugs

Several AMPA antagonists are in either pre-clinical or clinical development in various therapeutic areas. No other selective AMPA antagonists are currently approved for any indication.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Milestones since the US approval of Fycompa in 2012 are summarized below:
7/15/2014 – Pre-sNDA meeting
7/31/2014 – Additional FDA feedback provided regarding content & format for the sNDA

2.6 Other Relevant Background Information

For additional background information and presubmission regulatory activities, the reader is referred to Dr. Sheridan's clinical review of efficacy.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

For detailed information on submission quality and integrity, the reader is referred to Dr. Sheridan's clinical review of efficacy. Datasets submitted by the Applicant for the 120-Day Safety Update did not contain the new safety data from the subjects (n=24) who had completed the Study 332 Core before the sNDA was submitted but who had no safety data from the Extension Phase 332 available as of the cutoff date for the Summary of Clinical Safety. However, new datasets were submitted by the Applicant that contained this new data (on March 11, 2015) and, overall, the clinical safety sections of the submission were acceptable for review.

3.2 Compliance with Good Clinical Practices

For detailed information on compliance with good clinical practices, the reader is referred to Dr. Sheridan's clinical review of efficacy.

3.3 Financial Disclosures

For detailed information on financial disclosures, the reader is referred to Dr. Sheridan's clinical review of efficacy.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Not applicable.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Not applicable.

4.4 Clinical Pharmacology

For details on the Clinical Pharmacology of perampanel, the reader is referred to the Clinical Pharmacology review. The following information has been excerpted from the applicant's overview of clinical pharmacology.

4.4.1 Mechanism of Action

Please see Section 2.1 of this review.

4.4.2 Pharmacodynamics

The population PD analysis of the data from the Phase 3 study, Study 332, in subjects with primary generalized tonic-clonic seizures, demonstrated that the percent reduction in 28-day average primary generalized tonic-clonic seizure frequency from baseline during maintenance treatment increased as a function of perampanel exposure and that the probability of being a primary generalized tonic-clonic seizure responder increased with an increase in perampanel plasma concentration.

4.4.3 Pharmacokinetics

The population PK analysis based on pooled data from all subjects in Study 332 and the three Phase 3 studies in subjects with refractory partial-onset seizures (Studies 304, 305, 306) in the original application demonstrated that the PK of perampanel was similar in subjects with refractory POS and PGTC seizures and that there was a reduction in perampanel exposure when perampanel was co-administered with the concomitant CYP3A inducers carbamazepine, oxcarbazepine, and phenytoin.

5 Sources of Clinical Data

During the review cycle, the applicant responded diligently to multiple FDA informational requests. The dates of the Safety Information Amendments are listed below. Unless otherwise noted, this review covers information submitted to Supplement NDA 202-834 up to March 19, 2015. The 120-day Safety Update was submitted on December 22, 2014 (Seq 103, #233). Safety Information Amendments were submitted by the Applicant on the following dates in 2014 and 2015: October 10 (Seq 99, #201), October 14 (Seq 98, #202), December 5 (Seq 102, #225), January 23 (Seq 109, #241), January 30 (Seq 110, #244), March 2 (Seq 113, #252), March 11 (Seq 114, #253), and March 19, 2015 (Seq 115, #254).

5.1 Tables of Studies/Clinical Trials

The efficacy and safety of perampanel as adjunctive therapy in PGTC seizures is based on data from the following Phase 3 study:

- E2007-G000-332 (Study 332)
  Double-blind, randomized, placebo-controlled, multicenter, parallel-group study with an open-label extension phase designed to evaluate the efficacy, safety, and PK of perampanel in adolescents (aged ≥12 years) and adults with uncontrolled PGTC seizures despite being maintained on a stable dose of 1 to a maximum of 3 AEDs.

The Summary of Clinical Safety included key safety results from 2 additional studies:

- E2007-G000-235 (Study 235)
  Double-blind, placebo-controlled study that evaluated the effects of perampanel on cognition, growth, safety, tolerability, and PK in adolescents (≥12 to <18 years) with uncontrolled POS.
- E2007-G000-232 (Study 232)
  Pilot, open-label study that evaluated the pharmacokinetics and preliminary safety, tolerability, and efficacy of perampanel oral suspension in pediatric subjects (≥2 to <12 years old) with uncontrolled POS.

5.2 Review Strategy

This review will primarily focus on the analysis of the safety of oral perampanel in the treatment of primary generalized tonic-clonic seizures using data from Study 332 Core.

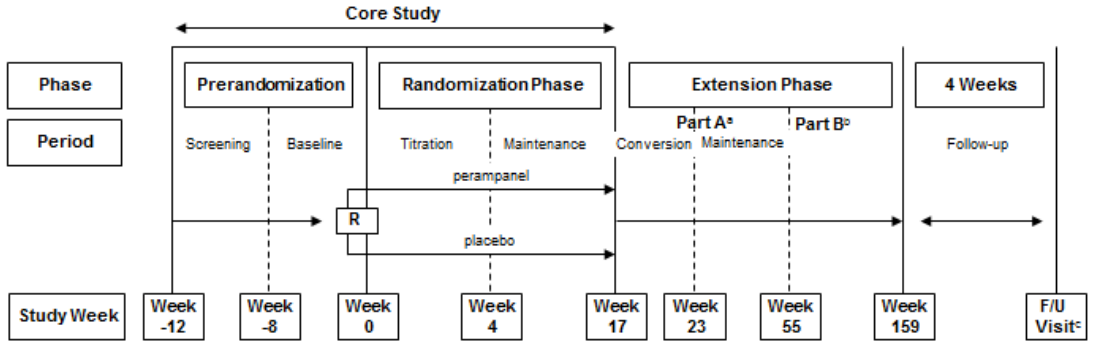
Safety will be presented for deaths, serious AEs, discontinuations due to AEs, AEs of interest, common AEs, laboratory evaluations, and vital signs. Safety data from Study 235 were also reviewed and pertinent findings are included. (Study 232 will only be briefly mentioned in this review due to the different ages of the study population). The efficacy of oral perampanel as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures will be evaluated by Dr. Sheridan.

5.3 Discussion of Individual Studies/Clinical Trials

The detailed characteristics of Study 332 are provided below and in the following figure.

- Core Study:
  - Prerandomization Phase: 12 weeks
  - Randomization Phase:
    - Titration: 4 weeks (Visit 4 and 5)
      - Perampanel dose increased 2 mg at weekly intervals to 8 mg/day
    - Maintenance: 13 weeks (Visit 6, 7, and 8)
      - No more than 1 up-titration or down-titration allowed unless approved by Medical Monitor (maximum perampanel dose 8 mg/day)
    - Follow-up: 4 weeks (only for subjects not entering Extension Phase)
- Extension Phase:
  - Part A: 6-week Conversion Period + 32-week Maintenance Period
    - Subjects randomized to placebo group in Core Study started perampanel at 2 mg/day and up-titrated weekly in 2 mg increments to optimal dose at the investigator's discretion
    - Subjects randomized to perampanel group in Core Study continued dose received during Core Study Maintenance Period
  - Part B: 104-week (maximum) Maintenance Period
    - Maximum dose of perampanel 12 mg/day
    - Dose of perampanel could be decreased (due to intolerance) and increased if needed for seizure control

Figure 1. Design for Study 332



R = Randomization.
F/U = Follow-up.
a = All subjects should be retained in the study through the last visit of Extension Part A.
b = Subjects only need to complete Part B if perampanel is not made available free of charge according to the appropriate local country-specific mechanism (revised per Amendment 03)
c = The Follow-up visit should be conducted for all subjects 4 weeks after their last on-treatment visit.

Source: CSR 332 Figure 1

The following table summarizes the characteristics of Study 235.

Table 1. Details of Study 235

Study Identifier	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Duration of Treatment
E2007-G000-235 (Core)	To compare the short-term effect of perampanel on cognition to placebo by using the Cognitive Drug Research (CDR) System when administered as an adjunctive therapy in adolescents (12 to <18 years of age) with inadequately controlled POS (with or without secondarily generalized seizures)	Randomized, double-blind, placebo-controlled, parallel- group	Perampanel 2 mg tablets or matching placebo; oral. 2 mg/day up titrated in weekly 2 mg increments to a target dose range of 8 to 12 mg/day.	N=133 Randomized (85 perampanel, 48 placebo)	19 weeks
E2007-G000-235 Cognition Report	To compare the short-term effect of perampanel on cognition to placebo by using the Cognitive Drug Research (CDR) System when administered as an adjunctive therapy in adolescents (12 to <18 years of age) with inadequately controlled POS (with or without secondarily generalized seizures)	Randomized, double-blind, placebo-controlled	Perampanel 2 mg tablets or matching placebo; oral. 2 mg/day up titrated in weekly 2 mg increments to a target dose range of 8 to 12 mg/day.	N=133 Randomized (85 perampanel, 48 placebo)	19 weeks

Source: 5.2 Tabular Listing of Clinical Studies

6 Review of Efficacy

The reader is referred to Dr. Sheridan's review of efficacy.

7 Review of Safety

Safety Summary

This perampanel sNDA submission summarizes the safety data of 273 perampanel-exposed subjects from 3 trials conducted in subjects (adult and pediatric subjects) with GTCS (n=138) and subjects with partial-onset seizures (n=135). Overall, the safety findings from this submission are consistent with data from the original NDA submission for partial-onset seizures. No new safety signals were identified.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The focus of this safety review is Study 332 Core, the Phase 3 DB clinical trial performed in subjects with PGTC. Please see design of the trial detailed in Section 5.3 above. The key inclusion and exclusion criteria for Study 332 are listed below (per CSR Study 332).

Key Inclusion Criteria

1. Male or female and **≥ 12 years** of age (except for in Germany, subjects ≥18 yrs of age and in India, <65 years of age).
2. Females of **nonchildbearing potential** or of childbearing potential with negative pregnancy tests prior to treatment (abstinent or use ≥1 method of contraception during the study and for 30 days after study drug discontinuation).
3. Diagnosis of **PGTC seizures** in setting of idiopathic generalized epilepsy.
4. During 8-wk Prerandomization Period, subjects must have had **≥ 3 PGTC** seizures.
5. Computed tomography or magnetic resonance **imaging** within the last 10 years that ruled out a progressive cause of epilepsy.
6. Had routine EEG ≤ 5 years prior to baseline with **EEG features consistent with primary generalized epilepsy**.
7. On fixed doses of **1, 2 or a maximum of 3 approved AEDs**. Only 1 inducer AED (defined as carbamazepine, oxcarbazepine, phenytoin) was allowed.
8. On a **stable dose** of the same concomitant AED(s) for 1 month prior to baseline.
9. A **vagal nerve stimulator** was allowed but it must have been implanted ≥ 5 months prior to baseline. Stimulator parameters could not be changed.

Key Exclusion Criteria

1. **Pregnant** and/or lactating women.
2. Presence of **concomitant diagnosis of partial onset seizures**.
3. Presence of **progressive neurological disease**.
4. Presence or previous history of **Lennox-Gastaut syndrome**.
5. History of **status epilepticus** within approximately 12 months prior to baseline.
6. **Seizure clusters** where individual seizures could not be counted.

7. History of **psychogenic seizures**.
8. Evidence of **clinically significant disease** (e.g., cardiac, respiratory, renal, gastrointestinal disease) that "in the opinion of the investigator(s) could have affected the subject's safety or study conduct"
9. Significant **active hepatic disease**. Stable elevations of liver enzymes, ALT and AST were allowed if they were ≤3 times the upper limit of normal (ULN).
10. Active **viral hepatitis** (A, B, or C) as demonstrated by pre-existing positive serology.
11. Positive for **human immunodeficiency virus**.
12. Had any **suicidal ideation with intent** ≤ 6 months prior to Visit 2.
13. **Drug or alcohol dependency** or abuse within approximately the last 2 years.
14. Multiple drug allergies or a **severe drug reaction** to an AED(s), including dermatological, hematological, or organ toxicity reactions.
15. If **felbamate** was used as a concomitant AED, subjects were on felbamate for ≥2 years, with a stable dose without a history of hepatic or bone marrow dysfunction.
16. If had a past history of use of **vigabatrin**, vigabatrin must have been discontinued for > 5 months prior to baseline.
17. Concomitant use of **barbiturates** (except for seizure control indication) or other **inducers of CYP3A**.
18. Use of intermittent rescue **benzodiazepines** ≥2 times in one month prior to baseline.

Comment: The exclusion criteria may limit the generalizability of the safety data, as subjects with some of the excluded conditions would likely receive perampanel in the clinical practice (e.g., patients with any "clinically significant" disease, active hepatic disease, and suicidal ideation).

Data Cutoff Dates
At the time of the NDA submission, the main Phase 3 Study, Study 332 Core along with the core periods for Studies 232 and 235 were complete. All 3 studies had ongoing OLE studies. In the NDA, the Applicant identified March 1, 2014 as the cutoff date for the ongoing OLE portion of Study 332 and identified June 30, 2014 as the cutoff date for information regarding deaths and SAEs for the OLE portions of Studies 232 and 235. The Applicant reported that the CSR for Study 232 was still in preparation at the time of the sNDA submission date (but later provided in an information amendment on October 13, 2014).

In the 120-day Safety Update, the Applicant identified September 1, 2014 as the cutoff date for the safety data primarily from the extension phase of Study 332.

7.1.2 Categorization of Adverse Events

The safety population was defined as subjects who received at least one dose of study drug (perampanel or placebo) and had at least one safety assessment after taking the first dose of study drug.

An adverse event (AE) was defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product (CSR 332). Adverse events included the following (CSR 332):

- Any unfavorable and unintended sign (including an abnormal laboratory finding),
- symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (e.g., ECG, x-ray) that resulted in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (e.g., headache) not present pretreatment (baseline)

An abnormal laboratory test result was considered an AE if the identified laboratory abnormality led to any type of intervention. Additionally, a laboratory result was considered by the investigator to be an AE if it (CSR 332):

- Resulted in the withdrawal of study drug
- Resulted in withholding of study drug pending some investigational outcome
- Resulted in the initiation of an intervention, based on medical evaluation
- Resulted in any out-of-range laboratory value that in the investigator's judgment fulfilled the definitions of an AE with regard to the subject's medical profile
- Resulted in a worsening (increased) in severity relative to baseline by at least 2 grades with the exception of lymphocytes, albumin, cholesterol, glucose, and phosphate. For these tests, if the change of ≥2 grades was considered to be of clinical significance by the investigator, the laboratory result was considered an AE.

Abnormal laboratory values were not listed as separate AEs if they were considered to be part of the clinical syndrome that was being reported as an AE.

The investigators were instructed to record all AEs (on the CRF for the question, "Did the subject experience any Adverse Events?") that the subjects experienced from the time of signing the informed consent form to 14 days after the last visit (ongoing adverse events followed for 30 days). Any AE that were recorded on the CRF during the 14 days following the last visit will be following until resolution or for up to 30 days after last visit, whichever comes first. All SAEs that occur within 30 days following the last dose of study drug were collected on the CRF and followed until the event resolved or sequelae stabilized.

Comment: Of note, a period of up to 30 days covers 4 to 5 elimination half-lives of approximately 4.5 days (mean).

Treatment-emergent adverse events (TEAEs) were defined as AEs that either began on or after the date of the first dose of study drug and up to 30 days after the date of the last dose of study drug; or AEs that began before the first dose date and increased in severity (or reemerged) during the treatment period (or reemerged during treatment).

The Applicant used Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 for coding AEs reported in Study 332 (and version 16.0 for Study 235). The Applicant provided an adverse event coding dictionary (mapping of verbatim terms to coded terms) for Study 332 with the Reviewer's Guide in Appendix 1.

Comment: After reviewing the AE dataset for Study 332 Core to assess the coding of the verbatim terms to the MedDRA preferred terms, the coding process overall seemed appropriate and allowed for reliable estimates of AE risks. However, there were cases that appeared to be coding omissions. For example, the verbatim term of "cold with headaches" was only coded to the PT nasopharyngitis (and not also to headache) and "nausea from head bump" was only coded to the PT head injury (and not also to nausea). Additionally, the following verbatim terms were not coded to the PT fall: "contusion on head due to fall from a seizure," "head injury secondary to fall," "hand pain secondary to fall due to seizure," and "left arm pain secondary to fall." However, the Applicant notes in the submission that in Study 332, to "distinguish seizure-associated events from independent ones, a systematic review of reported events of falls was conducted, and queries were sent to the investigator to establish whether these events were related to a seizure or not. The only falls that were reported as TEAEs were those that did not occur in connection with seizures."

There were also instances where the coding process resulted in splitting likely related AEs into separate SOCs leading to an underestimation of the true incidence for a particular event or syndrome. Therefore, in order to account for the splitting of the preferred terms into different system organ classes in this NDA, additional analyses were performed by the reviewer (in Section 7.3) to group these preferred terms across SOCs to provide more accurate estimates of adverse event syndromes.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data in the Epilepsy population were not pooled.

7.2 Adequacy of Safety Assessments

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

7.2.1.1 Exposure

The following table summarizes the overall perampanel exposure of the safety analysis set.

Table 2. Perampanel Exposure by Duration and Study

Exposure to Perampanel	332 Core only	332 Core plus Extension	Study 232	Core 235	TOTAL
≥ 1 dose	81	138	50	85	273
> 6 months	0	107	0	0	107
> 12 months	0	68	0	0	68
Subject-weeks	1268.1	7590.1	498.0	1532.0	9620.1

Source: Summary of Clinical Safety (Table 5) and 120-day safety update (Table 4), CSR 232 (Table 14), CSR 235 (Table 18)

Study 332 Core
A total of 81 subjects with PGTC seizures received perampanel in Study 332 Core (and 82 subjects received placebo). Subject 12021033, assigned to the perampanel group, elected to withdraw from the study before receiving the first dose of study drug.

The following table summarizes extent of exposure by randomized dose for Study 332 Core. The median duration of exposure for both treatment groups was 17.0 weeks (the length of the double-blind period of this study). However, the percentages of subjects who received treatment for more than 10 weeks (and >14 weeks) were lower in the perampanel group than placebo (86.4% vs 92.7% and 85.2 vs 89.0%, respectively).

Table 3. Extent of Exposure by Randomized Dose, Study 332 Core

Extent of Exposure	Placebo n (%)	Perampanel n (%)
Any exposure[a], n (%)	82	81
0-1 week	82 (100.0)	81 (100.0)
> 1 to 2 weeks	82 (100.0)	81 (100.0)
> 2 to 4 weeks	80 (97.6)	81 (100.0)
> 3 to 4 weeks	80 (97.6)	81 (100.0)
> 4 to 5 weeks	79 (96.3)	79 (97.5)
> 5 to 6 weeks	79 (96.3)	78 (96.3)
> 6 to 10 weeks	79 (96.3)	77 (95.1)
> 10 to 14 weeks	76 (92.7)	70 (86.4)
> 14 to 18 weeks	73 (89.0)	69 (85.2)
> 18 weeks	6 (7.3)	2 (2.5)
Duration of exposure(wks)[b]		
n	82	81
Mean	16.18	15.66
Median	17.00	17.00
Number of subject-weeks[c]	1327.0	1268.1

Source: Study 332 Core, Table 14.3.1.1.1
a: Subjects were counted in each applicable exposure category
b: Duration of exposure = date of last dose of study drug – date of first dose of study drug + 1
c: Number of subject-weeks = summation over all subjects' exposure durations

In addition to discontinuing, some subjects were unable to reach and maintain the 8 mg dose of perampanel. While the maximum daily dose received was 8 mg for most perampanel subjects (95.1%, n=77), the last dose received was 8 mg for 84.0% of the perampanel subjects (CSR 332 Core, Table 14.3.1.1.9). Of the 77 subjects who received the maximum dose of 8 mg, down-titrating or discontinuations occurred in 24.7% (n=19) (CSR 332 Core, Table 14.3.1.1.16). For most of these subjects, the dose reduction or discontinuation was due to a TEAE (73.7%, n=14) or subject choice (15.8%, n=3).

Study 332 Extension
As of the cutoff date of September 1, 2014 (for the 120-day Safety Update), 138 subjects had entered the Extension Phase contributing 7590.1 subject-weeks of cumulative exposure (120 day safety update, Table 4). As of the cutoff date, 105 subjects were still ongoing in the Extension phase.

The following table summarizes the extent of exposure by modal dose group for Study 332 Core and Extension. The median duration of exposure was 50.7 weeks. The median average daily dose of perampanel for the Study 332 Extension Phase was 8.0 mg and the majority of the subjects were in the >4 to 8 mg/day modal dose group (120 day safety update, Table 4).

Table 4. Extent of Exposure by Modal Dose, Study 332 Extension

	Perampanel (modal daily dose)				
	<4 mg	4 mg	>4-8 mg	>8-12 mg	Total
Duration of exposure(wks)					
n	1	9	98	30	138
Mean	3.6	54.5	51.7	67.7	55.0
Median	3.6	62.6	44.3	64.9	50.7
Number of subject-weeks[a]	5.1	490.7	5064.4	2031.4	7590.1

Source: 120 day safety update, Table 4
The exposure to perampanel is defined as the exposure during the double-blind and open-label studies
a: Number of subject-weeks = summation over all subjects' exposure durations rounded to 1 decimal place

In Study 235, the mean maximum dose of perampanel in the Core Study was 10 mg while the mean daily dose was 8.3 mg (CSR 235).

7.2.1.2 Demographics

The Applicant categorized the demographic characteristics into the following population subgroups: age group (≥12 to <17 years, ≥17 to <65 years, ≥65 years), sex (male, female), race (white, black/African American, Asian/Pacific, other), and baseline AEDs. Additionally for the Study 332 Core only, subgroup analyses were performed for region (Europe, North America, Asia-Pacific), pooled country (Austria/Greece/Serbia/Israel; Lithuania/France; Czech Republic/Poland; all other countries were not pooled), and whether the subjects were receiving inducer AEDs or noninducer AEDs at baseline (for selected safety tables).

The demographic characteristics of the safety analysis set for Study 332 Core are summarized in the following table. Most of the subjects were adults (17 to <65 years old) with 8.6% who were 12 to <17 years old in the placebo group and 13.6% who were 12 to <17 in the perampanel group. There was only 1 subject who was 65 years of age or older (in the placebo group). In accordance with the inclusion/exclusion criteria, no subject was less than 12 years old. The race of the safety analysis set was predominantly white (53.7%) or Asian (42.0%). Female subjects represented 56.2%. The subjects were enrolled in sites worldwide: Europe (25%), North America (24%), and Asia-Pacific (51%). Overall, baseline demographic characteristics were similar between the placebo and perampanel treatment groups.

Table 5. Baseline Demographic Characteristics, Study 332 Core

	Placebo n=81	**Perampanel** n=81
Sex (male)	36 (44.4)	35 (43.2)
Age (mean years)	29.5	27.3
Age Group		
12 to <17 years	7 (8.6)	11 (13.6)
17 to <65 years	73 (90.1)	70 (86.4)
≥65 years	1 (1.2)	0
Race		
Caucasian	43 (53.1)	44 (54.3)
Black	3 (3.7)	1 (1.2)
Japanese	6 (7.4)	5 (6.2)
Chinese	18 (22.2)	18 (22.2)
Other Asian	10 (12.3)	11 (13.6)
Other	1 (1.2)	2 (2.5)
Region		
Europe	20 (24.4)	20 (24.7)
North America	20 (24.4)	19 (23.5)
Asia-Pacific	42 (51.2)	42 (51.9)

Source: Study 332 Core CSR, Table 14.1.4.1.1 and created by reviewer using JReview (datasets: ADSL)
Percentages are based on the total number of subjects with nonmissing values in relevant treatment group.

Baseline Disease characteristics
For details about the disease characteristics the reader is referred to Dr. Sheridan's review of efficacy.

Baseline and Concomitant AEDs
Subjects enrolled in Study 332 Core were being treated with 1, 2, or a maximum of 3 approved AEDs at stable doses for ≥ 30 days prior to the first visit. Only 1 enzyme-inducing AED (defined as carbamazepine, phenytoin, or oxcarbazepine) was allowed. Most of the subjects in the safety analysis set were treated at baseline with 2 AEDs (46.0%), fewer with 1 AED (33.7%), and fewest with 3 AEDs (19.6%) (CSR 332 Core, Table 14.1.4.2.2). (The Applicant notes that Table 14.1.4.2.2 incorrectly shows that 1 subject in the placebo group was taking 4 AEDs due to an error in coding. The subject was actually taking 3 AEDs at baseline and received a benzodiazepine as rescue medication that was miscoded as a baseline AED).

The Applicant notes that among the 6 most frequently used AEDs (lamotrigine, valproic acid, levetiracetam, topiramate, zonisamide, valproate semisodium), there was more than a 2-fold difference in use between the 2 treatment groups for topiramate (8.5% placebo and 22.2% perampanel) and zonisamide (15.9% and 7.4%, respectively). While inducer AEDs were used by 16.6% of subjects overall, the use of an inducer AED was higher in the placebo group (22.0% [n=18]) than in the perampanel group (11.1% [n=9]), largely due to an imbalance in the use of carbamazepine (11.0% [n=9] and 4.9% [n=4], respectively). (CSR 332 Core, Table 14.1.4.2.3)

Comment: In the Summary of Clinical Safety, the Applicant mainly compares the perampanel group in Study 332 Core (randomized to titrate up to 8 mg of perampanel) with the 8 mg perampanel randomized dose group from the original NDA submission (three pooled Phase 3 studies performed in POS). However, in those studies (304, 305, 306), approximately half of the total perampanel group was taking an enzyme-inducing AED at baseline (47.9%, ISS Table 20.2-3) compared to 11.1% of the perampanel group in Study 332 Core. Therefore, the exposure of the perampanel group in Study 332 Core may be higher than similar randomized dose groups in the POS studies. Thus, in this review, I will compare the perampanel group in Study 332 Core to both the 8 and 12 mg perampanel dose groups from my original review of the POS pooled double-blind studies (rather than only the 8 mg dose group).

Concomitant medications were defined as medications that either (1) started before first dose of study drug and were continuing at the time of first dose of study drug, or (2) started on or after first dose of study drug up to 14 days after the last dose of study drug. The most common concomitant AEDs, (taken by ≥ 10% of the subjects in any group), were lamotrigine, levetiracetam, valproic acid, topiramate, valproate semisodium, zonisamide, clonazepam, and carbamazepine (in order of decreasing frequency in the perampanel group) (CSR 332 Core, Table 14.1.4.3.3).

The only concomitant non-AED medication taken by at least 10% of the subjects in either group was paracetamol (6.2% placebo and 12.3% perampanel).

7.2.2 Explorations for Dose Response

Not applicable as there was only 1 randomized dose group in Study 332 Core.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

In Study 332, safety was evaluated using the following parameters: TEAEs, clinical laboratory tests, vital signs (including weight), concomitant medication use, Columbia Suicide Severity Rating Scale (C-SSRS), withdrawal questionnaire, and premature termination. The clinical testing in the trial protocol appeared adequate to allow assessment of the safety of perampanel. Routine and special safety assessments in are presented in the following table. All of these assessments were also performed during early discontinuation visits for subjects who were withdrawn from the study for any reason.

Table 6. Schedule of Assessments, Study 332 Core

Phase	Pre-randomization	Double-blind Phase					Follow up[b]	Unscheduled
Period		Titration[a]		Maintenance[b]				
Week	Week -12 to 0	2	4	8	12	17	23	
Day	to Day 1	15	29	57	85	120	161	
Visit	Visit 1 to 3	4	5	6	7	8	9	
Assessment								
Adverse events	X	X	X	X	X	X	X	X
C-SSRS[e]	X	X	X	X	X	X	X	
Vitals and weight[c]	X	X	X	X	X	X	X	X
Laboratory tests	X		X		X		X	X[f]
Perampanel concentration[d]				X	X	X	X	
Withdrawal questionnaire	X					X	X	
Physical examination	X			X			X	
Neurological exam	X			X			X	
12-lead ECG	X							

Source: Clinical Study Report Study 332, Table 3
[a] Titration Period visits has a window of ± 3 days with >10 days between visits.
[b] Maintenance and Follow-up visits had a window of ± 7 days of the schedule. Note the follow-up visit only applied to subjects who completed the study (or who discontinued the study early), but did not enroll into the OLE Study.
[c] Height was measured only at the Screening Visit.
[d] Blood samples collected at 1 timepoint per designated visit.
[e] An assessment of suicidality using C-SSRS was performed at Baseline Visits 2 and 3, every scheduled visit, including after the last dose of study drug.
[f] At the discretion of the investigator.

The following table summarizes the laboratory data that were captured.

Table 7. Laboratory Assessments, Study 332 Core

Hematology	hematocrit, hemoglobin, red blood cell (RBC) count, platelet count, white blood cell (WBC) count with differential
Chemistry	
Electrolytes	sodium, potassium, chloride, calcium, bicarbonate, phosphorus
Liver function tests	alkaline phosphatase, ALT, AST, total bilirubin, direct bilirubin
Renal function tests	blood urea nitrogen and creatinine
Other	albumin, cholesterol, globulin, glucose, lactate dehydrogenase, uric acid, triglycerides, total protein
Urinalysis	pH, ketones, protein, glucose, RBCs, WBCs, casts, bacteria, crystals, epithelial cells, occult blood, specific gravity

Source: Clinical Study Report Study 332, Table 2

A laboratory value was determined to be a treatment-emergent markedly abnormal value (TEMAV) if the postbaseline grade using the modified National Cancer Institute Common Toxicity Criteria (NCI-CTC) increased from baseline and the postbaseline grade was greater than or equal to 2. The only exception was phosphate, which required a change of ≥ 3 grades to be a TEMAV. Potentially clinically significant changes were postbaseline values with NCI-CTC grade of 2 (3 for phosphate) or more in subjects with normal values at baseline. For laboratory abnormalities meeting criteria of an SAE ("any treatment emergent significant laboratory abnormality"), the study site

was required to fax the SAE report including the laboratory report to the Applicant using the SAE Form (CSR 332). The following table summarizes the modified NCI-CTC grades and criteria used by the Applicant.

Table 8. Modified National Cancer Institute Common Toxicity Criteria (NCI-CTC)

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	< LLN – 10.0 g/dL < LLN – 100 g/L < LLN – 6.2 mmol/L	< 10.0 – 8.0 g/dL < 100 – 80 g/L < 6.2 – 4.9 mmol/L	< 8.0 – 6.5 g/dL < 80 -65 g/L < 4.9 -4.0 mmol/L	< 6 5 g/dL < 65 g/L < 4.0 mmol/L
Leukocytes (total WBC)	< LLN – 3.0 x 10^9/L < LLN – 3000/mm^3	< 3.0 – 2.0 x 10^9/L < 3000 – 2000/mm^3	< 2.0 – 1.0 x 10^9/L < 2000 – 1000/mm^3	< 1.0 x 10^9/L < 1000/mm^3
Lymphocytes • 7-12 years old • 13 years or older	NA < LLN – 800/mm^3 < LLN – 0.8 x 10^9/L	NA < 800 – 500/mm^3 < 0.8 – 0 5 x 10^9/L	<minimum (500, LLN) – 200/mm^3 <minimum (0.5, LLN) – 0.2 x 10^9/L < 500 – 200/mm^3 < 0.5 – 0.2 x 10^9/L	< 200/mm^3 < 0.2 x 10^9/L < 200/mm^3 < 0.2 x 10^9/L
Neutrophils	< LLN – 1.5 x 10^9/L < LLN – 1500/mm^3	< 1.5 – 1.0 x 10^9/L < 1500 – 1000/mm^3	< 1.0 – 0.5 x 10^9/L < 1000 – 500/mm^3	< 0.5 x 10^9/L < 500/mm^3
Platelets	< LLN – 75.0 x 10^9/L < LLN – 75,000/mm^3	< 75.0 – 50.0 x 10^9/L < 75,000 – 50,000/mm^3	< 50.0 – 25.0 x 10^9/L < 50,000 – 25,000/mm^3	< 25.0 x 10^9/L < 25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia) • 18 years or older • 12-17 years old	< LLN – 3 g/dL < LLN – 30 g/L NA	< 3 – 2 g/dL < 30 – 20 g/L <minimum (3 , LLN) – 2 g/dL <minimum (30 , LLN) – 20 g/L	< 2 g/dL < 20 g/L < 2 g/dL < 20 g/L	NA NA
Alkaline phosphatase	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
ALT, SGPT (serum glutamic pyruvie transaminase)	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
AST, SGOT (serum glutamic oxaloacetic transaminase)	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
Bicarbonate, serum-low	< LLN – 16 mEq/L	< 16 – 11 mEq/L	<11 – 8 mEq/L	< 8 mEq/L
Bilirubin (hyperbilirubinemia)	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 10.0 x ULN	> 10.0 x ULN
Calcium, serum-low (hypocalcemia)	< LLN – 8.0 mg/dL < LLN – 2.0 mmol/L	< 8.0 – 7.0 mg/dL < 2.0 – 1.75 mmol/L	< 7.0 – 6.0 mg/dL < 1.75 – 1.5 mmol/L	< 6.0 mg/dL < 1.5 mmol/L
Calcium, serum-high (hypercalcemia)	> ULN – 11.5 mg/dL > ULN – 2.9 mmol/L	> 11 5 – 12.5 mg/dL > 2.9 – 3 1 mmol/L	> 12.5 – 13.5 mg/dL > 3.1 – 3.4 mmol/L	> 13 5 mg/dL > 3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	> ULN – 300 mg/dL > ULN – 7.75 mmol/L	> 300 – 400 mg/dL > 7.75 – 10.34 mmol/L	> 400 – 500 mg/dL > 10.34 – 12.92 mmol/L	> 500 mg/dL > 12.92 mmol/L
Creatinine	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 6.0 x ULN	> 6.0 x ULN
GGT (γ-Glutamyl transpeptidase)	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
Glucose, serum-high (hyperglycemia)	> ULN – 160 mg/dL > ULN – 8.9 mmol/L	> 160 – 250 mg/dL > 8.9 – 13.9 mmol/L	> 250 – 500 mg/dL; > 13.9 – 27.8 mmol/L;	> 500 mg/dL; > 27.8 mmol/L; or ketoacidosis
Glucose, serum-low (hypoglycemia)	< LLN – 55 mg/dL < LLN – 3.0 mmol/L	< 55 – 40 mg/dL < 3.0 – 2 2 mmol/L	< 40 – 30 mg/dL < 2.2 – 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L
Phosphate, serum-low (hypophosphatemia)	<LLN- 2.5 mg/dL <LLN – 0.8 mmol/L	2.0- <2.5 mg/dL 0.6- <0.8 mmol/L	1.0- <2.0 mg/dL 0.3- <0.6 mmol/L	< 1.0 mg/dL < 0.3 mmol/L

Potassium, serum-high (hyperkalemia)	> ULN – 5.5 mmol/L	> 5.5 – 6.0 mmol/L	> 6.0 – 7.0 mmol/L	> 7.0 mmol/L
Potassium, serum-low (hypokalemia)	< LLN – 3.0 mmol/L	NA	< 3.0 – 2.5 mmol/L	< 2.5 mmol/L
Sodium, serum-high (hypernatremia)	> ULN – 150 mmol/L	> 150 – 155 mmol/L	> 155 – 160 mmol/L	> 160 mmol/L
Sodium, serum-low (hyponatremia)	< LLN – 130 mmol/L	NA	< 130 – 120 mmol/L	< 120 mmol/L
Triglyceride, serum-high (hypertriglyceridemia)	> ULN – 2.5 x ULN	> 2 5 – 5.0 x ULN	> 5.0 – 10 x ULN	> 10 x ULN
Uric acid, serum-high (hyperuricemia)	> ULN – 10 mg/dL ≤ 0.59 mmol/L without physiologic consequences	NA	> ULN – 10 mg/dL ≤ 0.59 mmol/L with physiologic consequences	> 10 mg/dL > 0.59 mmol/L

Source: Study 332 SAP Appendix II

Comment: I compared the modified NCI-CTC grades and criteria used by the Applicant to identify treatment-emergent markedly abnormal laboratory values with the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (published June 14, 2010 by the NCI).[1] The values were similar. However, the following differences were noted. The ranges for both ALT and GGT for Grade 1 and Grade 2 were >ULN-2.5 x ULN and >2.5-5.0 x ULN, respectively, in CTCAE Version 4.03 instead of >ULN-3.0 x ULN and >3.0-5.0 x ULN, respectively, used by the Applicant. Additionally, more severe cases of hypertriglyceridemia were categorized in each Grade by the Applicant when compared to CTCAE Version 4.03 (e.g., Grade 4 included triglyceride levels >10 xULN by the Applicant, while the CTCAE Version 4.03 included lower triglyceride levels of >6.67 x ULN such that a higher threshold was used for shifts in toxicity grade for triglyceride levels by the Applicant).

Vital signs measurements included systolic blood pressure, diastolic blood pressure, pulse, and weight (orthostatic measurements were not performed in Study 332 Core). Criteria for identifying clinically notable values are listed in the following table. For the Core Study only, additional summaries were provided of the number of subjects with increases or decreases of 5 to 10, 11 to15, 16 to 20, or >20 mmHg in blood pressure and who developed Stage 1 or 2 hypertension while on treatment.

1 Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Published June 14, 2010. U.S. Department of Health and Human Services. National Institutes of Health. National Cancer Institute. Accessed January 30, 2015. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Table 9. Criteria for Identifying Clinically Notable Values, Vital Signs and Weight

Variable	Criterion Value	Change Relative to Baseline
Systolic Blood Pressure	> 180 mmHg	Increase of ≥ 20 mmHg
	< 90 mmHg	Decrease of ≥ 20 mmHg
Diastolic Blood Pressure	> 105 mmHg	Increase of ≥ 15 mmHg
	< 50 mmHg	Decrease of ≥ 15 mmHg
Pulse	> 120 bpm	Increase of ≥ 15 bpm
	< 50 bpm	Decrease of ≥ 15 bpm
Weight	NA	Increase of > 7%
	NA	Decrease of > 7%

Source: Summary of Clinical Safety, Table 1

ECG assessments were performed only at screening in Study 332. Withdrawal questionnaire was administered at baseline, at the end of treatment, and at the end of follow up. For the Core Study only, subjects who met ≥1 of the following criteria for metabolic syndrome at any time during treatment was summarized by treatment group and body weight gain category and also by baseline concomitant AED: triglyceride value ≥150 mg/dL, SBP/DBP ≥130/85 mmHg, and BMI >30 kg/m^2.

7.2.5 Metabolic, Clearance, and Interaction Workup

The reader is referred to the Clinical Pharmacology Review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

No other drugs in this class are currently approved for clinical use.

7.3 Major Safety Results

7.3.1 Deaths

In Study 332 Core, the Applicant reported that there were a total of 2 deaths: 1 death in a perampanel-treated subject (1.2%) and 1 death in a placebo-treated subject (1.2%). In Extension Study 332, the Applicant reported 1 additional death in a perampanel-treated subject. The Applicant reported that there were no deaths that occurred in either Study 232 or Study 235. (In the 120-day Safety Update, the Applicant reported no additional deaths as of the data cut-off date of November 1, 2014 in any of the studies).

Comment: In terms of sudden, unexplained death in epilepsy (SUDEP) cases, none of these deaths in perampanel-treated subjects were classified as SUDEP by the Applicant. I reviewed these cases and agree with the Applicant.

The following table summarizes the deaths. Additionally, the available clinical details for the 2 deaths in patients treated with perampanel are summarized below (from details provided by the Applicant).

Table 10. Summary of All Deaths

Subject	Study	Age/sex/race /Study Day	Last treatment	Last dose	Preferred Term
Study 332 Core					
2623-1002	Core	20/ M/ W/ 64	Perampanel	8 mg	Drowning
2611-1001	Core	27/ F/ W/ 11	Placebo	Placebo	Convulsion
Study 332 Extension					
2207-1002	Ext	58/ M/ W/ 313	Perampanel	10 mg	Pancreatitis acute

Source: Summary of Clinical Safety, Tables 20 and 21
F=Female, M=Male, W=White

Comment: After reviewing the available clinical details for the 2 deaths in perampanel-treated subjects, it is difficult to draw any definitive conclusions about the causal role of perampanel in these deaths: 1 drowning death (not a case of SUDEP with marked pulmonary edema on autopsy per the latest SUDEP definitions[2]) and 1 death from complications of acute pancreatitis (on Study Day 313 and on concomitant medications known to cause pancreatitis).

Subject 2623-1002, a 20 year-old white male in Study 332 Core who died from drowning. The subject had a history of epilepsy with tonic-clonic seizures, ADHD, and bipolar disorder with concomitant medications of levetiracetam, lamotrigine, venlafaxine, atomoxetine, and quetiapine. On Study Day (b) (6) while on 8 mg of perampanel), the subject went fishing and was found dead from drowning. Autopsy report *(submitted by the Applicant in response to the Division's information request dated 9/26/14)* confirmed the death was due to drowning (without any evidence of assault or lethal injuries) with evidence of marked pulmonary edema and therapeutic concentrations of the antiepileptic drugs.

Subject 2207-1002, a 58 year-old white male treated with perampanel for 317 days who died from acute pancreatitis in Study 332 Extension. The subject was randomized to the perampanel group in the Study 332 Core which the subject completed and subsequently entered Study 332 Ext. On Study Day (b) (6) while on 10 mg of perampanel, the subject was hospitalized with acute necrotizing pancreatitis and multi-organ failure/septic shock requiring care in the intensive care unit and prolonged ventilator support**.** Perampanel was discontinued on Day (b) (6) Course was complicated by pneumonia and status epilepticus. About 2 months later (Study Day (b) (6), the subject died. The subject had a history of epilepsy with absence and tonic-clonic seizures, diabetes, mellitus, hypertension, and hyperlipidemia. Concomitant medications included metformin, glimepiride, levetiracetam, valproic acid, and lamotrigine along with the following recently initiated medications (started on ~Study Day 36): bisoprolol, hydrochlorothiazide, fenofibrate, atorvastatin, and ramipril.
Comment: Of note, acute pancreatitis is included in labeling for ramipril, hydrochlorothiazide, fenofibrate, and atorvastatin. The Applicant reported that the autopsy report was not available for this subject but provided a translated hospital discharge report (submitted by the Applicant in response to the Division's information request dated 9/26/14) which included information consistent with the Applicant's subject narrative.

2 Nashef L et al. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia. 2012; 53(2): 227-233.

7.3.2 Nonfatal Serious Adverse Events

The Applicant defined serious adverse events (SAEs) as those that resulted in death, were life-threatening, required hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability/incapacity or congenital anomaly or birth defect. Additionally, other important medical events that may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE were also considered to be SAEs by the Applicant. The following hospitalizations were not considered to be SAEs by the Applicant (there was no untoward medical occurrence): hospitalizations for respite care or for administration of study drug and planned hospitalizations required by the protocol or before informed consent. All SAEs were followed by the investigators until resolution or stabilization. This approach was acceptable to the reviewer.

The following table summarizes the TEAEs, SAEs, and TEAEs leading to discontinuation in Study 332 Core. While SAEs occurred in perampanel subjects at a lower frequency than placebo subjects, TEAEs (and TEAEs leading to discontinuation) were experienced by perampanel subjects more frequently than placebo.

Table 11. Overview of TEAEs, SAEs, and TEAEs leading to discontinuation, Study 332 Core

	Placebo n (%)	Perampanel n (%)
Total	**82 (100%)**	**81 (100%)**
Serious TEAEs	7 (8.5%)	6 (7.4%)
Deaths	1 (1.2%)	1 (1.2%)
Other SAEs	6 (7.3%)	5 (6.2%)
TEAEs leading to discontinuation	5 (6.1%)	9 (11.1%)
TEAEs	59 (72%)	67 (82.7%)

Source: CSR 332 Table 17

The following table summarizes the 5 SAEs experienced by only perampanel subjects and not placebo subjects in Study 332 Core.

Table 12. SAEs in Perampanel Subjects Greater than Placebo, Study 332 Core

	Placebo n (%)	Perampanel n (%)
Constipation	0	1 (1.2)
Drowning	0	1 (1.2)
Cholecystitis Chronic	0	1 (1.2)
Suicidal Ideation	0	1 (1.2)
Suicide Attempt	0	1 (1.2)

Source: Summary of Clinical Safety, Table 22

In Study 332 Ext, SAEs were experienced by 6.5% (n=9 out of 138) of the perampanel-treated subjects. The following additional SAEs were experienced by perampanel subjects in Study 332 Ext (120-day Safety Update, Table 10): 2 suicide attempt (1 also with SAE depression, 1 with convulsion), 1 aggression, 1 visual hallucination, 1

pancreatitis acute (described in Section 7.3.1 of this review in deaths), 2 convulsion (1 also with SAE mental status changes), 1 abortion spontaneous incomplete, 1 pneumonia (subject 26331004), 1 intervertebral disc prolapse (subject 10031003), and 1 retinal detachment (subject 160111002 in right eye on Day 206 with history of intraocular lens implant in the right eye (*confirmed in CIOMS form submitted by the Applicant in response to the Division's information request dated 1/15/15 that the implant was in the same eye as retinal detachment*).

The following additional SAEs were experienced by perampanel subjects greater than placebo in Study 235 Core: gastroduodenitis (n=1), nasopharyngitis (1), foot fracture (1), partial seizures with secondary generalization (1), and aggression (2). The following table lists the SAEs in Study 232 Core by treatment group. No SAE occurred in more than 1 perampanel subject.

Table 13. SAEs by SOC and PT, Study 232 Core

MedDRA System Organ Class Preferred Term	Perampanel		
	Cohort 2 ≥2 to <7 years (N=22) n (%)	Cohort 1 ≥7 to <12 years (N=28) n (%)	Total (N=50) n (%)
Subjects with any treatment-emergent, nonfatal SAE[a]	3 (13.6)	5 (17.9)	8 (16.0)
Congenital, familial and genetic disorders	1 (4.5)	0	1 (2.0)
Developmental hip dysplasia	1 (4.5)	0	1 (2.0)
Infections and infestations	1 (4.5)	3 (10.7)	4 (8.0)
Gastroenteritis	0	1 (3.6)	1 (2.0)
Mastoiditis	0	1 (3.6)	1 (2.0)
Otitis externa	0	1 (3.6)	1 (2.0)
Otitis media acute	0	1 (3.6)	1 (2.0)
Pneumonia	0	1 (3.6)	1 (2.0)
Respiratory syncytial virus bronchiolitis	1 (4.5)	0	1 (2.0)
Septic shock	0	1 (3.6)	1 (2.0)
Metabolism and nutrition disorders	0	1 (3.6)	1 (2.0)
Hypoglycaemia	0	1 (3.6)	1 (2.0)
Nervous system disorders	0	1 (3.6)	1 (2.0)
Convulsion	0	1 (3.6)	1 (2.0)
Psychiatric disorders	1 (4.5)	1 (3.6)	2 (4.0)
Abnormal behaviour	0	1 (3.6)	1 (2.0)
Mental status changes	1 (4.5)	0	1 (2.0)
Respiratory, thoracic and mediastinal disorders	0	1 (3.6)	1 (2.0)
Pleural effusion	0	1 (3.6)	1 (2.0)
Respiratory failure	0	1 (3.6)	1 (2.0)
Vascular disorders	0	1 (3.6)	1 (2.0)
Hypotension	0	1 (3.6)	1 (2.0)

Source: Appendix 1, Table 14.3.2.2.1.

Note: Number (percentage) of subjects in each SOC represents all subjects with SAEs in that SOC. Display is in decreasing order of frequency of SAEs in the Total perampanel group, first by SOC and then by preferred term within each SOC.

In the entire safety database, there were no treatment-emergent SAEs coded to the following preferred terms: aplastic anemia, agranulocytosis, Stevens Johnson syndrome, toxic epidermal necrolysis, acute renal failure, acute liver failure, rhabdomyolysis, angioedema, or anaphylaxis.

The following table lists the SAEs in the ongoing extensions of Studies 232 and 235.

Table 14. List of SAEs in Ongoing Extension Phases of Studies 232 and 235 as of June 30 2014

Study Number	Subject Number	SAE(s)
232	10010008	Convulsion Bradycardia
	10020001	Otitis media
	10030002	Status epilepticus
	10050001	Constipation
	10140002	Gastroenteritis[a] Convulsion[a] Dehydration Anticonvulsant drug level increased
	10140003	Muscle contracture Foot deformity
	10180005	Status epilepticus
	10200002	Mental status changes
235	10011002	Convulsion[a]
	10071001	Convulsion
	10091001	Accidental overdose
	10101001	Suicidal ideation
	10111001	Aggression[a]
	10311001	Suicide attempt
	10321002	Testicular necrosis
	10541001	Pneumonia
	10621001	Status epilepticus
	10621002	Hand fracture
	10621005	Intentional overdose
	10631005	Aggression Convulsion
	10911001	Convulsion
	10921003	Aggression Ligament rupture
	10951006	Simple partial seizures

Source: Summary of Clinical Safety, Table 47
a: Separate episodes of this TEAE were reported as SAEs for this subject in both the Core Study and the Extension Phase.

Comment: The case listed in the table above of "ligament rupture" was subject 235-1092-1003 (same subject as MfrControl # KR-EISAI INC-E2007-01220-CLI-KR in

FAERS confirmed by Applicant in email correspondence on March 5, 2015), a 17 year-old male who after 27 weeks of perampanel experienced aggression and wrist injury with ligament tearing. "After a bitter quarrel with his mother at his home, the subject broke the glass window. Shards of glass cut into his hands causing wrist injury with ligament tearing" that required surgical intervention. Perampanel was discontinued and events resolved.

Since the cutoff date for deaths and SAEs in the SCS (June 30 2014), the Extension Phase of Study 235 was completed. The Applicant reported that there were no additional deaths or SAEs after that date. The Extension Phase of Study 232 was still ongoing. Between June 30 2014 and the cutoff date for deaths and SAEs in the Safety Update (November 01, 2014), there was 1 new SAE reported during that period: vomiting (subject 10010008).

7.3.3 Dropouts and/or Discontinuations

In Study 332 Core, a higher percentage of perampanel subjects (16.0%, 13/81) discontinued compared to placebo subjects (12.2%, 10/82). After stratifying by the primary reason for discontinuation, discontinuations due to adverse events (11.1%) and subject choice (3.7%) occurred in perampanel subjects at a greater frequency than in placebo subjects (6.1% and 2.4%, respectively). However, discontinuations due to inadequate therapeutic effect occurred in perampanel subjects (0) at a lower frequency than in placebo subjects (2.4%). The following table summarizes the discontinuations by treatment group.

Table 15. Disposition and Primary Reason for Discontinuation, Study 332 Core

Category	Placebo n (%)	Perampanel n (%)
Treated	82 (100)	81 (100)
Discontinued	10 (12.2)	13 (16.0)
Primary reason for discontinuation*:		
Adverse event	5 (6.1)	9 (11.1)
Subject choice	2 (2.4)	3 (3.7)
Inadequate therapeutic effect	2 (2.4)	0
Lost to follow-up	1 (1.2)	1 (1.2)
Other	0	0

Source: Summary Clinical Safety, Table 2
*As reported on the subject disposition at Core case report form.

The following table summarizes the TEAEs leading to discontinuation in Study 332 Core by treatment group.

Table 16. TEAEs Leading to Discontinuation by SOC and PT, Study 332 Core

MedDRA System Organ Class Preferred Term	Placebo (N=82) n (%)	Perampanel (N=81) n (%)
Subjects with any TEAE leading to discontinuation	5 (6.1)	9 (11.1)
Eye Disorders	0	1 (1.2)
Lacrimation Increased	0	1 (1.2)
Gastrointestinal Disorders	0	2 (2.5)
Abdominal Discomfort	0	1 (1.2)
Vomiting	0	2 (2.5)
General Disorders And Administration Site Conditions	1 (1.2)	3 (3.7)
Drowning	0	1 (1.2)
Fatigue	0	1 (1.2)
Gait Disturbance	1 (1.2)	0
Irritability	0	1 (1.2)
Metabolism And Nutrition Disorders	0	1 (1.2)
Decreased Appetite	0	1 (1.2)
Musculoskeletal And Connective Tissue Disorders	1 (1.2)	1 (1.2)
Muscular Weakness	1 (1.2)	0
Musculoskeletal Stiffness	1 (1.2)	0
Myalgia	0	1 (1.2)
Nervous System Disorders	1 (1.2)	3 (3.7)
Convulsion	1 (1.2)	0
Dizziness	0	2 (2.5)
Sedation	0	1 (1.2)
Status Epilepticus	0	1 (1.2)
Psychiatric Disorders	3 (3.7)	5 (6.2)
Abnormal Behaviour	0	1 (1.2)
Aggression	0	1 (1.2)
Agitation	1 (1.2)	0
Anxiety	0	1 (1.2)
Confusional State	1 (1.2)	0
Depression	1 (1.2)	0
Insomnia	0	1 (1.2)
Mood Swings	0	1 (1.2)
Suicidal Ideation	2 (2.4)	1 (1.2)
Suicide Attempt	0	1 (1.2)

Source: Summary of Clinical Safety, Table 39

The adverse events most commonly leading to discontinuation (≥2% in the perampanel group and greater than placebo) were vomiting (2%) and dizziness (2%).

In Study 332 Core, a higher percentage of perampanel subjects (11.1%, 9/81) encountered TEAEs that resulted in the interruption of the study drug or dose reduction compared to placebo subjects (7.3%, 6/82). These TEAEs were consistent with those detailed above (primarily in the SOCs of Nervous System Disorders and Psychiatric Disorders, Summary of Clinical Safety, Table 44).

In Study 332 Extension, 21.7% (30/138) of the perampanel subjects discontinued treatment with the highest percentage (23.3%) in the >8 to 12 mg/day modal dose group (120-day Safety Update, Table 15.1.1.3.1). As of the data cut-off date (for the 120-day Safety Update), 74.6% (103) were still participating and 3.6% (5) completed the study. The most common reasons for discontinuation were subject choice (5.8%, n=8), adverse events (5.1%, n=7), and inadequate therapeutic effect (5.1%, n=7). The following table summarizes the TEAEs leading to discontinuation in Study 332 Ext. The adverse events most commonly leading to discontinuation (≥2% in the perampanel group) were in the SOC Psychiatric disorders (2.9%, suicidal ideation/attempt, depression, anger), Nervous system disorders (2.2%, dizziness), and Gastrointestinal disorders (2.2%, faecal incontinence, nausea, acute pancreatitis).

Table 17. TEAEs Leading to Discontinuation by SOC and PT, Study 332 Ext

MedDRA System Organ Class Preferred Term	Safety Update Total (N=138) n (%)
Subjects with any TEAE leading to discontinuation	10 (7.2)
Eye Disorders	1 (0.7)
Altered Visual Depth Perception	1 (0.7)
Gastrointestinal Disorders	3 (2.2)
Faecal Incontinence	1 (0.7)
Nausea	1 (0.7)
Pancreatitis Acute	1 (0.7)
Injury, Poisoning And Procedural Complications	1 (0.7)
Thermal Burn	1 (0.7)
Musculoskeletal And Connective Tissue Disorders	1 (0.7)
Pain In Extremity	1 (0.7)
Nervous System Disorders	3 (2.2)
Dizziness	3 (2.2)
Pregnancy, Puerperium And Perinatal Conditions	1 (0.7)
Abortion Spontaneous Incomplete	1 (0.7)
Psychiatric Disorders	4 (2.9)
Anger	1 (0.7)
Depression	1 (0.7)
Suicidal Ideation	1 (0.7)
Suicide Attempt	2 (1.4)
Renal And Urinary Disorders	1 (0.7)
Urinary Incontinence	1 (0.7)

Source: 120-day Safety Update, Table 21

In Study 232, the following isolated TEAEs leading to discontinuation (mainly in the ≥7 to <12 year old cohort) occurred in similar SOCs (mainly in Nervous System and Psychiatric Disorders): gait disturbance, irritability, grand mal convulsion, psychomotor hyperactivity, tremor, abnormal behaviour, and emotional distress.

In Study 235, the following isolated TEAEs leading to discontinuation (only in perampanel group) occurred in similar SOCs (mainly in Nervous System and Psychiatric Disorders): nausea, irritability, convulsion, depressed level of consciousness, dizziness, slow speech, somnolence, adjustment disorder, and bradyphrenia (Summary of Clinical Safety, Table 43).

In the entire safety database, there were no subjects who discontinued for the TEAEs of acute renal failure, Stevens Johnson syndrome, toxic epidermal necrolysis, acute liver failure, rhabdomyolysis, aplastic anemia, agranulocytosis, pancytopenia, or anaphylaxis.

7.3.4 Significant Adverse Events

In the next subsections, I will discuss my analyses along with the Applicant's analyses of the following major safety issues: psychiatric disorders and nervous system disorders.

7.3.4.1 Psychiatric Disorders

In Study 332 Core, a higher number of subjects in the perampanel group experienced TEAEs in the SOC Psychiatric disorders than in the placebo group (24.7% vs 19.5%). Furthermore, SAEs and discontinuations due to TEAEs in the Psychiatric disorders SOC occurred more often in perampanel subjects than placebo in Study 332 Core (and Study 235 Core). The following table provides an overview of TEAEs, SAEs, and TEAEs leading to discontinuation (in the SOC Psychiatric disorders) in Study 332 Core compared to Study 235 Core and the POS Phase 3 DB Pool (in the original NDA).

Comment: I have provided both the 8 mg and 12 mg randomized dose groups from the POS Phase 3 DB Pool as a comparison for perampanel groups (8 mg) for Studies 332 Core and 235 Core (see Section 7.2.1.2 of this review for details regarding possible differences in exposure due to differences in concomitant inducer use). The frequency of adverse events in the perampanel group for Study 332 Core (8 mg) was consistent with the POS DB Studies (with rates in between the 8 mg and 12 mg POS dose groups which had a higher frequency of concomitant inducer use).

Table 18. Summary of TEAEs, SAEs, DCs in the Psychiatric Disorders SOC, Controlled Studies

Category	POS Phase 3 DB Pool			Study 332 Core		Study 235 Core	
	Placebo	Perampanel[a]					
		8 mg	12mg	Placebo	Perampanel	Placebo	Perampanel[c]
n	442	431	255	82	81	48	85
TEAEs	12.4%	17.2%	22.4%	19.5%	24.7%	10.4%	25.9%
SAEs	0.9%	0.5%	2.8%	0	2.5%	0	2.4%
DC TEAE[b]	1.6%	0.9%	6.3%	3.7%	6.2%	0	2.4%

Source: ISS Tables 43, 69, 88 (NDA 202834) and CSR 332 (Tables 18, 20, and 22) and CSR 235 (Tables 20, 21, 23)
[a]Randomized dose groups
[b]TEAEs leading to DC
[c]mean daily dose = 8.3 mg in Core Study 235

Suicidality (Suicidal Behavior and Ideation)
In Study 332 Core, while perampanel subjects experienced less overall suicidality than placebo subjects, more of these events were considered SAEs (see table below).

Table 19. Summary of Suicidality TEAEs, Study 332 Core

	Study 332 Core	
	Placebo	Perampanel
	n=82	n=81
Suicidality group	3 (3.7%)	2 (2.5%)
Suicidal ideation	3 (3.7%)^	1 (1.2%)*
Suicide attempt	0	1 (1.2%)*

Source: CSR Study 332 Core, Table 14.3.2.6.2
*SAE and led to discontinuation of drug
^led to discontinuation of placebo in 2 out of the 3 subjects

In Study 332 Extension, there were 5 subjects (3.6%) with TEAEs related to suicidal ideation and behavior (including 1 subject who had experienced suicidal ideation during the Core Study while receiving placebo). In Study 232, 1 subject experienced suicidal ideation (was not considered an SAE and did not lead to discontinuation). In Study 235, 2 subjects experienced suicidal ideation and/or behavior: self-injurious ideation and intentional self-injury (were not considered an SAE and did not lead to discontinuation). There were no completed suicides in the entire safety database.

The Applicant also performed an analysis of suicidality using the Columbia Suicide Severity Rating Scale (C-SSRS). A lower percentage of perampanel subjects (3.7%, n=3) reported at least 1 positive suicide-related ideation than in the placebo group (6.1%, n=5) (Core Study 332 CSR, Table 14.3.4.7.1.1). Furthermore, all 3 of the perampanel subjects had a history of suicidality (while 2 of the 5 subjects in the placebo group had a history of suicidality, Core Study 332 CSR, Table 14.3.4.7.1.2). However, only perampanel-treated subjects (2.5%, n=2) and no placebo-treated subjects reported at least 1 positive suicide-related behavior.

In conclusion, suicidality is required by the Division to be included in the labeling of all antiepileptic drugs. I do not recommend any additional information regarding suicidality to be added to the suicidality class labeling from these analyses of the safety data in this application.

Hostility and Aggression
The following table summarizes the percentages of subjects reporting TEAEs in the Psychiatric SMQs Hostility/Aggression and Psychosis/Psychotic disorders in Study 332 Core. Perampanel subjects had a higher risk compared to placebo of experiencing TEAEs in the SMQ Hostility and Aggression (both broad and narrow searches). Using the broad search for the SMQ Psychosis/Psychotic disorders, a higher frequency of perampanel subjects experienced PTs in this SMQ than placebo subjects (although the narrow search resulted in similar frequencies between perampanel and placebo).

Table 20. Relative Risk of Psychiatric disorders SOC and SMQs, Study 332 Core

Category	Placebo		Perampanel		Relative Risk (95% C.I.)
	n (%)	total	n (%)	total	
SOC Psychiatric disorders	16 (19.5)	82	20 (24.7)	81	1.3 (0.7-2.3)
SMQ Hostility and Aggression					
Narrow SMQ	0	82	2 (2.5)	81	5.1 (0.25-104)
Broad SMQ	4 (4.9)	82	15 (18.5)	81	3.8 (1.3-11.0)
SMQ Psychosis and Psychotic disorders					
Narrow SMQ	3 (3.7)	82	3 (3.7)	81	1.0 (0.2-4.9)
Broad SMQ	3 (3.7)	82	6 (7.4)	81	2.0 (0.5-7.8)

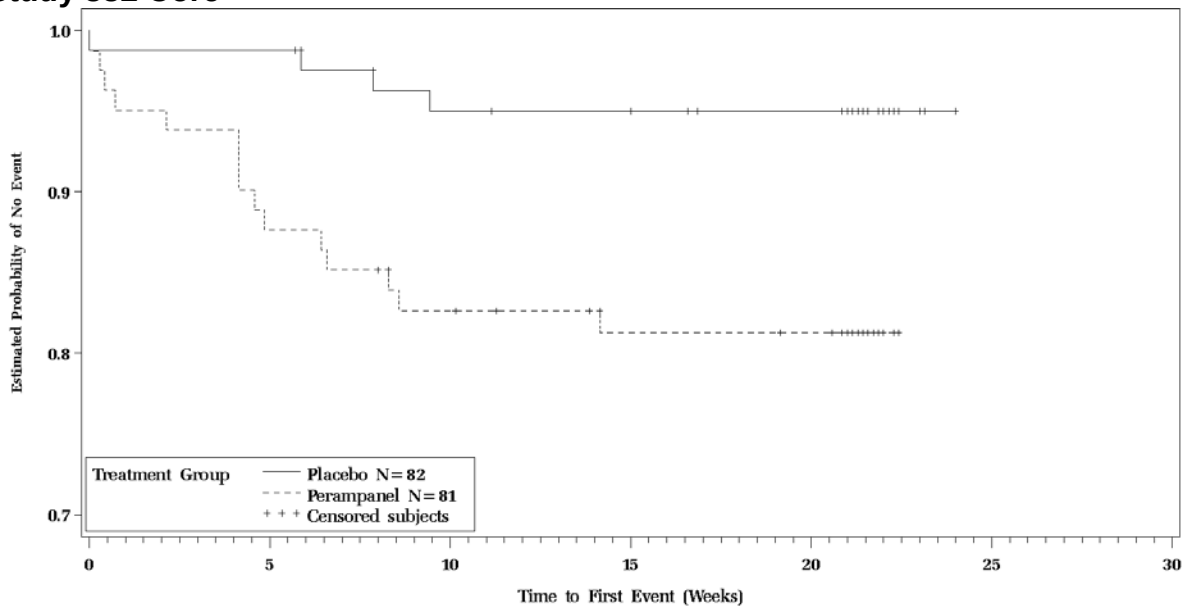
Source: Created by the reviewer using MAED (MedDRA-based Adverse Event Diagnostic) tool

In Study 332 Core, the following TEAEs (in the SMQ Hostility and Aggression) were experienced in perampanel subjects more frequently than placebo subjects: irritability (9 vs 2), laceration (2 vs 0), abnormal behaviour (1 vs 0), affect lability (1), aggression (1), drowning (1), paranoia (1), and physical abuse (1). Perampanel subjects experienced more SAEs (1 drowning in perampanel subject vs 0 placebo) and TEAEs leading to discontinuation (abnormal behavior, aggression, drowning in 3 perampanel subjects vs 1 placebo).

Comment: In response to an information request by the Division to provide more information regarding the events surrounding and leading up to the PTs of physical abuse and aggression, the Applicant reported (in a Safety Information Amendment dated 1/30/15) that subject 332-26291004 (PT physical abuse) was a suspected victim of abuse (and no additional information was provided) and that subject 332-15041001 (PT aggression) slapped her father in law during an argument (and no additional information as provided).

The following figure summarizes the time to first occurrence of TEAEs in the Hostility and Aggression SMQ (broad search) in Study 332 Core. Most of these events in the perampanel subjects occurred early in the trial.

Figure 2. Time to First Occurrence of TEAEs in Hostility/Aggression Broad SMQ, Study 332 Core



Source: Summary of Clinical Safety, Figure 1

In Study 235, a higher percentage of perampanel subjects than placebo experienced TEAEs in the Hostility/Aggression SMQ (narrow search: 10.6% vs 2.1% with RD 8.5 and RR 5.1 driven by the PTs anger and aggression and broad search: 17.7% vs 4.2% with RD 13.5 and RR 4.2). Two of these TEAEs (PT aggression) in perampanel subjects were SAEs and 1 led to discontinuation (irritability). No placebo subjects had SAEs or TEAEs that led to discontinuation in this SMQ. The following table summarizes the TEAEs in the SMQ Hostility and Aggression for Study 332 Core, Study 235 Core, and the pooled POS Phase 3 DB studies (from the original NDA).

Table 21. Summary of TEAEs in the SMQ Hostility and Aggression, Controlled Studies

Category	POS Phase 3 DB Pool			Study 332 Core		Study 235 Core	
	Placebo	Perampanel[a]					
		8 mg	12mg	Placebo	Perampanel	Placebo	Perampanel[c]
n	442	431	255	82	81	48	85
Narrow	0.7%	2.8%	6.3%	0	2.5%	2.1%	10.6%
Broad	5.7%	12.3%	20.4%	4.9%	18.5%	4.2%	17.7%

Source: Created by the reviewer using MAED (MedDRA-based Adverse Event Diagnostic) tool

Comment: The frequency of adverse events in the perampanel group for Study 332 Core (8 mg) was consistent with the POS DB Studies (with rates in between the 8 mg and 12 mg POS dose groups).

The following table summarizes the incidence of developing TEAEs in the SMQ Hostility and Aggression (broad search) stratified by sex and age group.

Table 22. Hostility/Aggression Broad SMQ by Demographics, Study 332 Core

Category	Placebo		Perampanel	
	n (%)	total	n (%)	total
Sex:				
Male	4 (11.1)	36	7 (20.0)	35
Female	0	46	8 (17.4)	46
Age:				
Adults (≥17 yrs)	3 (4.1)	74	12 (17.1)	70
Adolescents (12-<17 yrs)	1 (14.3)	7	3 (27.3)	11

Source: Created by the reviewer using JReview and MAED

Comment: In terms of risk factors, it is difficult to make any conclusions due to the small sample sizes. The Applicant recommended that information regarding aggression occurring more commonly in adolescents than in adults be included in the US PI: "Aggression was observed more commonly in adolescents than in adults." However, the data for adolescents in Study 332 Core is limited by small sample size. Furthermore, the data suggests that adolescents have a similar or slightly lower risk than adults in experiencing TEAEs in the SMQ Hostility and Aggression (risk difference (RD) for both adults and adolescents = 13 while the relative risk (RR) =1.9 for adolescents and RR=4.2 for adults). Interestingly, in Study 235 (a study performed in adolescents 12 to <18 years of age) the risk of developing TEAEs in the SMQ Hostility and Aggression was higher (RR 4.2) than the adolescents in Study 332 Core (RR 1.9) but similar to the adults (RR 4.2).

In Study 332 Ext, hostility/aggression-related TEAEs (narrow and broad SMQ terms) were considered serious for 1 (0.9%) aggression (subject 26281002, who experienced the verbatim SAE term of postictal aggression. This subject recovered from the SAE with continuation of the perampanel dose. An additional subject discontinued due to the PT anger (subject 26151001). There were no TEAEs related to psychosis or psychotic disorders that were considered SAEs but 1 perampanel treated subject was discontinued from the study due to abnormal behavior (subject 10011001).

In the OLE of Study 235, subject 235-1092-1003, a 17 year-old male experienced aggression and wrist injury with ligament tearing after 27 weeks of perampanel. "After a bitter quarrel with his mother at his home, the subject broke the glass window. Shards of glass cut into his hands causing wrist injury with ligament tearing" that required surgical intervention. Perampanel was discontinued and events resolved.

Comment: I reviewed all of the narratives for the SAEs reported in the broad search of the SMQ Hostility and Aggression in the entire safety database. None of the narratives contained any verbatim terms of homicidal ideations/threats or homicide.

Postmarketing Database
The Applicant reported a total of 108 postmarketing reports with events that fell under the narrow SMQ of hostility/aggression, with 44 events that met serious criteria (164 met the broad SMQ of which 26 or 16% were patients under the age of 18 years old).

The majority of the reports were events of aggression (96 reports). There were 7 reports of suicide attempt, 1 of self-injurious behaviour, 2 of intentional self-injury, 1 of pyromania, 6 reports of homicidal ideation, 2 reports of physical assault, and 1 report each of hostility and violence-related symptom.

Comment: Case reports were submitted by the Applicant (in a Safety Information Amendment dated March 2, 2015) in response to the Division's information request. Details of these postmarketing case reports are provided below.

Cases of homicidal ideation or threat:
E2007-01206-SPO-IL: 15 year-old male who started 10 mg of perampanel and 7 weeks later experienced severe violence that he "wanted to murder his father" and aggravated seizures. Perampanel was discontinued. Outcome was not reported.
E2007-01637-SPO-US: 20 year-old male who experienced "homicidal ideation" and suicide attempt (hanging) after dose of perampanel was increased (date not reported). Perampanel was discontinued. Outcome was not reported.
E2007-01676-SPO-US: female in her "30's" who experienced homicidal ideation (chasing her mother with a butcher knife) after dose of perampanel was increased (date not reported). Perampanel was discontinued and event resolved.
E2007-01714-SPO-US: 36 year-old male who started 4 mg of perampanel and became irritable and aggressive. After dose of perampanel was increased, pt experienced suicidal thoughts 1 month later. Two months later, the patient was hospitalized for homicidal ideation (threatening his siblings). Perampanel dose was reduced. Outcome was not reported.
EC-2014-000608: male in his "30's" who experienced worsening of his depression 3 months after starting perampanel. His antidepressants were adjusted and the pt developed suicidal and homicidal ideations requiring hospitalization. Perampanel was discontinued. Outcome was not reported.
EC-2014-001144: 40 year-old female who experienced "intense murder ideation against her husband without any reason" after starting perampanel and dose was increased (date unknown). Perampanel was discontinued. Outcome was not reported. Concomitant medications included carbamazepine and clobazam.

Cases of physical assault (ideation) or use of a weapon and/or self-injurious behaviour:
E2007-01462-SPO-GB: 32 year-old male who "hit out at a care worker"
E2007-01727-SOL-IE: 53 year-old female who "went at her husband with a knife" and he feared for his safety
E2007-01303-SPO-DE: 21 year-old female with self-injury (scratch, manipulations in the mouth).
E2007-01184-SPO-SE: 36 year-old male with self-injury "scratched himself in the face so bad that the wound had to be treated with [antibiotics]"
EC-2014-000745: 14 year-old female who tried to light a couch on fire.
E2007-01603-SPO-US: 41 year-old female experienced violent ideation (thoughts toward wanting to stab her roommate).

Cases of suicidal ideation/attempt:
E2007-01327-SPO-GB (unknown age)
E2007-01440-SPO-GB: 28 year-old female with suicide attempt (overdose of paracetamol)
E2007-01441-SPO-GB: 52 year-old female with suicide attempt (drowning herself in a canal preempted by passerby who intervened and talked her out of proceeding).
E2007-01471-SPO-GB: 22 year-old female with suicide ideations and attempt (tried to stick a knife in her thigh).
E2007-01568-SPO-GB: male in his 30's with suicide attempt (intentional overdose)
E2007-01872-SPO-US: 11 year-old male with suicide attempt (jump through the window with visual and auditory hallucinations)
E2007-01581-SPO-GB: 39 year-old female with suicidal ideation

Additionally, the following case was reported to FDA and identified in FAERS by the reviewer on December 19, 2014 (after the data-cut off for this submission): EC-2014-002589: male patient (age not reported) who became hostile and grabbed an ax after starting perampanel (date not reported). Additional details were requested by the Division on January 6, 2105 and the following information was submitted by the Applicant on January 23, 2015:

> *"Case EC-2014-002589 reported by a healthcare provider on 17 Dec 2014 to an Eisai Sales Representative during a sales visit. Follow-up attempts with the reporting physician are ongoing. Upon receipt of this report from the Sales Representative, a message was left for the physician and/or nurse practitioner to obtain more information and a letter was mailed. Two weeks later a second letter was mailed and a phone call placed where the office staff noted that the nurse practitioner could not recall the patient and did not wish to report the event and the Physician was out of the office on vacation. Additional follow-up phone calls were attempted when the Physician returned from vacation but the Physician was not available and it was noted that he would respond when able. At the time of this response, no additional information has been provided by the reporting healthcare provider. We have no additional information to report at this time on the dates of Fycompa® treatment initiation or the date of the onset of symptoms. We do not have additional information on whether the subject or another individual was injured. As additional information is received through the ongoing follow-up attempts, follow-up reports on the event will be filed in the appropriate manner. We will also inform the Project Manager for S-005 if additional information is reported."*

As of March 30, 2015, no additional information pertaining to this case was submitted by the Applicant.

The applicant estimated that the cumulative worldwide patient exposure to perampanel from the international birth date of product launch in the EU (July 23, 2012) to October 22, 2014 to be 2,700,000 patient-days (or 7397 patient-years). Therefore, the reporting rate of homicidal ideation and/or threat for perampanel subjects is 0.81 per 1000 patient-years (or 1 per 1232.8 patient years or 6/7397 patient-years). This is similar to the rate in the original NDA for POS where there were 3 perampanel subjects who reported homicidal ideation and/or threat out of 4368 perampanel-treated subjects (0.1%) or 3 per 3933.4 subject-years in the epilepsy and nonepilepsy trials (0.76 per 1000 patient-years). Finally, this information regarding the rate of 1 per 1232.8 patient years for homicidal ideation and/or threat in the postmarketing database should be added to current Fycompa labeling that currently mentions that 0.1% of 4368 perampanel-treated patients exhibited homicidal ideation and/or threat in controlled and open label studies, and that includes homicidal ideation/threat in the boxed warning.

In conclusion, there are serious, life-threatening neuropsychiatric events associated with perampanel use. Perampanel use was associated with aggression, hostility, and changes in mood, behavior, and personality. In the Study 332 Core, perampanel subjects had a higher incidence of TEAEs in the Hostility and Aggression MedDRA SMQ as compared to placebo subjects. After experiencing these hostility TEAEs, some perampanel subjects developed suicidal and homicidal ideations and committed harmful acts (suicide attempts, physical assaults, and threats with a weapon). As required by the Division for all antiepileptic medications, suicidal behavior and ideation is already in

the Warnings section of the Applicant's proposed labeling. I recommend continuation of the boxed warning to highlight the hostility and aggression adverse reactions associated with perampanel. Pursuant to 21 CFR § 201.57(c)(1), the hostility and aggression adverse reactions associated with perampanel are serious events that may lead to serious injury or death (homicides or suicides) that are essential in assessing the risks and benefits of using this drug.[3] Furthermore, this is a serious adverse reaction that might be reduced in frequency or severity by the following appropriate use of the drug as outlined in the current boxed warning.

7.3.4.2 Nervous System Disorders

In Study 332 Core, a higher number of subjects in the perampanel group experienced TEAEs in the SOC Nervous system disorders than in the placebo group (50.6% vs 28%). Furthermore, discontinuations due to TEAEs in the Nervous system disorders SOC occurred more often in perampanel subjects than placebo in both Study 332 Core and Study 235 Core. Interestingly, SAEs in this SOC occurred less frequently in perampanel subjects than placebo. The following table provides an overview of TEAEs, SAEs, and TEAEs leading to discontinuation (in the SOC Nervous system disorders) in Study 332 Core compared to Study 235 Core and the POS Phase 3 DB Pool (in the original NDA).

Comment: I have provided both the 8 mg and 12 mg randomized dose groups from the POS Phase 3 DB Pool as a comparison for perampanel groups (8 mg) for Studies 332 Core and 235 Core (see Section 7.2.1.2 of this review for details regarding possible differences in exposure due to differences in concomitant inducer use). The frequency of adverse events in the perampanel group for Study 332 Core (8 mg) was consistent with the POS DB Studies.

Table 23. Summary of TEAEs, SAEs, DCs in the Nervous System Disorders SOC, Controlled Studies

Category	POS Phase 3 DB Pool			Study 332 Core		Study 235 Core	
	Placebo	Perampanel[a]					
		8 mg	12mg	Placebo	Perampanel	Placebo	Perampanel[c]
n	442	431	255	82	81	48	85
TEAEs	31%	56.6%	69.0%	28.0%	50.6%	33.3%	50.6%
SAEs	2.5%	1.9%	2.8%	4.9%	2.5%	2.1%	1.2%
DC TEAE[b]	2.9%	4.2%	11.4%	1.2%	3.7%	0	2.4%

Source: ISS Tables 43, 69, 88 (NDA 202834) and CSR 332 (Tables 18, 20, and 22) and CSR 235 (Tables 20, 21, 23)
[a]Randomized dose groups
[b]TEAEs leading to DC
[c]mean daily dose = 8.3 mg in Core Study 235

3 Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format. HHS FDA CDER CBER. October 2011.

To address the issue of the splitting of potentially similar neurological events into multiple preferred terms, I performed additional analyses in order to pool together related events (please see Section 7.1.2 of this review for a detailed discussion regarding splitting). I reanalyzed the AEs in the following main groups: Dizziness and coordination, Somnolence and fatigue, and Cognitive dysfunction. The preferred terms for these groups were chosen after reviewing the AE dataset for relevant PTs but prior to analyzing the relative frequencies in the treatment groups. In this section, I will also further discuss falls (in the context of injuries and seizures).

Dizziness and Coordination

The following table summarizes the percentages of subjects who reported the following TEAEs: dizziness, vertigo, ataxia, gait disturbance, balance disorder, and coordination abnormal. In Study 332 Core, subjects treated with perampanel experienced these TEAEs at a higher frequency than placebo subjects, resulting in more than 4 times higher incidence of this AE group for perampanel subjects than placebo. This result was comparable to the POS Phase 3 DB Pool in the original NDA (42% in the perampanel 8 mg dose group and 54.1% in the perampanel 12 mg dose group compared to 10.9% in the placebo group).

Table 24. Dizziness and Coordination Group, Study 332 Core

MedDRA PT	Study 332 Core	
	Placebo	**Perampanel**
	n=82	n=81
Dizziness	5 (6.1)	26 (32.1)
Vertigo	2 (2.4)	7 (8.6)
Ataxia	1 (1.2)	2 (2.5)
Total subjects	7 (8.5)	33 (40.7)

Source: Created by the reviewer using JReview and Core 332 ADAE, ADSL datasets (SAFFL=Y and AEEMFL=Y)

Somnolence and Fatigue

The following table summarizes the percentages of subjects who reported the following TEAEs: somnolence, fatigue, asthenia, lethargy, and sedation. In Study 332 Core, subjects treated with perampanel experienced these TEAEs (except for lethargy) at a higher frequency than placebo subjects, resulting in twice the incidence of this AE group for perampanel subjects than placebo. This result was comparable to the POS Phase 3 DB Pool in the original NDA (25.8% in the perampanel 8 mg dose group and 31% in the perampanel 12 mg dose group compared to 12.2% in the placebo group).

Table 25. Somnolence and Fatigue Group, Study 332 Core

MedDRA PT	Study 332 Core	
	Placebo	Perampanel
	n=82	n=81
Somnolence	3 (3.7)	9 (11.1)
Fatigue	5 (6.1)	12 (14.8)
Asthenia	0	2 (2.5)
Lethargy	2 (2.4)	2 (2.5)
Sedation	0	1 (1.2)
Total subjects	10 (12.2)	20 (24.7)

Source: Created by the reviewer using JReview and Core 332 ADAE, ADSL datasets (SAFFL=Y and AEEMFL=Y)

Cognitive dysfunction

Cognitive dysfunction is related to the neurological events of confusion, psychomotor slowing, difficulty with concentration and attention, difficulty with memory, and speech or language problems with word-finding difficulty (associated with the following TEAEs: memory impairment, confusional state, disturbance in attention, aphasia, speech disorder, disorientation, amnesia, cognitive disorder, apraxia, delirium mental impairment, and incoherent). In Study 332 Core, only 1 perampanel subject (1.2%) reported a TEAE in this cognitive dysfunction group (PT aphasia) compared to no placebo subjects.

Falls

In Study 332, the Applicant performed a systematic review of reported events of falls in order to distinguish seizure-associated fall events from independent ones (via queries sent to investigators to establish whether these events were or were not related to a seizure event). The Applicant only reported as TEAEs falls that did not occur in connection with seizures. In Study 332 Core, TEAEs related to falls occurred in more perampanel subjects (2.5%, n=2) than placebo subjects (1.2%, n=1) (Core Study 332 CSR, Table 14.3.2.6.12.2). The 2 perampanel subjects had a total of 5 episodes of falls, including 1 during the 4-week Titration Period and 4 during the 13-week Maintenance Period. The fall in the placebo subject (subject 17041001) was a SAE, while the falls in the 2 perampanel subjects (subjects 20071001 and 26211001) were not. None of the events of falls led to discontinuation. In Study 332 Extension, TEAEs related to falls (PT fall) occurred in 4 (2.9%) perampanel subjects. None of these falls was considered serious or led to treatment discontinuation. This incidence of TEAEs related to falls was lower than in the POS Phase 3 DB Pool in the original NDA, in which falls were reported in 5% and 10% of patients randomized to receive perampanel at doses of 8 mg and 12 mg/day, respectively, compared to 3% of placebo subjects.

In conclusion, the causal relationship between perampanel use and dizziness/coordination, somnolence/fatigue, and falls/injuries (currently included in the Warnings and Precautions section of Fycompa labeling) in this application is consistent with the original NDA (although the incidence of falls was less than observed in the original NDA).

7.3.5 Submission Specific Primary Safety Concerns

In the following subsections, I will discuss my analyses along with the Applicant's analyses of the following areas: skin/immune, hepatobiliary, tendon/ligament rupture, cardiac, renal, and gastrointestinal disorders.

Skin and Immune System Disorders
In Study 332 Core, TEAEs in the SOC Skin and Subcutaneous Tissue Disorders occurred in a higher number of subjects in the perampanel group (n=12, 14.8%) than the placebo group (n=7, 8.5%). The PT rash was the most common of these events. None of these adverse events in the SOC Skin and Subcutaneous Tissue Disorders were serious or led to discontinuation. There were also no perampanel subjects in Study 332 Core who reported any TEAEs in the narrow searches of the following SMQs: Severe cutaneous adverse reactions and Anaphylactic reaction. In the narrow search for the SMQ Angioedema, there was 1 perampanel subject who reported the PT urticaria along with 1 placebo subject with swelling face. In the narrow search for the SMQ hypersensitivity, there were more perampanel subjects than placebo subjects who reported rash (3 vs 1), dermatitis contact (2 vs 0), and urticaria (1 vs 0).

In the entire clinical trial safety database, there were no perampanel subjects who reported TEAEs coded to the following preferred terms: anaphylaxis, angioedema, bronchospasm, drug hypersensitivity, drug reaction with eosinophilia and systemic symptoms (DRESS), stridor, laryngeal oedema, laryngospasm, throat tightness, Stevens-Johnson syndrome, or toxic epidermal necrolysis.

Comment: Of note, there was one case of DRESS identified with perampanel use in the postmarketing database (described in Section 8 of this review).

In conclusion, although perampanel use was associated with an increased occurrence of rash compared to placebo use, there were no cases of any severe cutaneous adverse reactions or anaphylactic reaction associated with perampanel use in the placebo-controlled database for this supplement.

Hepatobiliary Disorders
In the entire safety database, one perampanel subject developed chronic cholelithiasis (versus 0 placebo subjects) in Study 332 Core. One subject, who had received perampanel during the Core Study, developed acute pancreatitis during the Extension Phase and died approximately 2 months later (discussed in Section 7.3.1).

In the postmarketing database, the Applicant performed a search for events coded to the MedDRA HLTs of cholecystitis and cholelithiasis, Acute and chronic pancreatitis, Pancreatic disorders NEC, Pancreatic therapeutic procedures, and the MedDRA PT of cholecystectomy. Cumulatively the Applicant identified 2 spontaneous reports of pancreatitis. The Applicant noted that the number of reported cholelithiasis and

pancreatic reactions in perampanel users was low and consistent with the background rate expected for the European and American population.

Comment: Furthermore, Karen Long, PharmD in the Division of Pharmacovigilance I in the Office of Surveillance and Epidemiology conducted an 18-month NME Postmarket Safety Summary: Less Than 10,000 Patients Exposed for perampanel (dated 2/12/15). After reviewing the 152 unduplicated case reports identified in their search of FAERS (received by the FDA from Oct 22, 2012 to September 18, 2014), she identified three cases reporting adverse events of special interest related to cholelithiasis or pancreatitis, and one case reporting cholecystitis. One case reported acute pancreatitis resulting in hospitalization and death, and two cases reported acute pancreatitis requiring hospitalization and treatment. All four cases included concomitant medications labeled for pancreatitis. The team concluded that there were no new potential safety signals requiring additional safety reviews.

In conclusion, due to the rare nature of these events, it is difficult to determine the association between perampanel use and the development of cholelithiasis and pancreatitis. Therefore, I recommend that postmarketing surveillance of acute pancreatitis should be continued.

The Applicant assessed the potential for drug induced liver injury with perampanel by reviewing lab data results and liver-related AE risks from perampanel clinical trials. The Applicant did not identify any subjects in the entire safety database (Phase 1, Epilepsy, Nonepilepsy) who had laboratory values that met the criteria for Hy's Law. I verified this search and did not find any subjects who met Hy's Law criteria.

In Study 332 Core, there were 2 perampanel subjects who experienced the following liver-related TEAEs: liver disorder (resolved during treatment) and aspartate aminotransferase increased. None of the liver-related TEAEs were SAEs or led to discontinuation. While treatment-emergent markedly abnormal laboratory values (for liver tests) occurred in 1 placebo subject (1.2%) and 2 perampanel subjects (2.5%), all 3 subjects had elevated hepatic enzyme values (ALT, AST, or both) at the baseline assessment. Furthermore, for all 3 subjects, the elevated hepatic enzyme values declined on treatment to within or near the normal range. In conclusion, the evidence presented by the Applicant does not suggest that perampanel use is associated with liver injury.

Tendon/Ligament Rupture
There was only 1 perampanel subject who experienced ligament rupture in the entire clinical database: a 16 year-old male (subject 1061-1008 in Study 235) who developed ligament rupture in right ankle on Study Day (b) (6) Subject recovered and perampanel was continued. Subject remained in extension phase as of data cut-off of the narrative. No additional details surrounding this event were provided in narrative. (*Of note, this ligament rupture was not identified in the Applicant's Summary of Clinical Safety*). There were additional cases in Study 332 of ligament sprain (n=3) but no

tendon/ligament ruptures or tears. Of note, there was a case of ligament tear in the OLE of Study 235 due to trauma (smashing fist into a window).

In conclusion, with only one case of ligament rupture, it is difficult to attribute this to perampanel exposure. Although it is reported that perampanel binds to elastin (for years) in preclinical studies, it is not yet known whether this leads to deleterious effects in the fibrous connective tissues of tendons and ligaments in humans. Therefore, I recommend the continued postmarketing surveillance of tendon and ligament rupture (as recommended in the original NDA for POS).

Cardiac Disorders
In the SOC Cardiac disorders, 2 perampanel subjects experienced the TEAEs of bradycardia and sinus arrhythmia. There were no TEAEs in the SOC Investigations (related to cardiac lab/vital/ECG abnormalities). None of the cardiac TEAEs reported in the Core Study were serious or led to discontinuation. One perampanel subject reported the TEAE syncope: a 12 year-old female (subject 235-1003-1001) who experienced mild syncope (not SAE) on Study Day (b) (6) (in the DB follow up period). Subject recovered without intervention.

Renal and Urinary Disorders
In the safety database, there were no TEAEs of acute renal failure reported in perampanel subjects. There were no SAEs reported in the SOC Renal and urinary disorders. There was 1 TEAE leading to DC (PT urinary incontinence) reported in a perampanel subject in Study 332 Extension.

Gastrointestinal Disorders
In Study 332 Core, TEAEs in the SOC Gastrointestinal disorders that occurred in ≥2% perampanel subjects and greater than placebo were nausea (6.2% vs 4.9%), vomiting (8.6% vs 2.4%), and abdominal pain (4.9% vs 1.2%) along with smaller signals of hypoaesthesia oral (2.5% vs 0) and constipation (2.5% vs 1.2%). There were no SAEs or TEAEs leading to discontinuation in Study 332 Core in this SOC. In the extension phases and studies of other indications, there were isolated SAEs of gastroduodenitis and vomiting that occurred in perampanel subjects. In conclusion, perampanel use is associated with nausea, vomiting, and abdominal pain. These TEAEs should be included in the Adverse Reactions section of labeling.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The following table provides an overview of TEAEs, SAEs, and TEAEs leading to discontinuation in Study 332 Core compared to Study 235 Core and the POS Phase 3 DB Pool (in the original NDA).

Comment: I have provided both the 8 mg and 12 mg randomized dose groups from the POS Phase 3 DB Pool as a comparison for perampanel groups (8 mg) for Studies 332 Core and 235 Core (see Section 7.2.1.2 of this review for details regarding possible differences in exposure due to differences in concomitant inducer use). The frequency of adverse events in the perampanel group for Study 332 Core (8 mg) was consistent with the POS DB Studies (with rates in between the 8 mg and 12 mg POS dose groups which had a higher frequency of concomitant inducer use). The frequency of adverse events in the perampanel group for Study 235 Core (8 mg) was also consistent with the POS DB Studies (with rates similar to the 8 mg POS dose group).

Table 26. Overview of TEAEs, SAEs, and TEAEs leading to discontinuation, Controlled Studies

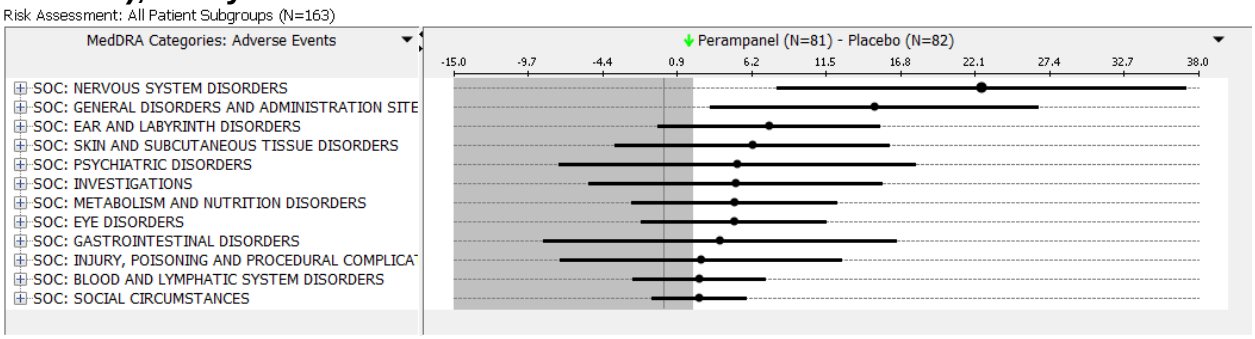
Category	POS Phase 3 DB Pool			Study 332 Core		Study 235 Core	
	Placebo	Perampanel[a]					
		8 mg	12mg	Placebo	Perampanel	Placebo	Perampanel[c]
n	442	431	255	82	81	48	85
TEAEs	294 (66.5)	350 (81)	227 (89)	59 (72.0)	67 (82.7)	31 (64.6)	68 (80.0)
SAEs	22 (5.0)	24 (5.6)	21 (8.2)	7 (8.5)	6 (7.4)	2 (4.2)	5 (5.9)
DC TEAE[b]	21 (4.8)	33 (7.7)	49 (19.2)	5 (6.1)	9 (11.1)	0	4 (4.7)

Source: ISS Table 46 (NDA 202834), CSR 332 Table 17, CSR 235 Table 19
[a]Randomized dose groups
[b]TEAEs leading to DC
[c]mean daily dose = 8.3 mg in Core Study 235

Comment: Of note, TEAEs were also reviewed for Study 232. A higher percentage of TEAEs occurred in perampanel subjects in Study 232 (27/28 or 96.4% in Cohort 1 (≥7 to <12 years) and 22/22 or 100% in Cohort 2 (≥2 to <7 years) as compared to Study 332 and 235. However, since the age of the subjects in Study 232 was lower than the indicated age of this submission (>12 years), this data will not be analyzed in detail in this review. Instead, this data will need to be more fully evaluated during the next submission for this age group.

The following forest plots summarize the risk differences of TEAEs by SOC, HLT, and PT between the perampanel group and placebo. The largest differences between the perampanel and placebo groups were in the incidences of TEAEs in the following SOCs: Nervous system, General, Ear/Labyrinth, Skin/Subcutaneous tissue, and Psychiatric disorders.

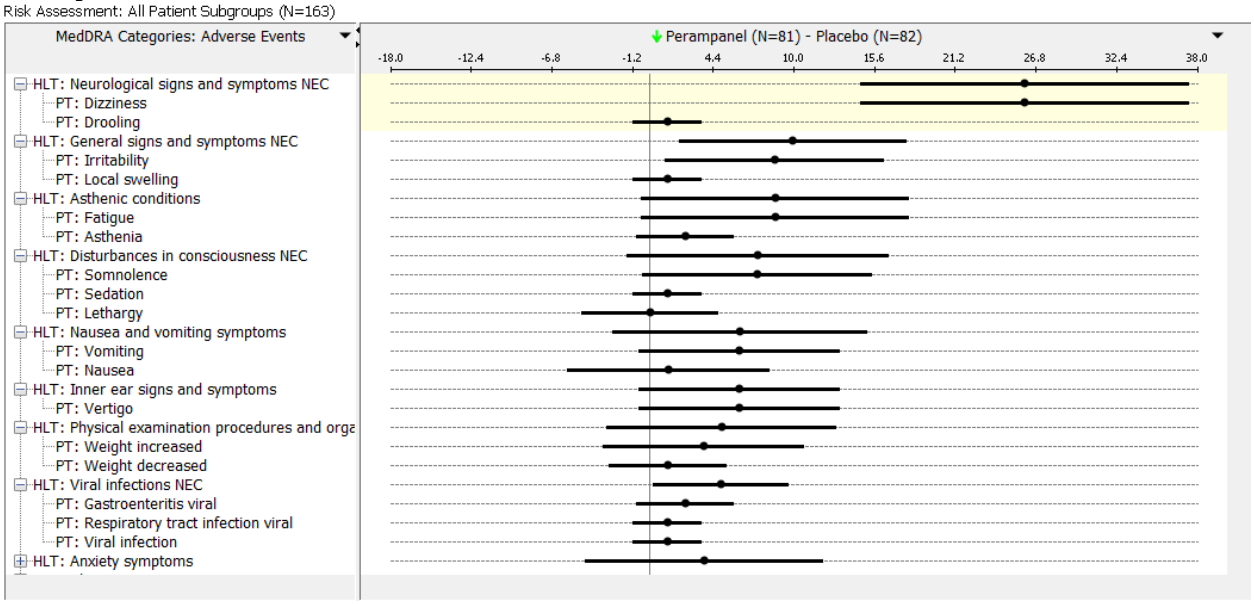
Figure 3. TEAEs by SOC with Risk Difference per hundred ≥ 2.0% (Perampanel-Placebo), Study 332 Core



Source: Created by the reviewer using JReview and Core 332 ADAE, ADSL datasets (SAFFL=Y and AEEMFL=Y)

For more detailed evaluation, TEAE analysis was performed by HLT which revealed TEAEs consistent with safety issues already described in perampanel labeling: neurologic events (dizziness, vertigo, fatigue, somnolence), psychiatric events (irritability, anxiety), and gastrointestinal events (nausea, vomiting). Interestingly, while weight increased was reported more frequently in perampanel subjects than placebo subjects, weight decreased was also reported slightly more frequently in perampanel subjects than placebo subjects.

Table 27. TEAEs by HLT with Risk Difference ≥ 5.0% (Perampanel-Placebo), Study 332 Core

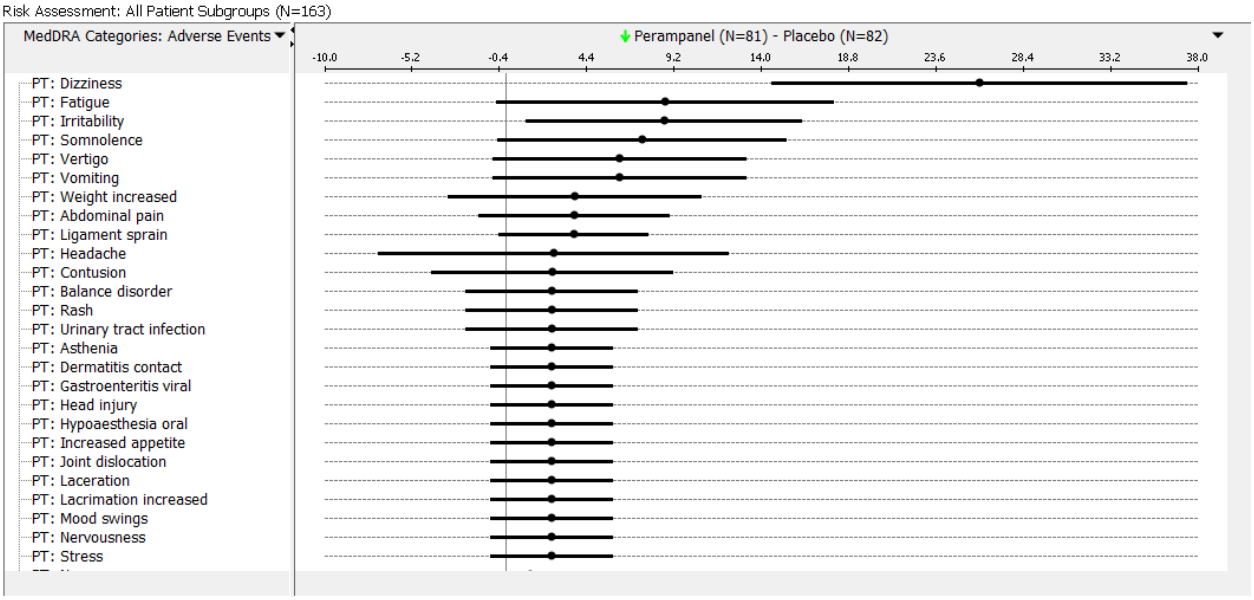


Source: Created by the reviewer using JReview and Core 332 ADAE, ADSL datasets (SAFFL=Y and AEEMFL=Y)

The largest differences between the perampanel and placebo groups were in the incidences of the following PTs: dizziness, irritability, fatigue, somnolence, vertigo,

vomiting, weight increased, abdominal pain, and ligament sprain as shown in Figure 4, below.

Figure 4. TEAEs by PT with Risk Difference ≥ 2.0% (Perampanel-Placebo), Study 332 Core

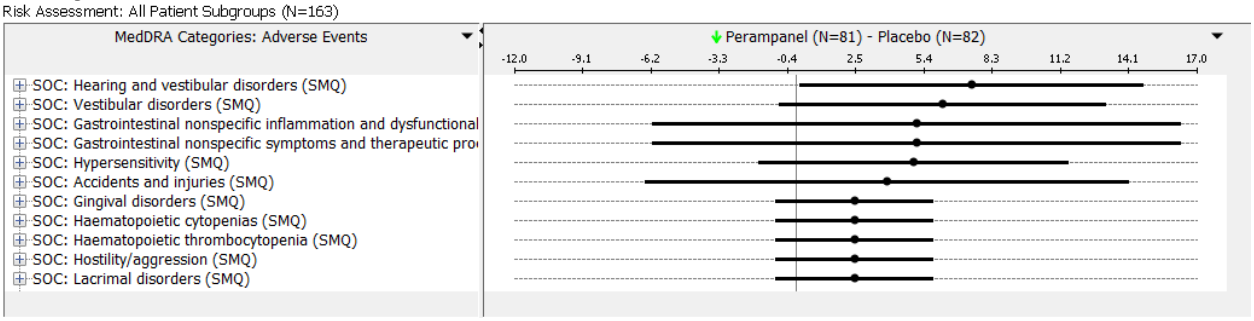


Source: Created by the reviewer using JReview and Core 332 ADAE, ADSL datasets (SAFFL=Y and AEEMFL=Y)

Further analyses were performed using Standardized MedDRA Queries to address possible splitting of MedDRA terms. The following forest plot summarizes the TEAEs by Standardized MedDRA Query (Narrow search SMQ) with a risk difference of ≥2% between the perampanel group and placebo in Study 332 Core. The following SMQs had the largest risk differences: Hearing and vestibular disorders (driven by the PT vertigo), Gastrointestinal nonspecific inflammation and dysfunctional conditions (PTs vomiting, abdominal pain), Hypersensitivity (PT rash), and Accidents and injuries. None of the algorithmic SMQs (SMQs that employ an algorithmic search strategy rather than narrow and broad search terms) had risk differences greater than zero between the perampanel and placebo groups.

Table 28. SMQs (Narrow PTs) with Risk Difference ≥ 2% (Perampanel-Placebo), Study 332 Core

Risk Assessment: All Patient Subgroups (N=163)



Source: Created by the reviewer using JReview and MAED tools and Core 332 ADAE, ADSL datasets (SAFFL=Y and AEEMFL=Y)

The following table summarizes the TEAEs that occurred in at least 2% of the perampanel subjects and more frequently than placebo for the Study 332 Core.

Table 29. TEAEs by SOC and PT (Events ≥ 2% of perampanel subjects and more frequent than placebo), Study 332 Core

MedDRA System Organ Class **Preferred Term**	**Placebo (N=82) n (%)**	**Perampanel (N=81) n (%)**
Subjects with any TEAE	59 (72.0)	67 (82.7)
Ear And Labyrinth Disorders	3 (3.7)	9 (11.1)
Vertigo	2 (2.4)	7 (8.6)
Eye Disorders	2 (2.4)	6 (7.4)
Lacrimation Increased	0	2 (2.5)
Vision Blurred	2 (2.4)	2 (2.5)
Gastrointestinal Disorders	16 (19.5)	19 (23.5)
Abdominal Pain	1 (1.2)	4 (4.9)
Constipation	1 (1.2)	2 (2.5)
Hypoaesthesia Oral	0	2 (2.5)
Nausea	4 (4.9)	5 (6.2)
Vomiting	2 (2.4)	7 (8.6)
General Disorders And Administration Site Conditions	9 (11.0)	21 (25.9)
Asthenia	0	2 (2.5)
Fatigue	5 (6.1)	12 (14.8)
Irritability	2 (2.4)	9 (11.1)
Infections And Infestations	21 (25.6)	20 (24.7)
Gastroenteritis Viral	0	2 (2.5)
Nasopharyngitis	7 (8.5)	7 (8.6)
Urinary Tract Infection	1 (1.2)	3 (3.7)
Injury, Poisoning And Procedural Complications	9 (11.0)	11 (13.6)

Contusion	3 (3.7)	5 (6.2)
Fall	1 (1.2)	2 (2.5)
Head Injury	0	2 (2.5)
Joint Dislocation	0	2 (2.5)
Laceration	0	2 (2.5)
Ligament Sprain	0	3 (3.7)
Investigations	9 (11.0)	13 (16.0)
Weight Decreased	1 (1.2)	2 (2.5)
Weight Increased	3 (3.7)	6 (7.4)
Metabolism And Nutrition Disorders	3 (3.7)	7 (8.6)
Decreased Appetite	1 (1.2)	2 (2.5)
Increased Appetite	0	2 (2.5)
Musculoskeletal And Connective Tissue Disorders	10 (12.2)	8 (9.9)
Myalgia	2 (2.4)	2 (2.5)
Nervous System Disorders	23 (28.0)	41 (50.6)
Ataxia	1 (1.2)	2 (2.5)
Balance Disorder	1 (1.2)	3 (3.7)
Dizziness	5 (6.1)	26 (32.1)
Headache	8 (9.8)	10 (12.3)
Lethargy	2 (2.4)	2 (2.5)
Somnolence	3 (3.7)	9 (11.1)
Psychiatric Disorders	16 (19.5)	20 (24.7)
Anxiety	3 (3.7)	4 (4.9)
Depression	2 (2.4)	2 (2.5)
Hallucination	2 (2.4)	2 (2.5)
Mood Swings	0	2 (2.5)
Nervousness	0	2 (2.5)
Stress	0	2 (2.5)
Skin And Subcutaneous Tissue Disorders	7 (8.5)	12 (14.8)
Dermatitis Contact	0	2 (2.5)
Rash	1 (1.2)	3 (3.7)

Source: CSR 332 Core, Table 18

In Study 332 Core, the most frequently reported adverse reactions in patients receiving perampanel (≥5% and higher than in the placebo group) included dizziness (32.1%), fatigue (14.8%), headache (12.3%), somnolence (11.1%), and irritability (11.1%), vertigo (9%), vomiting (9%), increased weight (7%), nausea (6%), contusion (6%), abdominal pain (5%), and anxiety (5%).

Comment: I compared these adverse events to the adverse reactions listed in Table 2 of the current Fycompa label from the pooled POS DB Studies. All of these adverse events from Study 332 Core are included in Table 2 except for the PT abdominal pain.

7.4.2 Laboratory Findings

In this submission, the Applicant identified potentially clinically significant (PCS) changes (treatment-emergent markedly abnormal results, an increase in the modified NCI-CTC grade of greater than or equal to 2, in subjects with normal values at baseline) The only exception was phosphate, which required a change of ≥ 3 grades to be a treatment emergent markedly abnormal value (TEMAV)(see Section 7.2.4 of this review for the modified NCI-CTC). The Applicant also provided analyses of mean changes from baseline and shifts in values from baseline for the laboratory data. This approach was acceptable to the reviewer.

Hematology Parameters
In Study 332 Core, for the hematology parameters (erythrocytes, hematocrit, hemoglobin, leukocytes, platelets), the mean changes from baseline to the end of treatment were small and of unknown clinical significance. The mean changes were similar in the perampanel and placebo groups (Core Study 332 CSR, Table 14.3.4.1.1). Shifts to abnormal values (from normal baseline) were similar in the perampanel and placebo groups for the hematology parameters (CSR Study 332 Core, Table 14.3.4.1.2.1). The number of subjects with 2 consecutive abnormal laboratory values was low and similar in the perampanel and placebo groups for the renal parameters (CSR Study 332 Core, Table 14.3.4.4.3). TEMAVs were rare and occurred in similar frequencies in the perampanel and placebo groups (Core Study 332 CSR, Table 14.3.4.4.1.1).

Renal Parameters
In Study 332 Core, for the renal laboratory parameters (BUN, urate, and creatinine), the mean changes from baseline to the end of treatment were small and of unknown clinical significance. The mean changes were similar in the perampanel and placebo groups (Core Study 332 CSR, Table 14.3.4.2.1). Shifts to high values were similar in the perampanel and placebo groups for the renal parameters (CSR Study 332 Core, Table 14.3.4.2.2.1). The number of subjects with 2 consecutive abnormal laboratory values was low and similar in the perampanel and placebo groups for the renal parameters (CSR Study 332 Core, Table 14.3.4.4.4). TEMAVs were rare and occurred in similar frequencies in the perampanel group (1.2%, n=1) and placebo (1.2%, n=1), both with high urate (Core Study 332 CSR, Table 14.3.4.4.1.9).

Hepatobiliary Parameters
In Study 332 Core, for the hepatobiliary laboratory parameters (ALT, AST, alkaline phosphatase, bilirubin, and lactate dehydrogenase), the mean changes from baseline to the end of treatment were small and of unknown clinical significance. The mean changes were similar in the perampanel and placebo groups (Core Study 332 CSR,

Table 14.3.4.2.1). The following shifts to high values at the end of treatment from normal baseline were slightly higher in perampanel subjects than placebo subjects: ALT (7.4% vs 3.8%), AST (2.5% vs 0), AP (7.4% vs 3.8%), LDH (3.8% vs 0) (CSR Study 332 Core, Table 14.3.4.2.2.1). The number of subjects with 2 consecutive abnormally high laboratory values (from normal baseline) was higher in the perampanel group than placebo groups for the following hepatobiliary parameters: ALT (2.5% vs 0), AP (2.5% vs 1.3%), LDH (1.3% vs 0) (CSR Study 332 Core, Table 14.3.4.4.4). However, these differences were small (<4%) and TEMAVs were rare (<3%). TEMAVs occurred in 2 perampanel subjects (2.5%) and 1 placebo subject (1.2%) for ALT only. When the analysis was limited to subjects whose baseline values were within the normal range, no subject had TEMAVs (Core Study 332 CSR, Table 14.3.4.4.1.9). There were no subjects with TEMAVs in Study 235 Core. No perampanel-treated subject met the laboratory criteria for Hy's Law either at the same visit or over the course of treatment in the entire safety database.

Electrolytes and Other Chemistry Parameters
In Study 332 Core, for electrolytes (bicarbonate, chloride, phosphate, potassium, sodium) and other chemistry parameters (albumin, calcium, cholesterol, glucose, globulin, protein, triglycerides), the mean changes from baseline to the end of treatment were small and of unknown clinical significance. The mean changes were similar in the perampanel and placebo groups (Core Study 332 CSR, Table 14.3.4.2.1). The following shifts to high values at the end of treatment from normal baseline were slightly higher in perampanel subjects than placebo subjects: cholesterol (11.1% vs 5%), triglycerides (4.9% vs 0). (CSR Study 332 Core, Table 14.3.4.2.2.1). The number of subjects with 2 consecutive abnormally high laboratory values (from normal baseline) was higher in the perampanel group than placebo groups for the following parameters: cholesterol (3.7% vs 2.5%), triglycerides (3.7% vs 0) (CSR Study 332 Core, Table 14.3.4.4.4). TEMAVs were rare and occurred in similar frequencies (with ≤1% risk difference) in the perampanel group and placebo (Core Study 332 CSR, Table 14.3.4.4.1.9).

Comment: The Applicant attributed the higher rate of triglyceride abnormalities in the perampanel group compared to placebo to "transient changes that occurred in subjects who were not fasting" on page 118 of the Summary of Clinical Safety.

Of note, there was 1 SAE related to a chemistry parameter: hypoglycaemia reported in subject 10010004 in Study 232 (narrative revealed that the subject's parents reported symptoms of hypoglycemia started months preceding first perampanel dose).

Urinalysis Parameters
In Study 332 Core, the mean changes and shifts values for urinalysis parameters (specific gravity, pH, occult blood, ketones, protein) tended to be small and of unknown clinical significance (CSR Study 332 Core, Tables 14.3.4.3.1 and 14.3.4.3.2.1). Urinalysis parameters were not analyzed by the Applicant for Study 332 Extension.

In conclusion, for cholesterol and triglycerides laboratory values, there was a greater frequency of shifts to high values at the end of treatment from normal baseline in perampanel subjects than placebo subjects. However, consecutive values occurred at a low frequency, TEMAVs were rare, and mean changes were small and similar between the two groups (see association with weight gain in the following section). Perampanel was not associated with changes in other chemistry parameters or in hematology parameters in Study 332 Core.

7.4.3 Vital Signs

Blood Pressure, Pulse Rate, Respiratory Rate, and Temperature
In Study 332 Core, for vital signs (diastolic blood pressure, systolic blood pressure, pulse rate, respiratory rate, temperature), the mean changes from baseline to the end of treatment were small and of unknown clinical significance. The mean changes were similar in the perampanel and placebo groups (Core Study 332 CSR, Table 14.3.4.5.1.1).

The number of subjects who had increases or decreases in SBP or DBP of 5-10, 11-15, 16-20, and >20 mmHg (from baseline to the end of treatment) was higher in the perampanel group than placebo group for the following category: SBP and DBP increase of 5-10 mmHg (12.3% vs 8.6% and 24.7% vs 16%, respectively) (CSR Study 332 Core, Tables 14.3.4.5.2.2 and 14.3.4.5.2.3). However, the frequencies of this category (SBP and DBP increase of 5-10 mmHg) fluctuated during the trial (e.g., at week 12, the percentages in the perampanel and placebo group were 22.1% vs 19.2 and 8.8% vs 21.9%, respectively).

The number of subjects who had increases or decreases in SBP or DBP of increments of ≥10, 20, or 40 mmHg (from baseline to the end of treatment) was higher in the perampanel group than placebo group for the following categories: DBP increment ≥10 mmHg (46.9% vs 34.6%) and SBP increment ≥20 mmHg (19.8% vs 17.3%) (Core Study 332 CSR, Table 14.3.4.5.2.1).

Shifts to abnormal values (from normal baseline) were similar in the perampanel and placebo groups (CSR Study 332 Core, Table 14.3.4.5.2.4). No clinically notable vital signs were recorded in either the perampanel or placebo group (Core Study 332 CSR, Table 14.3.4.5.3.1).

Orthostatic measurements were not performed in Study 332 Core. In Study 332 Core, no subjects had TEAEs suggestive of hypotension or orthostatic hypotension based on the PTs of blood pressure orthostatic decreased, dizziness postural, orthostatic hypotension, blood pressure ambulatory decreased, blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, mean arterial pressure decreased, diastolic hypotension, systolic hypotension, hypotension, and postural lightheadedness.

Weight
In Study 332 Core, for weight, the mean change from baseline to the end of treatment was higher for perampanel subjects (+1.8 kg) than placebo subjects (+0.1 kg) (Core Study 332 CSR, Table 14.3.4.5.1.1). After stratifying by age category, the mean change was less among adults (+1.69 kg vs +0.02 kg) than in adolescents (+2.58 kg vs +0.37 kg). Shifts to abnormal values were higher in perampanel subjects than placebo subjects. Clinically notable increases in weight occurred in a higher percentage of perampanel subjects (14.8%) than placebo subjects (4.9%) (Core Study 332 CSR, Table 14.3.4.5.3.1).

In terms of weight categories, a higher percentage of perampanel subjects (11.1%) had a weight gain of ≥7% at the end of treatment than placebo subjects (3.7%) (Core Study 332 CSR, Table 14.3.4.5.3.6). After stratifying by age, the difference between the treatment groups (for weight gain of ≥7%) was less among adults (10% vs 4.1%, respectively) than in adolescents (18.2% vs 0%, respectively). For the ≥15% weight gain category, while similar rates were seen in adults (1.4% vs 1.4%, respectively), a difference was seen in adolescents (9.1% vs 0%, respectively). There was 1 perampanel-treated adolescent who gained ≥25% of baseline weight during this trial. The median exposure was 17 weeks in Study 332 Core.

These results are summarized in the table below. These results for Study 332 Core were consistent with the POS Phase 3 DB Pool (in the original NDA) in which the percentages of adults who gained at least 7% and 15% of their baseline body weight in perampanel subjects were 9.1% and 0.9%, respectively, as compared to 4.5% and 0.2% of placebo-treated patients, respectively. In these trials with a median exposure of 19 weeks, perampanel subjects gained a mean of 1.1 kg compared to 0.3 kg in placebo subjects.

Table 30. Weight Gain at End of Treatment, Study 332 Core

	Placebo (N=82)	**Perampanel (N=81)**
Number of subjects with weight assessments at baseline and end of treatment	81	81
Adults (≥17 years old)	74	70
Adolescents (<17 years old)	7	11
Median exposure (weeks)	17.00	17.00
Adults (≥17 years old)	17.00	17.00
Adolescents (<17 years old)	17.57	17.00
Mean change from baseline (kg)	0.05	1.81
Adults (≥17 years old)	0.02	1.69
Adolescents (<17 years old)	0.37	2.58
Subjects (%) who gained ≥7% of baseline weight	3 (3.7)	9 (11.1)
Adults (≥17 years old)	3 (4.1)	7 (10.0)
Adolescents (<17 years old)	0	2 (18.2)

Subjects (%) who gained ≥15% of baseline weight	1 (1.2)	2 (2.5)
Adults (≥17 years old)	1 (1.4)	1 (1.4)
Adolescents (<17 years old)	0	1 (9.1)
Subjects (%) who gained ≥25% of baseline weight	0	1 (1.2)
Adults (≥17 years old)	0	0
Adolescents (<17 years old)	0	1 (9.1)
Subjects (%) who discontinued due to AE of 'Weight Increased'	0	0

The number of subjects with weight assessments at baseline and end of treatment is the sample size for the mean values and the denominator for the percentages.
Source: Core Study CSR, Table 14.3.4.5.3.6

The following table summarizes the percentages of subjects in Study 332 Core with a body weight gain of >5%, >7%, or >10% meeting 1 or all of the criteria for metabolic syndrome (triglyceride of ≥150 mg/dL, blood pressure ≥130/85 mmHg, BMI >30 kg/m^2).

Table 31. Incidence of Metabolic Syndrome, Study 332 Core

Metabolic Syndrome Value during Treatment	Weight Gain Category	Placebo (N=82)	Perampanel (N=81)
Triglycerides ≥150 mg/dL	n[a]	80	81
	> 5%	2 (2.5)	10 (12.3)
	> 7%	2 (2.5)	6 (7.4)
	> 10%	0	2 (2.5)
Blood Pressure ≥130/85 mmHg	n[a]	81	81
	> 5%	0	6 (7.4)
	> 7%	0	2 (2.5)
	> 10%	0	1 (1.2)
Body Mass Index >30 kg/m^2	n[a]	81	81
	> 5%	3 (3.7)	9 (11.1)
	> 7%	3 (3.7)	5 (6.2)
	> 10%	0	2 (2.5)
All of the Above	n[a]	80	81
	> 5%	0	1 (1.2)
	> 7%	0	0
	> 10%	0	0

a: Indicates the number of subjects with observed data during the treatment period and is used for calculating the percent.
Source: Core Study CSR, Table 14.3.4.5.3.9

For every category of weight gain, perampanel subjects had a higher frequency than placebo subjects of having (at some time during the trial), an elevated triglyceride value,

blood pressure ≥130/85 mmHg, or met the BMI criterion for obesity. One perampanel subject met all of these criteria: subject 16011002 who was a 42 year-old male who met all of these criteria at baseline (BMI 33.4 kg/ m^2, triglyceride 315 mg/dL, and blood pressure 136/87) and at week 17 experienced weight gain (of 6.6%) and an increase in triglycerides (of 53 mg/dL) without a change in blood pressure. The subject continued treatment in Study 332 Extension in which his triglyceride value returned to baseline.

In Study 235 Core, the mean change from baseline to the end of treatment was higher for perampanel subjects (+1.9 kg) than placebo subjects (-1.0 kg) (Core Study 235 CSR, Table 29).

In conclusion, perampanel use was associated with weight gain in both adults and adolescents. The information regarding adults is already in perampanel labeling in the Adverse Reactions section (in which clinical monitoring of weight is recommended). However, I recommend the addition of information regarding weight gain in adolescents associated with perampanel use. Furthermore, I recommend a postmarket requirement for further evaluation of the safety signal of weight gain and other metabolic changes. Perampanel was not associated with any significant changes in other vital signs in Study 332 Core.

7.4.4 Electrocardiograms (ECGs)

ECG assessments were performed only at screening in Study 332 Core.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable as there was only 1 randomized dose group in Study 332 Core.

7.5.2 Time Dependency for Adverse Events

Time dependency for adverse events was consistent with data from the original NDA.

7.5.3 Drug-Demographic Interactions

Age - Pediatric Subjects
Specific information regarding the safety profile of adolescents is further discussed in appropriate sections within Section 7, particularly with respect to hostility and aggression.

Sex
The reader is referred to Clinical Pharmacology for further details regarding these analyses regarding sex. Specific information regarding the differences in the AE safety profile between males and females, particularly with respect to hostility/aggression, is further discussed in appropriate sections within Section 7.

Race
Specific information regarding the differences in the AE safety profile among race subgroups, particularly with respect to hostility/aggression, is further discussed in appropriate sections within Section 7. In general, however, small sample sizes limited any definitive conclusions regarding differences in safety by race.

7.5.4 Drug-Disease Interactions

The reader is referred to the Clinical Pharmacology review for further details regarding drug-disease interactions.

7.5.5 Drug-Drug Interactions

The reader is referred to the Clinical Pharmacology review for further details regarding drug-drug interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

In Study 332, 232, and 235, there was only 1 patient with any preferred terms coded to the MedDRA SOC Neoplasms benign, malignant and unspecified (including cysts and polyps): Subject 235-1003-1002 with a benign pituitary tumour diagnosed on Study Day 10.

7.6.2 Human Reproduction and Pregnancy Data

There was minimal data on the use of perampanel in pregnant women as the protocols for the studies required that female participants of child-bearing potential to be abstinent or to use at least one medically acceptable method of contraception (e.g., a double-barrier method [e.g., condom + spermicide, condom + diaphragm with spermicide],

intrauterine device, or have a vasectomized partner) throughout the entire study period and for 30 days after study drug discontinuation.

As of the cutoff date for the 120-day Safety Update, there was a total of 1 pregnancy in the entire safety database that resulted in an incomplete spontaneous abortion (subject 332-2101-1001).

Of note, in the entire safety database, there were 2 perampanel subjects with the following TEAEs coded to the SOC Congenital, Familial and Genetic Disorders (however, due to post-natal exposure of perampanel): phimosis (4 year-old male) and developmental hip dysplasia (5 year-old male).

7.6.3 Pediatrics and Assessment of Effects on Growth

The reader is referred to the Pharmacology, Toxicology review by Dr. Christopher Toscano for further details regarding the preclinical studies. In the current perampanel prescribing information, the following information is included in Section 8.4 Pediatric Use:

> Juvenile Animal Data
> Oral administration of perampanel (1, 3, 3/10/30 mg/kg/day; high dose increased on postnatal days [PND] 28 and 56) to young rats for 12 weeks starting on PND 7 resulted in reduced body weight, reduced growth, neurobehavioral impairment (water maze performance and auditory startle habituation) at the mid and high doses, and delayed sexual maturation at the high doses. CNS signs (reduced activity, incoordination, excessive grooming/scratching), pup death, decreased hindlimb splay, and decreased hindlimb grip strength were observed at all doses. Effects on pup body weight, pup growth, hindlimb splay, impairment in the water maze performance, and auditory startle persisted after dosing was stopped. A no-effect dose for postnatal developmental toxicity was not identified in this study.

Of note, in labeling submitted with this application, the Applicant wanted to add the following (in red) regarding pediatric use:

> **8 USE IN SPECIFIC POPULATIONS**
> **8.4 Pediatric Use**
> The safety and efficacy of FYCOMPA for the adjunctive therapy of partial-onset seizures was established by three randomized double-blind, placebo-controlled, multicenter studies, which included 72 pediatric patients between 12 and 16 years old exposed to perampanel [see Clinical Studies (14.1), Clinical Pharmacology (12.3)]. The safety and efficacy of FYCOMPA for the adjunctive therapy of primary generalized tonic-clonic seizures was established in a single randomized double-blind, placebo-controlled, multicenter trial (n=164), which included 11 pediatric patients ages 12 to (b) (4) 16 years old exposed to FYCOMPA; an additional (b) (4) FYCOMPA in the open label extension of the study. The safety and effectiveness of FYCOMPA in pediatric patients <12 years old have not been established.
> (b) (4)

(b) (4)

Study 235 (a randomized, double-blind, placebo-controlled, parallel group study with an open-label extension phase) evaluated the effect of perampanel on cognition and growth parameters. (Only the CSR for the randomized, double-blind, placebo-controlled, parallel-group phase of the study was submitted by the Applicant). The primary objective of the study was to compare the short-term effect of perampanel on cognition to placebo by using the Cognitive Drug Research (CDR) System when administered as an adjunctive therapy in adolescents (12 to less than 18 years of age) with inadequately controlled POS (with or without secondarily generalized seizures). The key secondary objective was to assess the short-term effect of perampanel in adolescents on each of the CDR System 5 core cognitive domains of: Power of Attention, Continuity of Attention, Quality of Episodic Memory, Quality of Working Memory, and Speed of Memory. Additional secondary objectives were as follows:
1. To evaluate the short-term safety and tolerability of perampanel in adolescents
2. To evaluate the short-term effects of perampanel in adolescents on language by using the COWAT
3. To evaluate the short-term effects of perampanel in adolescents on visuomotor skills by using the LGPT
4. To evaluate the pharmacokinetics of perampanel in adolescents using a population PK approach and to explore the PK/ PD relationship
5. To evaluate the efficacy of perampanel in adolescents as determined by percent change in seizure frequency and responder rate

Though not specified as objectives in the protocol, behavior, quality of life (QoL), growth and development, withdrawal questionnaire responses, and photosensitivity were evaluated in the Core Study.

For these endpoints, the Applicant reported the following conclusions in the CSR: "There is no evidence of an overall effect of perampanel on cognitive function as measured by the primary outcome measure (CDR System Global Cognition Score) when compared to placebo, which is corroborated by the PK/PD analyses. Although a firm conclusion cannot be drawn, evaluation of domain scores suggested a worsening effect of perampanel for Continuity of Attention and a beneficial effect of perampanel for Episodic Secondary Memory; both of these findings were further supported by PK/PD analyses which showed Continuity of Attention change from baseline decreased significantly with increasing perampanel concentration and Episodic Secondary Memory change from baseline increased significantly with increasing perampanel concentration. In addition, for Speed of Memory, there was a difference between perampanel and placebo in favor of placebo, although there was no effect of perampanel exposure on this domain score. At daily doses up to 12 mg, perampanel was safe and well tolerated. Perampanel does not have clinically important effects on language, visuomotor skills, behavior, quality of life, and growth and development."

Comment: I have discussed the findings in Study 235 and the Applicant's proposed labeling changes with Drs. Hershkowitz (CDTL) and Sheridan. I defer to the efficacy team regarding these results (b) (4) *. Drs. Hershkowitz and Sheridan did not agree* (b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The reader is referred to the Controlled Substance Staff review from the original NDA for POS for further details regarding drug abuse potential and withdrawal, to the Pharmacology/Toxicology review for details regarding the preclinical studies, and to Dr. Philip Sheridan's review of efficacy for details regarding rebound epilepsy.

The Applicant reported no overdose cases in Study 332 Core or the extension phase. In Core Study 232, 1 event of accidental overdose was reported in 1 subject (1003-0002 with concurrent TEAEs of weight increased, somnolence, attention deficit/hyperactivity disorder, and abnormal behavior). In Core Study 235, no events associated with overdose (or misuse, abuse, or medication error) were reported. In the post-marketing database (as of October 22, 2014), the Applicant reported 6 spontaneous reports of overdose with Fycompa with and without associated adverse events.

Comment: I reviewed the summaries of the cases that the Applicant provided in the 120-day Safety Update, Summary of Clinical Safety, and did not identify any new safety concerns. All of the cases were either limited by not enough information or confounded by concomitant medication or substance abuse.

One case was reported by the Applicant of abuse or misuse: a 38 year-old female who was given 2 mg Fycompa sample packs but requested additional sample packs and had an "addiction" to Fycompa and was doing her own dosing. The patient had a previous history of addiction to other antiepileptic drugs and addictive tendencies.

7.7 Additional Submissions / Safety Issues

The Division made several request for information and additional analyses after the NDA resubmission on August 19, 2014. The 120-Day Safety Update Report was submitted on December 22, 2104. Review of the responses to the FDA requests for information has been incorporated throughout this review up to March 19, 2015.

8 Postmarket Experience

This Applicant analyzed postmarketing safety data on perampanel received until the data lock point of October 22, 2014 (including data from the 120-day Safety Update).

Perampanel tablets are currently approved for marketing in 40 countries (b) (4) [redacted]

The applicant estimated that the cumulative worldwide patient exposure to perampanel from the international birth date of product launch in the EU (July 23, 2012) to October 22, 2014 to be 2,700,000 patient-days (*or 7397 patient-years)*. (Of note, while perampanel was approved by the FDA on October 22, 2012, the US DEA published a final ruling with an effective day of January 2, 2014.)

The Applicant provided postmarketing data derived from the following sources: spontaneous individual case safety reports (ICSRs) including reports from healthcare professionals, consumers, scientific literature, competent authorities (worldwide), and solicited noninterventional ICSRs, including those from noninterventional studies.

Cumulatively, the Applicant identified 547 reports with 1104 events (877 spontaneous and 30 solicited). The following table summarizes the postmarketing TEAEs reported in >= 10 patients. The most commonly reported postmarketing TEAEs were psychiatric (aggression, irritability, abnormal behavior, suicidal ideation/depression), followed by neurologic TEAEs (dizziness/gait disturbance/balance disorder, fatigue/somnolence, fall, and convulsion).

Table 32. TEAEs Reported in ≥10 Patients from July 23, 2012 to October 22, 2014

Preferred Term	Serious	Non-Serious	Total Cumulative	Serious Solicited
Aggression	27	66	9	3
Dizziness	8	67	7	1
Convulsion	39	2	4	1
Irritability	6	30	3	
Gait disturbance	7	26	3	1
Somnolence	3	29	3	
Drug ineffective	1	29	3	
Fatigue	1	27	2	
Suicidal ideation	8	14	2	
Abnormal behaviour	2	18	2	1
Rash	2	14	1	
Weight increased	2	13	1	
Depression	5	9	1	
Nausea	2	11	1	
Fall	5	6	1	
Balance disorder	2	9	1	
Confusional state	7	4	1	
Agitation	4	7	1	
Insomnia	3	8	1	
Vision blurred	2	9	1	
Ataxia	4	6	1	1
Dysarthria	7	3	1	1

Source: 120-Day Safety Update, 5.3.6 Postmarketing Experience and Literature Review, Table 1

Comment: Additionally, I reviewed all of the postmarketing events reported in <10 patients (5.3.6 Post-marketing Experience and Literature Review, Table VII.8.). There were a few notable isolated case reports (n=1) of the following preferred terms: cyanosis, cardiac arrest (see details of the case report below), ventricular tachycardia (see case report below), loss of consciousness (nonserious), renal failure, respiratory failure, DRESS. There were 4 case reports coded to the PT of SUDEP (with a reporting rate calculated by the reviewer to be 4/7397 or 0.54 per 1000 patient-years, which is much less than the incidence rate range of 3.5 to 5.9 per 1000 patient-years in subjects with refractory epilepsy reported in the literature.[4,5]

E2007-01120-SPO-DE: 49 year-old female who started perampanel and due to multiple antiepileptic drug therapy was monitored on 24-hour ECG. Pt was found to have asymptomatic asystole. Concomitant medication included phenytoin and citalopram (bradycardia listed in PI). Pacemaker implantation was performed and pt was continued on perampanel and events resolved.

E2007-01350-SPO-DE: 30 year-old male with a history of tuberous sclerosis started on perampanel and 6 weeks later developed ventricular tachycardia requiring hospitalization (it was noted that the pt became "slow, tachycardic, hypotonic, and hypoxic probably after a grand mal seizure"). Pt had started everolimus 3 months prior (tachycardia is listed in PI). EKG revealed

4 Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. Lancet Neurol. 2008; **7**: 1021–31.
5 Tellez-Zenteno JF et al. Sudden unexpected death in epilepsy: evidence-based analysis of incidence and risk factors. Epilepsy Research. 2005; 65: 101-15.

ventricular tachycardia and amiodarone was initiated. Events resolved despite continuation of perampanel and everolimus. (Of note, tuberous sclerosis has been associated with arrhythmias[6]).

There were a total of 353 events from 232 reports in the SOC Psychiatric disorders. Specifically, the Applicant reported that there were a total of 108 reports with events that fell under the narrow SMQ of hostility/aggression, with 44 events that met serious criteria (164 met the broad SMQ of which 26 or 16% were patients under the age of 18 years old). The majority of the reports were events of aggression (96 reports). In addition to the events listed in the table above, there were 7 reports of suicide attempt, 1 of self-injurious behaviour, 2 of intentional self-injury, 1 of pyromania, 6 reports of homicidal ideation, 2 reports of physical assault, and 1 report each of hostility and violence-related symptom. These case reports were submitted by the Applicant (in a Safety Information Amendment dated March 2, 2015) in response to the Division's information request. Detailed analysis of these postmarketing case reports are discussed in pertinent subsections of Section 7.3.4 of this review.

The isolated postmarketing case of DRESS was also reported in the literature (details of the case were confirmed by the Applicant with the CIOMS report in a Safety Information Amendment dated 12/5/14 upon the Division's request).[7] (Of note, I performed a search of FAERS and PubMed and did not identify any additional cases). This was a probable case of DRESS associated with perampanel use: RegiSCAR score of 4[8] (generalized rash suggestive of DRESS, renal failure, elevated liver enzymes), negative signs of SJS or TEN (negative Nikolsky sign, negative full thickness skin sloughing), temporal relationship with perampanel use (5 weeks after initiation), concomitant medications of lamotrigine and valproic acid were started > 2 years prior, and positive dechallenge (but all 3 AEDs were discontinued). However, with only 1 reported case of DRESS (probable and not definite) it is difficult to make any conclusions regarding the causal association between perampanel use and DRESS. Therefore, DRESS should be added to the Postmarketing subsection of the Adverse Reactions Section (rather than in the Warnings and Precautions Section). Furthermore, I recommend enhanced postmarket surveillance of DRESS.

Furthermore, the Applicant performed a search for events coded to the MedDRA high level terms (HLTs) of Tendon therapeutic procedures, Tendon disorders, Muscle, tendon and ligament injuries, and Ligament disorders. The Applicant did not identify any postmarketing reports of tendon or ligament rupture in perampanel treated patients.

Additionally, the Applicant performed a search for events coded to the MedDRA HLTs of cholecystitis and cholelithiasis, Acute and chronic pancreatitis, Pancreatic disorders

6 Gibbs JL. The heart and tuberous sclerosis: An echocardiographic and electrocardiographic study. Br Heart J. 1985; 54: 596-9.
7 Shimabukuro K et al. DRESS Associated with Perampanel Administration in a Child with Drug-Resistant Epilepsy. Neurology. Dec 2014; (83): 1-2.
8 Kardaun SH et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol. 2007; 156(3): 609-11.

NEC, Pancreatic therapeutic procedures, and the MedDRA PT of cholecystectomy. Cumulatively the Applicant identified 2 spontaneous reports of pancreatitis. The Applicant noted that the number of reported cholelithiasis and pancreatic reactions in perampanel users was low and consistent with the background rate expected for the European and American population.

Finally, the Applicant performed a search of the literature using the term "perampanel" in PubMed with a data cutoff date of September 24, 2014. The Applicant reviewed the articles for information related to the safety of perampanel in general and special safety topics of interest: cardiovascular safety; CNS (aggression- and hostility-related events; somnolence and fatigue; coordination difficulties, dizziness, and falls); suicidal behavior and ideation; and safety in subgroups and special populations; off-label use; abuse, misuse, and overdose; idiosyncratic reactions (eg, severe rash, drug rash with eosinophilia and systematic symptoms [DRESS]); and other notable events. The Applicant's literature review did not identify any new safety signals.

Comment: The one literature report of DRESS was identified by the Applicant in the 120-day Safety Update. See details of the case above.

The Applicant concluded that the postmarketing experience was consistent with the clinical trial experience and with the information in the current product information. However, the (b) (4)

(b) (4)

Comment: Detailed evaluation of psychiatric disorders associated with perampanel is discussed earlier in this review in Section 7.3.4. Any recommendations regarding changes to Fycompa labeling pertaining to psychiatric disorders are addressed in Section 7.3.4 (I did not agree with the (b) (4) *Otherwise, the TEAEs in other SOCs identified by the Applicant in the postmarketing arena are consistent with the events listed in the Warnings and Precautions section of current Fycompa labeling.*

Furthermore, Karen Long, PharmD in the Division of Pharmacovigilance I in the Office of Surveillance and Epidemiology has conducted an 18-month NME Postmarket Safety Summary: Less Than 10,000 Patients Exposed for perampanel (dated 2/12/15). After reviewing the 152 unduplicated case reports identified in their search of FAERS (received by the FDA from Oct 22, 2012 to September 18, 2014), they reported that all of the drug-event combinations with an EB05 ≥ 2 were labeled events with perampanel (and were consistent with the known risk in the labeling without any increase in severity) except for seizure-related events (consistent with treatment of the indication). The team concluded that there were no new potential safety signals requiring additional review.

9 Appendices

See below.

9.1 Literature Review/References

Literature citations have been incorporated into the body of this review as footnotes.

9.2 Labeling Recommendations

Draft labeling recommendations will be added to a working document.

9.3 Advisory Committee Meeting

The Division did not present the perampanel sNDA to an Advisory Committee.

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/s/

MARY DOI
05/11/2015

SALLY U YASUDA
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