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RESEARCH**

APPLICATION NUMBER:

202834Orig1s000

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
Safety Team Leader Memorandum

NDA: 202834
Drug: Perampanel (FYCOMPA)
Route: Oral
Indication: Adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization
Sponsor: Eisai, Inc.
Submission Date: 12/22/11
Review Date: 8/30/12
Reviewer: Sally Usdin Yasuda, Safety Team Leader
Division of Neurology Products

1. Background

Perampanel is, according to the Sponsor, a non-competitive antagonist of the AMPA glutamate receptor. The mechanism of action in epilepsy is not fully established. In addition to the clinical trials for epilepsy, clinical trials have been performed in patients with Parkinson's disease, multiple sclerosis, migraine, and neuropathic pain. Fycompa has been approved since July 2012 in Europe for the indication proposed in this NDA. The proposed dose is 4-12 mg per day, given as a single daily dose before bedtime in patients aged 12 years and older. Treatment is to be initiated with a dose of 2 mg/day, increasing in increments of 2 mg/day at intervals no more frequently than weekly.

In terms of the clinical pharmacology of perampanel, T_{max} ranges from 0.5 to 4 hours. Perampanel is extensively metabolized, primarily by CYP3A followed by glucuronidation. In clinical studies, the CYP3A4 inducers carbamazepine, oxcarbazepine, and phenytoin caused large, 2-3 fold increases in perampanel clearance. Mean elimination half-life is 105 hours (based on a population PK analysis of pooled data from 19 Phase 1 studies). Renal clearance is a minor route of elimination. Steady state is typically achieved by Day 21.

This memorandum primarily summarizes the findings of Dr. Mary Doi's primary safety review of the perampanel NDA. Please refer to Dr. Doi's review for more detail.

2. Summary of Findings from the Safety Review

2.1 Sources of Data, Exposure, and Demographics

Sources of Data

The NDA summarized safety data from 52 clinical trials. These include 27 Phase 1 trials (including a thorough QT study) evaluating single (0.2 to 36 mg) or multiple doses (1 to 12 mg), 10 studies performed in the primary indication of epilepsy, and 15 studies in non-epilepsy indications (Parkinson's disease, neuropathic pain, migraine, and multiple sclerosis). The Safety analysis pools in Dr. Doi's review were the Epilepsy Phase 3 Double-blind (DB) Pool, the Epilepsy Phase 2 DB Pool, the Epilepsy All Treated Pool (DB studies and open label extensions); the Nonepilepsy All Treated Pool

and the Nonepilepsy DB Pool; and the Phase 1 Pool (pooled into single dose studies and multiple dose studies; n=916)).

The Epilepsy Phase 3 DB trials (Studies 304, 305, and 306) were randomized, double-blind, placebo-controlled, dose-escalation, parallel-group studies to evaluate the efficacy and safety of perampanel given as adjunctive therapy in subjects with refractory partial seizures aged 12 years and older¹. As described in Dr. Doi's review, the three phases of the studies were the pre-randomization, double-blind (with 6 week titration period followed by a 13 week maintenance period) and follow-up phases. Subjects could be on stable doses of up to 3 approved antiepileptic drugs (AEDs); only 1 inducer AED (defined as carbamazepine, phenytoin, phenobarbital, or primidone) was allowed. Concomitant use of vigabatrin was excluded. Dose was not stratified by concomitant use of enzyme inducing AEDs. The maintenance doses in Studies 304 and 305 were 8-12 mg/day and in Study 306 they were 2-8 mg/day. During the titration period in each study, doses were increased in 2 mg increments (beginning with a 2 mg dose) on a weekly basis until the randomly assigned dose was attained. Down-titration was permitted for subjects experiencing intolerable adverse events (AEs) anytime during the double-blind phase. Following the DB studies, approximately 86% of placebo subjects and 81% of perampanel subjects subsequently enrolled in the open label extension (OLE) Study 307. In Study 307 subjects were titrated to 12 mg/day or the maximum tolerated dose (MTD) and remained on that dose unless further titration was necessary for efficacy or tolerability; in this study concomitant AEDs and doses could be changed at the discretion of the investigator.

In the Epilepsy Phase 2 DB pool, Study 203 evaluated doses of 1 and 2 mg/day, Study 206 evaluated doses of 4 mg/day (or the MTD) in 101 subjects, and Study 208 evaluated doses of 12 mg/day (or the MTD) in 38 subjects. Approximately 70% of the placebo group and 68% of the perampanel group of Study 206/208 subsequently enrolled in OLE Study 207.

The Nonepilepsy DB pool included safety data from six Phase 2 and Phase 3 studies in Parkinson's disease, evaluating doses of ≤ 4 mg/day (n=1462) except for Study 214 that evaluated doses of > 4 mg-8 mg (n=55). It also included the Neuropathic Pain DB pool with doses of > 4 -8 mg/day (n= 236) and ≤ 4 mg/day (n=141), and the Multiple Sclerosis and Migraine in DB studies that contributed 119 subjects to < 4 mg/day. The Nonepilepsy all-treated pool (n=2717) also included the OLE studies for Parkinson's disease and Neuropathic Pain.

Exposure

According to Dr. Doi's review, as of the 120 day Safety Update cutoff date 1651 subjects with epilepsy had received perampanel in the Phase 2 and 3 DB, placebo controlled trials and in the open-label extension studies. A total of 1231 subjects were exposed for at least 6 months and 996 subjects were exposed for at least 1 year. Dr. Doi notes that even after restricting the epilepsy population to subjects who received

¹Sites in Bulgaria, China, France, Germany, India, Lithuania, the Netherlands, and Portugal only enrolled subjects 18 years of age and older.

maximum daily doses at or above the proposed lowest dose for marketing (4 mg), the total number of subjects was 1573. She also notes that in the Epilepsy All Treated Pool, mean duration of exposure for the highest modal dose group (> 8 to 12 mg) was 89.1 weeks, and that 739 of the 952 subjects in this dose group were treated for over 51 weeks. Thus the Sponsor has met the ICH guidance recommendations of 1500 total, 300 for 6 months, and 100 for 1 year for the Epilepsy pools alone.

A total of 104 pediatric subjects (12 to ≤ 16 years old) were exposed to perampanel, all in the epilepsy Phase 3 trials, with 82 subjects exposed for greater than 6 months and 65 subjects exposed for greater than 1 year. The Sponsor recently initiated Study 235, a randomized, DB, placebo controlled study of the effects of adjunctive therapy with perampanel on cognition, growth, safety, tolerability, and PK in adolescents (12 to < 18 y.o). As of October 1, 2021, 39 subjects had been enrolled in Study 235, with an enrollment goal of 132 subjects.

Dr. Doi notes that fewer subjects completed the trial in the higher dose groups in the Epilepsy Phase 3 DB Pool (discussed in more detail in section 2.3.3 of this memo under Dropouts). In addition, she notes that subjects assigned in the higher dose groups were more likely to be unable to reach and maintain the randomized dose, with the target dose being the last dose taken by 98.3%, 93.6%, 81%, and 61.2% of subjects in the 2mg, 4mg, 8mg, and 12 mg dose groups, respectively. Of those randomized to the 12 mg group, 72.5% (n=185) reach the assigned dose, although 24.3% of those subjects later down-titrated or discontinued (twice the placebo rate of 11.3%). Of those randomized to the 8 mg group, 96% (n=414) reached the assigned dose, although 25.1% later down-titrated or discontinued. In the 2mg and 4 mg dose groups, 99% and 98%, respectively, reached their assigned doses and subjects in those groups down-titrated or discontinued at rates similar to placebo. Fewer subjects receiving non-enzyme inducing AEDs reached and maintained doses of 8-12 mg for the entire double-blind treatment phase when compared to subjects receiving enzyme-inducing AEDs. She also notes a lower mean duration of exposure in the ≥ 65 years age category compared to ≤17 to < 65 years or < 17 years in the 12 mg group. In the Phase 2 DB pool, subjects randomized to the >8-12 mg dose group were taking lower doses (median 6 mg, mean 7.5 mg). Dr. Doi notes that these subjects will likely not have the same AE profile as Phase 3 subjects in the highest dose group, and she shows (Table 32, p. 170 of her review) that the risk of discontinuation due to AEs was lower in the Phase 2 DB Pool than the Phase 3 DB pool at this dose.

Demographics –

In the Phase 3 epilepsy pool, the age range was 12 to 77 y.o. (ISS p. 69) and the mean age was 34.9 years. Approximately 47% of the pediatric patients were ages 15 and 16, while approximately 36% were ages 12 and 13. Approximately 2% of patients were 65 years or older. Forty-seven to 51% were male. Subjects were predominantly white (75%) or Asian (19%), with the mean BMI in the overweight category. Subjects were enrolled in sites worldwide, with 44% from Europe, 22% from North American, 18% from Asia-Pacific, and 11% from Central/South America. Among subjects from North America, 81.4% were white, 9.4% were black/African American, and 1.3% were Asian.

The highest dose group had the highest percentages of subjects from North America and Central/South America and the lowest dose groups had the highest percentage from Asia and Europe.

In the Nonepilepsy double-blind pools, subjects were older than in the Phase 3 epilepsy pool (mean age 61.8 years), and predominantly white (92%) males (57%). In the Phase 1 study pools, subjects were slightly younger (mean age 31.1 years) than the epilepsy population, primarily male (65.9%), and from North America (42.5%) or Europe (50.1%).

In the epilepsy Phase 3 studies, 51.3% were treated at baseline with 2 AEDs, and 34.5% with 3 AEDs. More than half were taking an enzyme-inducing AED (58.8%) and 93.3% were taking a non-enzyme inducing AED. Although Dr. Doi notes no significant differences in concomitant medications and diseases between placebo and total perampanel groups, she does note imbalances in specific dose groups, and particularly in the 12 mg dose group compared to placebo.

2.3 Significant Safety Findings

2.3.1 Deaths

Dr. Doi notes that there were 9 deaths in the Epilepsy studies. One occurred during the pre-randomization phase and did not receive study drug. The remaining eight deaths occurred in subjects receiving perampanel 12 mg in the open-label extension (OLE) studies. The mortality rate based on 8 subjects is 0.5% (8/1651). There were 3 sudden deaths: 1 SUDEP (Subject 306-1502-6004); 1 cardiac arrest on OLE Day 705 in Subject 0009-0176 with a history of morbid obesity and other cardiac risk factors; and 1 cause unknown in a 27 y.o. (Subject 2802-5014) who died suddenly on OLE Day 173 after a fall, with ventricular fibrillation noted by EMS, and with a previous history of hypotension and prior ECGs that revealed sinus bradycardia and left ventricular hypertrophy with repolarization changes. Based on the 1 death classified as SUDEP, the SUDEP rate in this epilepsy population is 0.44 per 1000 subject years (compared to rates in the literature of 3.5-9.3 per 1000 person years in subjects with refractory epilepsy, as cited by Dr. Doi). The other 5 deaths were due to disparate events: car accident (passenger), cerebral hemorrhage, pneumonia, head injury/hydrocephalus due to a seizure, and a neonatal death (maternal concomitant use of Pregnancy Class D medications carbamazepine and clobazam). I agree with Dr. Doi that it is difficult to draw definitive conclusions about the causal role of perampanel in these deaths.

In the Nonepilepsy studies, there were 32 deaths (26 in Parkinson's disease and 6 in neuropathic pain); 22 were in subjects treated with perampanel. After adjusting for exposure, the mortality rate for perampanel in the Nonepilepsy population is 13.2 per 1000 subject years of exposure compared to the epilepsy population where the rate is 3.51 per 1000 subject-years of exposure. I agree with Dr. Doi that this is likely due to the older population in the Nonepilepsy population, and more subjects with comorbidities due to less restrictive entry criteria in the Nonepilepsy trials. In the Parkinson's disease studies, 17 occurred in the DB studies: 7 (7/845 or 0.8%) in the

placebo group, 9/1517 (0.6%) in the perampanel group and 1/234 (0.4%) in the entacapone group. In the neuropathic pain group, 4 of the deaths occurred in the DB studies: 2 in placebo (2/121 or 1.7%) and 2 in perampanel (2/377 or 0.5%).

Subject 0112-0002 was a 65 y.o. male with Parkinson's disease who died from "multiple organ insufficiency" after developing severe cardiac failure having been treated with perampanel (.5 mg) for 14 days; Dr. Doi notes that based on the ECG, the subject most likely sustained a pulmonary embolism and that he had risk factors due to underlying lung cancer. Subject 0407-0015 was a 71 y.o. male with Parkinson's disease treated with perampanel for 258 days who died from hypotension on Day 259 (blood pressure was 80/50 on Day 258) after complaints of back pain on Study Day 258. The patient had previously been treated for hypertension with blood pressure reading within the year prior to the event as high as 170/100. Dr. Doi notes that the subject had many risk factors for vasculopathy and proposes that the hypotension and back pain may have been the result of an aortic aneurysm rupture. An autopsy was not performed. I agree with Dr. Doi that these 2 cases were unlikely due to perampanel.

Deaths in the Nonepilepsy population also included 3 deaths in Parkinson's disease studies resulting from post-surgical complications following injuries (hip fracture, femoral neck fracture, and cervical hematoma after a fall in a patient who had previously reported somnolence as an AE). There were 3 deaths due to malignancies 1 "primary chest malignancy", 1 malignant lung neoplasm, and 1 metastatic adenocarcinoma. Neoplasms are discussed in more detail in Section 7.6 of Dr. Doi's review. There was 1 death due to pancreatitis; cholelithiasis and pancreatitis are discussed in Section 7.3.5.1 of Dr. Doi's review. Other deaths in this population were attributed to left ventricular failure and pulmonary embolism; sick sinus syndrome; acute respiratory distress (in a patient hospitalized for "idiopathic colitis" and subsequently developing bronchopneumonia; circulatory collapse following complications after elective heart surgery; cardiac failure in a subject with a history of hypertension; sepsis 1 month after discontinuation of perampanel; multiorgan failure subsequent to a cerebrovascular accident that occurred 14 days after discontinuing a 3 day course of exposure to perampanel 2 mg in a patient with a history of coronary artery disease, hypertension, hyperlipidemia, diabetes mellitus; "general physical health deterioration"/"old age" in a 72 y.o. Parkinson's disease patient treated with perampanel for 813 days in an OLE study in addition to 84 days in a DB study; sudden worsening of cardiorespiratory function on Day 892 in a 53 y.o. male with Parkinson's disease and a history of hypertension and possible left atrial enlargement who had only 1 other AE recorded (drowsiness); cardiac failure on Day 74 in a 79 y.o. male with a past medical history including hypertension who developed acute myocardial infarct requiring coronary artery stenting and cardiac failure while on placebo in the DB study 301; and cardiopulmonary failure on Day 356 in a 77 y.o. male with Parkinson's disease with a history of bronchietasis, atherosclerosis, and hypercholesterolemia who had received perampanel for 355 in an OLE study in addition to 218 days in a DB study. I agree with Dr. Doi that most of these deaths occurred in subjects at high risk due to age and significant

comorbidities². I agree that it is difficult to draw definitive conclusions about the causal role of perampanel in these deaths.

2.3.2 Other Serious Adverse Events

In the *Epilepsy All Treated Pool*, 17.3% (285/1651) of perampanel exposed subjects experienced one or more treatment emergent SAEs. The SOC for which the most subjects had an SAE was Nervous System Disorders (6.7%) following by Injury, Poisoning and Procedural complications (3.9%) and Psychiatric Disorders (3.6%). The MedDRA preferred term (PT) for which the most subjects had an SAE was Convulsion (2.7%) followed by Status Epilepticus (1.1%) and Aggression (0.8%).

In the *Epilepsy DB pool*, a dose-response for SAEs was seen at doses of 8 and 12 mg. The SOCs for which the most subjects had an SAE and where incidence for perampanel was greater than placebo were Psychiatric disorders (1.1% for perampanel vs 0.8% for placebo) and Injury, Poisoning, Procedural complications (1.1% for perampanel vs 0.6% for placebo). Dr. Doi has provided a list of SAEs reported by at least 2 perampanel subjects and more frequent than placebo. The most common were dizziness, somnolence, aggression, and head injury each occurring in 0.3% vs 0 in placebo.

In the *Nonepilepsy All treated pool*, 11.7% (319/2717) of perampanel-exposed subjects experienced one or more treatment emergent SAEs. Although the percentage of subjects with SAEs was higher in the epilepsy all treated pool than in the Nonepilepsy all treated pool, after adjusting for differences in exposure the incidence in the epilepsy pool (2.4 per 1000 subject weeks) was less than in the Nonepilepsy pool (3.7 per 1000 subject weeks). The SOCs for which the most subjects had an SAE were Nervous System disorders (3.0%), Injury, Poisoning, and procedural Complications (1.9%), Infections and Infestations (1.7%), Cardiac Disorders (1.7%), and Psychiatric Disorders (1.6%). Compared to the Nonepilepsy pools, the epilepsy pool had a lower incidence rate of SAEs in the following SOCs: Cardiac, Neoplasms, Musculoskeletal, General, Renal, Respiratory, and Vascular disorders. I agree with Dr. Doi that the differences may be due in part to underlying diseases and comorbidities.

In the *Nonepilepsy DB pool*, the percent of SAEs in the > 4-8 mg groups was greater than placebo. The SOCs for which the most subjects had an SAE and where the incidence for perampanel was greater than placebo were for the following SOCs: Psychiatric disorders (0.8% for perampanel vs 0.6% for placebo) and Injury, Poisoning, Procedural complications (1.3% for perampanel vs 0.8% for placebo). The most frequently occurring SAEs that occurred in 2 or more perampanel subjects and more frequent than placebo were fall (0.4% for perampanel vs 0.2% for placebo).

In the epilepsy program, there were no treatment-emergent SAEs coded to the following preferred terms: aplastic anemia, agranulocytosis, Stevens Johnson syndrome, toxic

² In the Parkinson's disease studies, for example, subjects could have clinically significant, but stable disease; in the epilepsy studies, subjects with clinically significant disease were excluded.

epidermal necrolysis, acute renal failure, acute liver failure, rhabdomyolysis, angioedema, or anaphylaxis. There was one SAE of acute pancreatitis in the epilepsy OLE studies (in a subject with bile duct stone/acute pancreatitis; Day 810). In the Nonepilepsy trials there were SAEs coded to acute renal failure (section 7.3.5.4 of Dr. Doi's review; unlikely related to perampanel), acute pancreatitis (with cholelithiasis), and rhabdomyolysis (1 subject coded to rhabdomyolysis in the entire database; not likely related in this case; p. 188 of Dr. Doi's review). There was also 1 patient with acute pancreatitis in the Nonepilepsy pool on placebo. The three cases of acute pancreatitis are the only cases in the entire database; there does not appear to be a signal for acute pancreatitis in the database overall.

In the *Phase 1 studies*, there were 2 subjects who reported SAEs. Subject 1001-0285 experienced multiple falls, head injury, concussion, loss of consciousness) beginning on Day 11 that Dr. Doi proposes are likely a result of rapid titration to a 12 mg dose over a period of 10 days. Subject 1001-1009 developed SAEs of anxiety, paranoia, and unsteadiness on the last day of receiving 6 mg perampanel for 10 days that resolved by Day 36. Falls and anxiety and paranoia are discussed in sections 7.3.4.2 and 7.3.4.1 of Dr. Doi's review and in section 2.3.4 (p. 16) of my memo.

SAEs in ongoing OLE studies appear to be consistent with previously reported SAEs.

2.3.3 Dropouts

In the Phase 2/3 Epilepsy DB studies, 15.1% (179/1189) of perampanel subjects discontinued compared to 11.4% (58/510) placebo subjects. In the Epilepsy All Treated Pool, 46.7% (771/1651) of perampanel subjects withdrew from the studies. In the Nonepilepsy DB pool, 28.0% (563/2013) of perampanel subjects discontinued compared to 22.8% (246/1078) of placebo subjects. In the Nonepilepsy all treated pool, 74.3% (2018/2717) of perampanel subjects withdrew from the studies, but the most common reason was "other" (56.4%), and the sponsor reported that this was due to the decision to terminate some Parkinson's disease studies early.³

Adverse events (AE) were the most common reason for discontinuation in the Phase 2/3 Epilepsy DB studies (55.9% of perampanel and 38% of placebo subjects who discontinued), the Epilepsy All Treated Pool (35.8% of all subjects who discontinued), and the Nonepilepsy DB pool (54.7% of perampanel and 43% of placebo subjects who discontinued). In the Nonepilepsy all treated pool, 24.9% of subjects who discontinued did so due to an AE. A dose-response relationship was observed for discontinuations due to AEs in the DB studies (but not in the all treated pools). In all of these pools, TEAEs leading to discontinuation were greater for perampanel (overall) than placebo in

³ On page 72 of her review in the section on discontinuations in the Nonepilepsy population, Dr. Doi discusses reasons for discontinuation for "other" and notes that she reviewed the reasons for 112 perampanel subjects and 75 placebo subjects (ISS Table 20.1-15). Although described in the section discussion the Nonepilepsy All Pool, this information refers to the patients in the Nonepilepsy double-blind pool, not the Nonepilepsy all pool. She notes that "other" mostly included reasons due to sponsor decision, but did also include a few discontinuations due to AEs (disorientation, elevated liver enzymes', prolonged QTc on ECG, and abnormal ECG).

the Nervous system, Psychiatric, and General disorders SOCs. In all of these pools, dizziness was the most frequent TEAE leading to discontinuation (2% in the Phase 2/3 Epilepsy DB pool vs 0.8% for placebo, 4.5% in the Epilepsy All Treated Pool, 2.2% vs 0.6% for placebo in the Nonepilepsy DB pool, and 2.5% in the Nonepilepsy All Treated Pool).

In the Epilepsy and Nonepilepsy pools, no subjects discontinued for Stevens Johnson syndrome, toxic epidermal necrolysis, acute liver failure, aplastic anemia, agranulocytosis, pancytopenia, or anaphylaxis. In the Epilepsy pool, no subjects discontinued for acute renal failure or, rhabdomyolysis. However, there were discontinuations due to thrombocytopenia, CK elevation, QT prolonged, and toxic skin eruption. In the Nonepilepsy pool there were discontinuations due to rhabdomyolysis, acute renal failure, CK elevation, and QT prolonged. In both pools there were discontinuations due to transaminase elevations, acute pancreatitis. These issues will be discussed later.

In the Phase 1 trials, 35 perampanel subjects (35/916, 3.8%) discontinued prematurely due to TEAEs (4 in single-dose studies, 31 in multiple dose studies), with a higher discontinuation due to AEs in the multiple dose studies (9.0%, 31/343) than in the single dose studies (0.7%, 4/573). In the single dose studies, subjects who discontinued had received 8mg to 36 mg of perampanel. The AEs leading to discontinuation were coded to these preferred terms in the MedDRA SOC Investigations: electrocardiogram QT prolonged, hemoglobin decreased, blood creatine phosphokinase increased, and WBC count increased. Dr. Doi identified an additional subject who discontinued due to agitation and aggression. In the multiple dose studies, the AEs leading to discontinuation were coded most frequently to the Nervous system disorders SOC (somnolence and dizziness PTs) and Investigations SOC (positive rombergism PT).

In addition to these discontinuations, Dr. Doi notes that the Sponsor identified additional subjects where a safety related comment was included on the disposition page of the CRF, the subject had ongoing AEs or markedly abnormal laboratory values within 2 weeks of discontinuation/last visit, or AEs or markedly abnormal laboratory values resolved within 2 weeks of discontinuation/last visit and there were no safety related comments included on the disposition page of the CRF. She concludes that discontinuations due to AEs were even higher in the perampanel group than suggested by the original analysis.

Dr. Doi evaluated incidence of perampanel interruption, dose, reduction or discontinuation and finds that there were more subjects who experienced TEAEs resulting in interruption or dose reduction (17%, 202/1189) than discontinuation (8.9%, 106/1189) in the epilepsy DB pool. That was not observed in the Nonepilepsy DB pool. She shows a dose-response for drug interruption or reduction.

2.3.4 Significant Adverse Events

Dr. Doi has discussed her own analysis and the Sponsor's analyses of the safety concerns she considers most important and that she believes should be incorporated

into labeling or further evaluated in the postmarketing period: psychiatric disorders, nervous system disorders, metabolic changes, and tendon/ligament rupture.

Psychiatric Disorders –

Overview -

Dr. Doi notes that a higher number of subjects in the perampanel group than in the placebo group experienced TEAEs, SAEs, or discontinuations due to events in the Psychiatric disorders SOC, as shown in the table below from p. 84 of her review.

Table 42. Summary of TEAEs, SAEs, DCs in the Psychiatric Disorders SOC

	Epilepsy Phase 3 DB Pool		Nonepilepsy DB Pool	
	Placebo	Perampanel	Placebo	Perampanel
SOC Psychiatric Disorders	n=442	n=1038	n=1079	n=2013
TEAEs	12.4%	15.3%	10.5%	11.4%
Deaths	0	0	0	0
SAEs	0.9%	1.2%	0.6%	0.8%
Discontinuations (DCs)	1.6%	2.5%	1.1%	2.9%
	Epilepsy All Treated Pool		Nonepilepsy All Treated	
	n=1651		n=2717	
TEAEs n (%), most common PT	475 (28.8%), insomnia (4.9%)		501 (18.4%), insomnia (5.3%)	
Deaths	0		0	
SAEs n (%), most common PT	59 (3.6%), aggression		43 (1.6%), hallucination	
DCs n (%), most common PT	99 (6.0%), aggression		118 (4.3%), confusional state	

Source: ISS Tables 20.7-1, 160, 165, 55, 20.5-2, 63, 20.5-8, 75, 79, 20.5-36, 22.4-2, 22.4-27 and 120-day Safety Update Tables 20.5-75.1, 20.7-18.1, 20.8-44.1

Please refer to Dr. Doi’s review (Section 7.3.4.1, beginning on page 83 of her review) for details regarding SAEs and TEAEs related to psychiatric disorders in the safety database. I agree with Dr. Doi’s concern that only perampanel subjects (and no placebo subjects) in the epilepsy Phase 3 trials experienced SAEs of aggression (0.3%), and belligerence, impulse-control disorder, suicidal ideation that each occurred in 0.1%, and in the Nonepilepsy DB pools experienced suicide attempt (0.1%), and homicidal ideation (0.05%). This concern is strengthened by the psychiatric SOC TEAEs reported. These areas are discussed in more detail below.

Suicidal Behavior and Ideation

Dr. Doi has evaluated suicidal ideation or behavior (pages 87-92 of her review) using several different approaches. Only subjects in the perampanel group (and no placebo subjects) experienced suicide attempts (and overdoses) in the epilepsy phase 3 DB pool (n=1) and the Nonepilepsy DB pool (n=2). A higher number of perampanel subjects than placebo subjects experienced TEAEs in the MedDRA SMQ Depression and Suicide/Self-Injury (broad). There were a total of 25 subjects with AEs coded to suicidal ideation or behavior in the entire safety database: 23/5284 (0.4%) perampanel subjects and 2/1750 (0.11%) placebo subjects⁴. SAEs (n=17) and discontinuations (n=12) due to these TEAEs occurred only in the perampanel subjects. Dr. Doi has also noted coding omissions for suicidal ideations within narratives for hostility and

⁴ This is 11.16 per 100,000 subject weeks for perampanel and 7.2 per 100,000 subjects week for placebo, per 9/7/12 email from Dr. Doi.

aggression, and believes therefore that the numbers of suicidal ideations presented are underestimates.

Dr. Doi has summarized the narratives of 13 suicidal ideations (with physical assaults/harm to others), suicide attempts, overdoses, and in the epilepsy and nonepilepsy studies.⁵ Nine of the 13 had no prior psychiatric history. The onset ranged from approximately 2 weeks to more than 28 weeks, and resolution occurred within several days to approximately 20 days after the event, in most cases after discontinuing perampanel.⁶ In most cases there were confounding medications, although they may have been taken for more than 1 year prior to the event. The role of perampanel cannot be ruled out in these cases.

Hostility and Aggression

Dr. Doi has evaluated hostility and aggression (pages 92-111 of her review) using several different approaches. In the Epilepsy Phase 3 DB pool she finds that perampanel subjects had a higher risk of TEAEs in the Hostility/Aggression SMQ (4.40 relative risk using the Narrow SMQ). She notes that the Pharmacometric Review finds, in a PK/PD analysis, the probability of anger, aggression and irritability increased with perampanel concentration.

Dr. Doi quotes from the Prozac labeling regarding symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania representing precursors to emerging suicidality. Because these are not included in the Hostility and Aggression SMQ, Dr. Doi developed a modified SMQ to capture these terms. Although she finds an elevated risk with the modified SMQ (relative risk of 1.61), the relative risk was lower than for the original SMQ. In the Nonepilepsy DB pool as well as in Phase 1 single and multiple dose studies, perampanel subjects experienced TEAEs in this SMQ more frequently than placebo subjects. Of the TEAEs in the broad hostility and aggression SMQ and the modified hostility SMQ for the Phase 3 DB pool, perampanel subjects experienced more AEs that were serious, severe, and led to dose reduction, interruption, and discontinuation than placebo subjects.

Dr. Doi has summarized the narratives of 23 physical assaults, suicidal ideations, homicidal ideations, and damage to property in the Epilepsy and Nonepilepsy studies. Preferred terms included homicidal ideation, belligerence, aggression, affective disorder/psychotic disorder, personality change, irritability, aggression/impulse control disorder, anger, adjustment disorder, agitation, abnormal behavior, and personality disorder. Please refer to Dr. Doi's review (pages 95-101) for all of the narratives. Of the 23 cases, approximately 2/3 reported no previous psychiatric history or history of anxiety. Onset generally occurred during the titration period, but was as early as

⁵ Some of the narratives also contained separate events of aggressive behavior leading to physical assaults, threats of violence with a weapon (knife) and arrests as well as preceding TEAEs of delusions/hallucinations and irritability.

⁶ Dr. Doi states that the event in [Subject 305-3905-5004](#) could be related to perampanel use with the time course and positive dechallenge. However, I note that the narrative states that perampanel was continued and the event resolved 4 days later, so that there was no dechallenge prior to resolution.

approximately 2 weeks to more than 37 weeks after starting perampanel. Resolution generally occurred within 1 to 42 days after discontinuing perampanel or after reducing the dose, although characterization of a positive dechallenge was confounded in many cases by treatment of the event with another drug. In 2 cases perampanel was continued and aggression resolved. Some cases were confounded by concomitant treatment with drugs associated with aggression (such as levetiracetam), irritability and aggressiveness (associated with antidepressants) or psychosis (such as zonisamide). However, *I agree with Dr. Doi that the role of perampanel cannot be ruled out either in causing the event or in exacerbation of an underlying disorder.*

The Sponsor has reported that no homicides were committed by a subject while taking perampanel or within 30 days after drug discontinuation. Dr. Doi notes that in the placebo group there were 2 subjects with SAEs in the Hostility/Aggression SMQ. The AEs were coded to the PT psychotic disorder. Dr. Doi states that neither of the narratives contained events of physical assaults, abuse, homicidal ideations/threats, or suicidal ideations/attempts.

Dr. Doi shows a dose response relationship, with subjects randomized to the 8 mg and 12 mg dose groups having approximately 2-11 times higher incidence than placebo of experiencing hostility and aggression TEAEs, depending on the SMQ used for this evaluation (Broad, Narrow, or Modified). The strongest dose response was seen in the Narrow SMQ that used only the preferred terms of aggression, anger, belligerence, and physical assault compared to either of the other SMQs that included 18-21 preferred terms. The highest incidences of hostility and aggression TEAEs occurred in study 304 which has the highest percentage of subjects from the United States. Dr. Doi performed an analysis using the 294 subjects from the United States in studies 304/305 using randomized as well as actual dose groups, and finds 2-15 fold increased incidence of hostility TEAEs for perampanel vs placebo, depending on the SMQ used. *I note that in the various SMQs (broad, narrow, or modified), the dose –response relationship are driven by specific events. The most appropriate representation of this should be identified for inclusion in labeling, to allow for a clear and accurate presentation of the AE.*

Dr. Doi refers to the labeling of the anticonvulsant Keppra that contains information regarding Psychiatric Reactions as the first heading within the Warnings and Precautions section. According to the Keppra labeling, patients (adults) exhibited non-psychotic behavioral symptoms⁷ with a risk of 13% for Keppra vs 6% for placebo (and for pediatrics this was 38% for Keppra vs 19% for placebo). This is similar to the risk for Hostility/Aggression for perampanel using the broad SMQ for which the risk in adults was 11% for perampanel vs 6% for placebo and for adolescents was 17% for perampanel vs 8% for placebo. Dr. Doi discusses the narratives for levetiracetam-treated subjects who discontinued due to adverse behavioral events (hostility,

⁷ Includes aggression, anger, agitation anxiety, hostility, and irritability in common with the SMQ of Hostility/Aggression used for perampanel, but includes other terms not included in the SMQ. Similarly, there are terms in the SMQ for perampanel analyses that are not used in the Keppra analysis. As Dr. Doi notes, these analyses are not directly comparable.

psychosis, personality disorder, and emotional lability) as reported in the original clinical review of the Keppra NDA 21035. One was a completed suicide. One was a subject with a history of major aggressive episode who developed increasingly aggressive behavior after receiving levetiracetam for 4 days and threatened to kill his wife. She reports that there were no other narratives that described AEs of homicidal ideations (in subjects without prior psychiatric history), physical assaults, property damage, or homicides. *I agree that the Keppra findings are not directly comparable, but they can give some guidance as to labeling for this event.*

Dr. Doi has evaluated possible risk factors for hostility/aggression. In the Phase 3 DB epilepsy pool she reports a trend towards higher risk in males than females for experiencing hostility-related TEAEs. I note that the relative risk (95% CI) for perampanel vs placebo using the broad SMQ is approximately 2-fold in both groups, with a relative risk of 2.42 (1.34-4.39) in males and 1.81 (1.01-3.23) in females. In adolescents the risk using the modified SMQ is 4.22 (1.02-17.4) compared to adults where the risk is 1.49 (1.06-2.09). I note that the confidence interval in adolescents is broad, and the number of subjects is small (n=72) relative to adults (n=966), and that using the broad SMQ the risk is the same in adults and adolescents (2.11). Based on an analysis provided by the Sponsor, Dr. Doi reports that among subjects with TEAEs in the Hostility/Aggression Broad SMQ in the epilepsy Phase 3 DB pool, a lower percentage of perampanel subjects than placebo had the risk factors of prior psychiatric history (41% vs 60%), possible post-ictal psychosis (47% vs 56%), and Keppra use (33% vs 36%). Concomitant use of antipsychotics, antidepressants and benzodiazepines was lower in perampanel subjects than placebo and I agree this may reflect the lower prior psychiatric history. Concomitant use of AE inducers was similar between the 2 groups. The percentage of subjects with a history of hostility and aggression was similar between the 2 groups (perampanel vs placebo). Of the 937 perampanel treated patients who did not have a prior history of aggression/hostility, approximately 11% developed a TEAE in this modified SMQ. Of the 101 (approximately 10%) of perampanel subjects with a prior history of hostility/aggression, approximately 28% developed a TEAE in this modified SMQ⁸ (so that > 70% patients with a previous history did not develop this event). Based on this information, I do not think it is would be reasonable to restrict the use of perampanel to patients without a history of psychiatric illness or hostility/aggression. Dr. Doi notes that Phase 1 Study 030 found that the combination of alcohol and perampanel 12 mg significantly worsened mood with increased anger, tension, confusion, depression, and reduced vigor. She notes that the narratives provided by the Sponsor for SAEs and discontinuations lacked consistent information regarding alcohol use by the subjects.

Dr. Doi has evaluated time to first occurrence of TEAEs in Hostility/Aggression Broad SMQ, Epilepsy Phase 3 DB pool (p. 109 of her review) and shows that most of the perampanel subjects in the 8 and 12 mg dose groups developed the first episode within the first 6 weeks (titration period), and that a plateau is noted during the maintenance period). The Sponsor reported that for the all treated epilepsy pool, most of the perampanel subjects had the first occurrence within the first 14 weeks of treatment, and

⁸ Email communication from Dr. Doi on 9/4/12.

that subjects continued to have first occurrences of aggressiveness during perampanel treatment for up to 2 years.

Dr. Doi has reviewed the risk of recurrences of TEAEs in the Hostility/Aggression SMQ in subjects who did not have study drug discontinued. She reports that of subjects who continued in the study, a higher number of perampanel subjects (14%) than placebo subjects (9%) developed recurrences of TEAEs in this SMQ. Of subjects who continued in the study but had a reduction or interruption of perampanel due to TEAEs in this SMQ, 22% of perampanel subjects had recurrences of TEAEs in this SMQ. Dr. Doi notes a shorter time to recurrence for perampanel subjects vs placebo subjects (4-17 days vs 113 days).⁹

Dr. Doi notes that in all of the epilepsy studies an exclusion criterion was suffering from active psychotic disorder(s) and/or unstable recurrent affective disorder(s) with use of antipsychotics, or had a suicide attempt(s) within the past 2 years. I agree with her concern that the results from the epilepsy studies may not represent the effects of perampanel in the general population.

Dr. Doi recommends a boxed warning to highlight hostility and aggression adverse reactions associated with perampanel. The risk for perampanel is similar to the risk for Keppra, although based on the reviews there may be more cases that are serious in the perampanel database. However, many of the cases are confounded by concomitant medications or previous psychiatric history. Whether a boxed warning may result in use of other AEDs that have their own serious safety signals should be considered.

Nervous System Disorders –

Dr. Doi notes that a higher number of subjects in the perampanel group than in the placebo group experienced TEAEs and discontinuations (and SAEs in the nonepilepsy DB pool) due to events in the Nervous System Disorders SOC, as shown in the table below from p.112 of her review. The differences in TEAEs were generally driven by differences in dizziness and somnolence in the DB pools, and dizziness was the most common PT in the all treated

⁹ Dr. Doi notes that perampanel subjects had similar incidences vs placebo of subsequent TEAEs in the Suicidality SMQ but that after taking into account the coding omissions, believes that the incidences may be higher in the perampanel group than placebo. This has not been shown.

pools

Table 59. Summary of TEAEs, SAEs, DCs in the Nervous System Disorders SOC

SOC Nervous System Disorders	Epilepsy Phase 3 DB Pool		Nonepilepsy DB Pool	
	Placebo n=442	Perampanel n=1038	Placebo n=1079	Perampanel n=2013
TEAEs	31.0%	50.9%	28.6%	37.4%
SAEs	2.5%	1.8%	0.8%	1.6%
Discontinuations (DCs)	2.9%	5.1%	3.8%	9.0%
	Epilepsy All Treated Pool n=1651		Nonepilepsy All Treated n=2717	
TEAEs n (%), most common PT	1177 (71.3%), dizziness		1298 (47.8%), dizziness	
SAEs n (%), most common PT	110 (6.7%), convulsion		82(3.0%),on/off phenomenon	
DCs n (%), most common PT	156 (9.4%), dizziness		290 (10.7%), dizziness	

Source: ISS Tables 20.7-1, 160, 165, 55, 20.5-2, 63, 20.5-8, 75, 79, 20.5-36, 22.4-2, 22.4-27

Please refer to Dr. Doi's review (Section 7.3.4.2, beginning on p. 111 of her review) for details regarding SAEs and TEAEs related to psychiatric disorders in the safety database. Dr. Doi has reviewed AE terms by group to prevent splitting of potentially similar events into multiple preferred terms, as discussed below.

Dizziness and Coordination – This group included dizziness, vertigo, ataxia, gait disturbance, balance disorder, and coordination abnormal. In the epilepsy Phase 3 DB pool subjects treated with perampanel experienced all of these TEAEs at a higher frequency than placebo, resulting in a 3x higher incidence overall (37% for perampanel vs 11% for placebo). There is a dose-response with the higher dose groups (8 and 12 mg), with 4 and 5 times higher incidence than placebo (42% and 54%, respectively). Dizziness was the most common (followed by vertigo, ataxia, and gait disturbance) as shown in the table below from Dr. Doi's review. Dr. Doi notes that in the Phase 1 Study 013, the Romberg test was performed and showed a shift from normal to abnormal in a higher percentage of perampanel subjects vs placebo or moxifloxacin and Dr. Doi notes that this indicates a loss in proprioception (sensory) rather than a cerebellar cause for loss of coordination.

Table 62. Dizziness and Coordination Group, Epilepsy Phase 3 DB Pool

MedDRA PT	Placebo n (%)	Perampanel n (%)				Total
		2 mg	4 mg	8 mg	12 mg	
	442	180	172	431	255	1038
Dizziness	40 (9.05%)	18 (10.0%)	28 (16.28%)	137 (31.8%)	109 (42.8%)	292 (28%)
Vertigo	4 (0.90%)	6 (3.33%)	7 (4.07%)	14 (3.25%)	12 (4.71%)	39 (3.76%)
Ataxia	0	0	1 (0.58%)	14 (3.25%)	21 (8.24%)	36 (3.47%)
Gait disturbance	6 (1.36%)	1 (0.56%)	2 (1.16%)	18 (4.18%)	10 (3.92%)	31 (2.99%)
Balance disorder	2 (0.45%)	0	0	22 (5.10%)	8 (3.14%)	30 (2.89%)
Coordination abnl	0	0	1 (0.58%)	1 (0.23%)	4 (1.57%)	6 (0.58%)
Total subjects	48 (10.9%)	25 (13.9%)	36 (20.9%)	181 (42.0%)	138 (54.1%)	380 (37%)

Source: Created by the reviewer using JReview and Epilepsy ADAE, ADSL datasets

Somnolence and Fatigue – In the epilepsy Phase 3 DB pool, subjects treated with perampanel experienced the TEAEs of somnolence, fatigue, asthenia, and lethargy (but not sedation) at a higher frequency than placebo subjects as shown in the table below from Dr. Doi's review.

Table 64. Somnolence and Fatigue Group, Epilepsy Phase 3 DB Pool

MedDRA PT	Placebo n (%)	Perampanel n (%)				
		2 mg	4 mg	8 mg	12 mg	Total
	442	180	172	431	255	1038
Somnolence	32 (7.24%)	22 (12.2%)	16 (9.30%)	67 (15.5%)	45 (17.65%)	150 (14.5%)
Fatigue	21 (4.75%)	8 (4.44%)	13 (7.56%)	36 (8.35%)	31 (12.16%)	88 (8.48%)
Asthenia	2 (0.45%)	1 (0.56%)	1 (0.58%)	10 (2.32%)	6 (2.35%)	18 (1.73%)
Lethargy	1 (0.23%)	0	0	5 (1.16%)	3 (1.18%)	8 (0.77%)
Sedation	2 (0.45%)	0	0	1 (0.23%)	1 (0.39%)	2 (0.19%)
Total subjects	54 (12.22%)	30 (16.7%)	27 (15.7%)	111 (25.8%)	79 (30.98%)	247 (23.8%)

Source: Created by the reviewer using JReview and Epilepsy ADAE, ADSL datasets

Cognitive Dysfunction – Dr. Doi found that for the entire cognitive dysfunction group of terms, perampanel subjects have a higher incidence of TEAEs in the Epilepsy Phase 3 DB pool than placebo, but that this result is driven mainly by the PT dysarthria. As dysarthria (verbatim terms included slurred speech and dysarthria) is associated with muscle weakness/coordination, I do not believe that it should be included in the group of other TEAEs associated with cognitive dysfunction. When this term is removed from terms associated with cognitive dysfunction, memory impairment and confusional state account for the most frequent PTs (each approximately 2% in the 12 mg group, 1% in the 8 mg group, and 1% in placebo) as shown in the table below.

Table 65. Cognitive Dysfunction Group, Epilepsy Phase 3 DB Pool

MedDRA PT	Placebo n (%)	Perampanel n (%)				
		2 mg	4 mg	8 mg	12 mg	Total
	442	180	172	431	255	1038
Dysarthria	0	0	2 (1.16%)	13 (3.02%)	9 (3.53%)	24 (2.31%)
Memory Impairment	5 (1.13%)	2 (1.11%)	0	5 (1.16%)	5 (1.96%)	12 (1.16%)
Confusional State	2 (0.45%)	1 (0.56%)	1 (0.58%)	3 (0.70%)	4 (1.57%)	9 (0.87%)
Disturbance in Attention	6 (1.36%)	2 (1.11%)	1 (0.58%)	5 (1.16%)	1 (0.39%)	9 (0.87%)
Aphasia	3 (0.68%)	0	0	3 (0.70%)	3 (1.18%)	6 (0.58%)
Speech Disorder	2 (0.45%)	0	0	3 (0.70%)	2 (0.78%)	5 (0.48%)
Disorientation	1 (0.23%)	0	0	1 (0.23%)	2 (0.78%)	3 (0.29%)
Amnesia	1 (0.23%)	1 (0.56%)	0	1 (0.23%)	1 (0.39%)	3 (0.29%)
Cognitive Disorder	2 (0.45%)	0	0	2 (0.46%)	0	2 (0.19%)
Apraxia	1 (0.23%)	0	0	0	1 (0.39%)	1 (0.10%)
Delirium	1 (0.23%)	1 (0.56%)	0	0	0	1 (0.10%)
Mental Impairment	1 (0.23%)	0	1 (0.58%)	0	0	1 (0.10%)
Incoherent	0	0	0	0	0	0
Total subjects	20 (4.52%)	5 (2.78%)	5 (2.91%)	30 (6.96%)	27 (10.59%)	67 (6.45%)

Source: Created by the reviewer using JReview and Epilepsy ADAE, ADSL datasets

Paresthesia – Dr. Doi has included paraesthesia, hypoesthesia, hypoesthesia facial, paraesthesia oral, oral dysaesthesia, hypoesthesia oral, sensory disturbance, and hyperaesthesia in this group. Perampanel subjects reported terms in this group slightly more often than placebo (2.2% vs 1.6%), driven by paresthesia (2.35% in the 12 mg group vs 0.68% in placebo) and hypoesthesia (2.75% in the 12 mg group vs 0.68% in placebo).

Overall – In addition to the findings regarding TEAEs above, Dr. Doi shows that perampanel is associated with an increased incidence of SAEs and discontinuations related to coordination/dizziness, somnolence/fatigue, and paresthesias groups compared to placebo in the Epilepsy Phase 3 DB pool and for dizziness/coordination

and paresthesias in the Nonepilepsy DB pool.¹⁰ When considered by age, she finds that a higher percentage of elderly subjects experienced TEAEs in the dizziness/coordination and the somnolence fatigue groups of events than did adults or adolescents treated with perampanel, and that none of the events in the dizziness/coordination or somnolence/fatigue group were reported in the elderly placebo groups, but only in the perampanel groups.¹¹ The assessment was not performed for paresthesias due to small percentages of patients reporting terms in this group. The difference in risk between perampanel and placebo for the dizziness/coordination group and the somnolence/fatigue groups is greater in the titration period than in the maintenance period.

Eye Disorders – A higher number of perampanel subjects than placebo experienced vision blurred, diplopia, and visual impairment. Although these TEAEs were not SAEs, they led to discontinuation of perampanel more frequently than placebo. In the Epilepsy Phase 3 DB pool, the risk of vision blurred was 2.4% for perampanel and 1.4% for placebo; this risk of diplopia was 1.7% for perampanel and 0.9% for placebo. Four perampanel subjects discontinued due to vision blurred, and no placebo subjects withdrew due to eye-related TEAEs. In the Epilepsy Phase 2 DB pool, the following TEAEs occurred in 2 or more perampanel subjects and greater than placebo: diplopia (2% vs 1.5%), eye pain 1.3% vs 0) and visual impairment (1.3% vs 0); none of the TEAEs were SAEs or led to discontinuation. In the Nonepilepsy DB pool, 2 perampanel subjects experienced the SAE of cataract vs 0 placebo subjects. Perampanel subjects withdrew from studies due to diplopia, photophobia, and vision blurred (1 subject each), and no placebo subjects withdrew for eye related TEAEs. In the Phase 1 studies there were no eye-related SAEs although perampanel subjects withdrew due to vision blurred conjunctivitis, and ocular discomfort (1 each).

Falls and Injuries – A higher percentage of perampanel subjects experienced a fall than placebo subjects in every DB pooled group as shown in the table below. A dose response was observed with at least a 3x higher incidence of fall in the highest dose groups than placebo in every pool. In the Epilepsy Phase 3 DB pool, it appears that falls occurred slightly more often (and with a greater difference from placebo) during maintenance than during the titration period (shown in Dr. Doi's review).

¹⁰ Although Dr. Doi notes in her review that perampanel is associated with an increased incidence of SAEs and discontinuations related to cognitive dysfunction in both DB pools, excluding dysarthria from the cognitive dysfunction group decreases this association for TEAEs, SAEs, and discontinuations such that there is no difference in TEAEs (0.3% in perampanel vs 0.2% in placebo), no difference in SAEs (0.5% in perampanel and in placebo), and a small increase in discontinuations (0.6% for perampanel vs 0.2% for placebo).

¹¹ Although Dr. Doi included this information for the Cognitive dysfunction group, I have not included it here as the TEAEs in that group were driven by Dysarthria that is not a matter of cognition. However, Elderly had the highest risk of events in the cognitive dysfunction group, compared to adults and adolescents.

Table 71. Incidence of the PT Fall, DB pools

Pooled Group	Placebo n (%)	Perampanel n (%)				Total
		<4 mg	4 mg	>4-8 mg	>8-12mg	
Epilepsy Phase 3 DB Pool	15 (3.4)	2 (1.1)	3 (1.7)	22 (5.1)	26 (10.2)	53 (5.1)
Epilepsy Phase 2 DB Pool	0	0	5 (5.0)		1 (2.6)	6 (4.0)
Nonepilepsy DB Pool	37 (3.4)	49 (4.6)	42 (5.4)	19 (10.7)		110 (5.5)
Parkinson's DB Pool	33 (3.9)	42 (5.1)	35 (5.2)	3 (12.5)		80 (5.3)
Neuropathic pain DB Pool	2 (1.7)	4 (3.2)	7 (7.2)	16 (10.4)		27 (7.2)

Source: ISS Tables 20.5-2, 20.5-28, 20.5-54

It appears that *falls are more frequent in the elderly than in the adults or adolescents*. In the Epilepsy Phase 3 DB pool, the risk of falls in the elderly was 25% for perampanel vs 0 for placebo, the risk in adults < 65 y.o. was 5% for perampanel vs 4% for placebo, and the risk in adolescents was 3% for perampanel and 3% for placebo. In the Nonepilepsy pool, the risk in the elderly group was 6% for perampanel vs 3% for placebo, and in adults < 65 y.o. was 5% for perampanel vs 4% for placebo. Overall, in the Phase 3 DB pool, there were *more falls that occurred without seizure events* in perampanel vs placebo (40% vs 25%).

To assess for sequelae of the falls, Dr. Doi analyzed the data for fall-related events in the SOC Injury, Poisoning, and Procedural Complications and the SMQ Accidents and Injury and found that for all of the DB pooled groups, perampanel subjects experienced higher frequencies of these injury related TEAEs (n=13, 1.1%) than placebo (n=3, 0.6%), although I note that these differences are very small. She reports that a dose response relationship was observed in the epilepsy Phase 3 DB pool and the Nonepilepsy DB pool. SAEs in the SOC Injury occurring in at least 2 subjects included head injury and facial bones fracture that occurred at 0.3% and 0.2%, respectively in the epilepsy DB pools for perampanel vs none in placebo. In the Phase 3 DB pool in which 13 patients had SAEs due to injuries, 4 of those patients (31%) had injuries due to falls without seizures. In the Nonepilepsy DB pool, lumbar vertebral fracture and meniscus lesion each occurred in 0.1% of subjects (2 subjects each) taking perampanel and none in placebo. Overall, in the epilepsy Phase 3 DB pool there were *more injuries that occurred without a seizure event in perampanel (36%) vs placebo (21%)*, although the specific injuries are not characterized in that analysis. Finally, there were higher incidence rate ratios of total perampanel subjects compared to placebo experiencing either falls or TEAEs in the Accident/Injury SMQ in the absence of seizures (rate ratio approximately 3) when adjusted for exposure than observed for events with seizures (rate ratio approximately 1.2 and 1.6 for falls or TEAEs, respectively). Thus, Dr. Doi notes that there is an association between perampanel use and falls/injuries not confounded by seizures.

Dr. Doi suggests that there is evidence of a causal relationship between perampanel use and dizziness/coordination, somnolence/fatigue, and falls/injuries. She notes that these are clinically significant reactions, potentially fatal (there were deaths due to fall-related complications), serious, and could be mitigated through appropriate closer monitoring during the titration period and with high risk subgroups such as the elderly. Therefore she recommends that these be included in the Warnings and Precautions section. She finds a lesser degree of a relationship between perampanel use and

dysarthria, paresthesias, and visual changes and recommends that these adverse reactions be included in the adverse Reactions section of perampanel labeling. I agree with this recommendation.

Metabolic Changes -

Weight gain – In the epilepsy Phase 3 DB pool, adult perampanel subjects gained an average of 1.12 kg compared to an average 0.3 kg weight gain in placebo subjects with a median exposure of 19 weeks. More than twice as many perampanel subjects than placebo subjects had gained $\geq 7\%$ of baseline weight (9.1% vs 4.5%) and ≥ 15 of baseline weight (0.9% vs 0.2%). These changes occurred to a lesser degree in adolescents who gained an average of 1.98kg on perampanel vs 1.41kg on placebo with a median exposure of 19 weeks. The mean change in weight for adults was at least 3x higher (up to 18 times higher) in the total perampanel group than placebo in each of the DB pooled groups, with smaller differences in adolescents. A dose response was observed for most of the double-blind pooled groups. In adults the average weight increase across all double-blind pooled groups was 1.23 to 1.77 kg for the > 4-8 mg dose group. In an outlier analysis in the Epilepsy Phase 3 DB pool, Dr. Doi found that for every category of weight loss or no weight change, there were fewer perampanel subjects than placebo subjects. For every category of weight gain for adults, there were more perampanel subjects than placebo subjects, and a dose response was observed for most weight gain categories. Those results are shown in the table below.

Table 81. Weight Change Categories, Adults in Epilepsy Phase 3 DB Pool

Amount Gained (kg) from baseline	Placebo n (%)	Perampanel n (%)				
		2 mg	4 mg	8 mg	12 mg	Total
Total subjects	n=401	n=166	n=162	n=398	n=235	n=961
≤ 0	202 (50.4)	85 (51.2)	66 (40.7)	154 (38.7)	78 (33.2)	383 (39.9)
0 to ≤ 5	187 (46.6)	75 (45.2)	85 (52.5)	208 (52.3)	132 (56.2)	500 (52.0)
>5 to ≤ 10	11 (2.7)	6 (3.6)	11 (6.8)	32 (8.0)	22 (9.4)	71 (7.4)
>10 to ≤ 15	0	0	0	3 (0.8)	1 (0.4)	4 (0.4)
>15 to ≤ 20	1 (0.2)	0	0	1 (0.3)	2 (0.9)	3 (0.3)
>20 to ≤ 25	0	0	0	0	0	0

Source: Safety Information Amendment (7/27/12) Table 23.12-18.1

For adolescents, more subjects gained weight across all doses in the 0 to ≤ 5 kg category in drug than placebo, but this was not observed in the >5 to ≤ 19 kg category.

In the Nonepilepsy DB pool, Dr. Doi notes similar results as in the epilepsy DB pool with less perampanel subjects than placebo without any weight gain (45.4% vs 55.2%) and more perampanel subjects than placebo with weight gain of >0 to ≤ 5 kg (49.6% vs 42.6%), >5 to ≤ 10 kg (4.5% vs 1.7%), and >10 to ≤ 15 kg (0.4% vs 0.2%). A dose response was observed for the weight gain categories.

In the Epilepsy Phase 3 DB studies, Dr. Doi notes that for adult perampanel subjects, weight gain was observed across all baseline BMI categories, while in placebo, weight loss or clinically insignificant weight gain were observed. For adolescent perampanel subjects, weight gain was observed across all baseline BMI categories, while inconsistent results were observed for placebo.

In the Epilepsy all treated pool including the OLE studies, the mean weight gain at the end of treatment in the total perampanel group was 1.5 kg for adults and 5.2 kg for adolescents. Median exposure time was 71.2 weeks for adults and 75.9 weeks for adolescents. The percentages of adult subjects who gained at least 7%, 15%, or 25% of their baseline body weight were 18.4%, 4.8% and 1.1%, respectively. For adolescents those values were 46.6%, 24.3%, and 9.7% respectively. Discontinuations due to TEAE of weight gain occurred in 0.5% of adults and 1.0% of adolescents. For adolescents and for adults, progressively large increases in weight occurred up to 24 months (with smaller sample sizes limiting analyses beyond 24 months).

Dr. Doi found that in the epilepsy Phase 3 studies, the TEAE of weight increased was reported by more perampanel subjects (3.8%) than placebo (1.4%); there is no difference in the TEAE of increased appetite (1.2% vs 1.1%). None of these events were SAEs. The TEAE of decreased appetite was also reported as a TEAE, and although Dr. Doi notes that this occurred in 2.2% of perampanel and 1.6% of placebo patients, I note that these numbers are not different. However, Dr. Doi notes that the TEAE of weight decreased was reported less frequently in perampanel subjects than placebo (0.2% vs 0.9%) and decreased appetite and weight decreased led to discontinuation less frequently in perampanel subjects than placebo.

In the Nonepilepsy DB pool, the TEAE of weight increased was reported more by perampanel subjects than placebo (1.2% vs 0.5%), along with the TEAE of increased appetite (0.4% vs 0.2%), with weight decreased and decreased appetite similar in drug and placebo. None of these events were SAEs. Five perampanel subjects discontinued due to the TEAE of weight increased (vs 0 placebo subjects).

Hyperlipidemia and hyperglycemia –

Total cholesterol, triglyceride, and blood glucose levels were measured in the perampanel studies (subjects were not required to fast before having blood drawn). HDL levels were not measured. In both adults and adolescents in the phase 3 DB epilepsy pool, perampanel subjects had higher incidences of total cholesterol increases and shifts than placebo subjects. In adults, 6.5% of perampanel subjects vs 2.8% of placebo had an increase of ≥ 50 mg/dL and 0.5% of perampanel vs 0 placebo had an increase of ≥ 100 mg/dL. In adolescents, 8.3% of perampanel subjects vs 2.9% of placebo had an increase of ≥ 40 mg/dL. For triglycerides and glucose, adult perampanel subjects had similar increases and shifts as placebo. As triglycerides are affected by fasting status, the lack of effect on triglyceride values vs placebo could be due to variability in fasting status. While there were no adolescent subjects who had shifts to abnormal values of glucose, there were conflicting results for shifts in triglycerides: a higher percentage of adolescent perampanel subjects than placebo had shifts from normal to high triglycerides, and a lower percentage of perampanel than placebo had shifts from borderline to high triglycerides. In the Nonepilepsy DB pool perampanel subjects had a higher incidence of total cholesterol increases and shifts than placebo subjects, as well as higher incidences of increases and shifts to high triglyceride values and shifts to high nonfasting glucose values. Shifts to high fasting glucose were similar in perampanel and placebo subjects.

Hypertension –

Dr. Doi notes a shift toward high blood pressure categories observed in the perampanel group vs placebo in the epilepsy Phase 3 DB pool, most evident in shifts from normal (< 120/80 mm Hg) to Stage 2 hypertension (\geq 160/100 mm Hg), although the numbers were small (6 subjects (0.6%) for perampanel vs 0/438 for placebo). At the end of week 6 and 12, treatment with perampanel was associated with higher percentages of subjects with increases of 5 to 10 mm Hg in both systolic and diastolic blood pressure, and by the end of the study perampanel subjects had even greater increases in both systolic (11-15 mm Hg) and diastolic (16-20 mm Hg) blood pressure. By the end of the study, 16.2% vs 14.2% (perampanel vs placebo) subjects had systolic blood pressure increases of > 10 mm Hg.

Dr. Doi also analyzed blood pressure data for decreases from baseline. There were no differences between perampanel and placebo subjects for diastolic blood pressure at the end of the study (29% vs 30%) in terms of diastolic blood pressure decreases \geq 5 mm Hg. By the end of the study 34.0% vs 33.3% of perampanel vs placebo subjects had systolic blood pressure decreases of \geq 5 mm Hg.

Overall metabolic effects –

Dr. Doi stratified the number of subjects who had weight gain of > 5%, >7%, and > 10% by the number of subjects who also newly developed other metabolic effects (triglycerides \geq 150 mg/dL, blood pressure \geq 130/85 mm Hg, and BMI >30 kg/m²) during the study and at the end of treatment. Across all weight gain categories there were more perampanel subjects than placebo subjects who developed metabolic syndrome values of triglycerides, blood pressure, and BMI. (and in most cases the risk in perampanel was 2x that in placebo). Please refer to Table 93 on page 135 of Dr. Doi's review.

Dr. Doi concludes that there is reasonable evidence of a causal relationship between perampanel use in adults and weight gain, increases in lipids (particularly total cholesterol) and blood pressure elevations. Because of the potential for increase in cardiovascular risk, Dr. Doi recommends that these adverse reactions (grouped together as metabolic effects) be included in the Warnings and Precautions section of the perampanel labeling. I agree.

Tendon/Ligament Ruptures –

Dr. Doi noted that tendon and ligament ruptures were experienced by subjects in the safety database. A relationship could be biologically plausible as in the preclinical studies perampanel binds to elastin with a very slow turnover. There could be a possibility that long term accumulation could cause damage of fibrous tissues such as tendons and ligaments in humans. However, overall, Dr. Doi has found similar incidences of total tendon and ligament disorders between perampanel and placebo subjects. Some of the tendon ruptures occurred in subjects at higher risk (older, history of diabetes mellitus, possible debility with Parkinson's disease, corticosteroid use,

trauma). The incidence of tendon rupture (0.18%)¹² as well as the incidence of tendonitis and tendon rupture combined (0.37%) in the Nonepilepsy all treated pool was in the range reported for fluoroquinolone-induced tendinopathy (ruptures + tendonitis, 0.14% to 0.4%). There were no tendon ruptures in the Epilepsy all treated pool, and Dr. Doi hypothesizes that this may be due to the younger age of the epilepsy pool and lack of significant comorbidities such as diabetes mellitus. She notes that there were cases of other fibrous connective tissue injuries such as ligament rupture seen in the epilepsy population (n=2). I agree that it is difficult to attribute the tendon ruptures in the Nonepilepsy population to perampanel exposure in the absence of a control group and no signal in the DB pools. Dr. Doi recommends postmarketing surveillance to continue to investigate the effects of perampanel exposure on the fibrous connective tissues, tendons, and ligaments in humans. Depending on the strength of the nonclinical finding, and because of the potential for long-term exposure to perampanel, I agree with that recommendation.

2.3.5 Submission Specific Primary Safety Concerns

Dr. Doi discusses her analyses and the Sponsor's analyses of safety concerns in major organ systems.

Hepatobiliary –

Cholelithiasis – In the epilepsy Phase 3 DB pool, a higher number of perampanel subjects (n=3) than placebo subjects (0) developed cholelithiasis. In the entire epilepsy population a total of 8 subjects (0.5%) reported TEAEs of cholelithiasis (including 1 subject with bile duct stone/acute pancreatitis). These were SAEs in 5 perampanel subjects in the all treated pool (2 perampanel subjects vs 0 placebo in the Phase 3 DB pool). In the Nonepilepsy DB pool, a similar percentage of perampanel subjects (0.1% with cholelithiasis) and placebo subjects (0.1% with bile duct stone) developed these TEAEs. In the Nonepilepsy all treated pool a total of 7 subjects (0.3%) reported TEAEs of cholelithiasis. Some of the same subjects also reported cholecystitis and acute pancreatitis. These were SAEs in 3 perampanel subjects. There were no AEs for lipase elevation in the safety population.

Dr. Doi notes that important risk factors for developing gall bladder disease are obesity and age over 40 years old. After excluding cases in subjects with a prior history (n=1) or too early in the study (n=1, Study Day 6), there are 2 subjects in the epilepsy DB pools and 4 in the OLE studies with cholelithiasis. Of these, most were females in their 40s and 50s and some were obese (BMI > 30, n=2). In the Nonepilepsy studies, most of the subjects were overweight.

I agree it is difficult to determine whether there is a signal. I agree that it can be followed post-marketing.

¹² 5 subjects, mean age of 59 y.o. developed tendon ruptures in this pool. Most occurred during a traumatic event, with 1 case of possible spontaneous tendon rupture. None were taking oral steroids or fluoroquinolones. Two had a history of diabetes mellitus. None had a history or concurrent events of tendinitis, tendon injury or tendon disorder.

Drug-Induced Liver Injury – A review of lab data results and liver-related AE risks from perampanel clinical trials did not identify any subjects in the entire safety database who had laboratory values that met criteria for Hy's Law. However, Dr. Doi did find a slightly higher percentage of perampanel subject compared to placebo (1.3% vs 0.7%) who developed TEAEs in the liver related investigations SMQ (but not the drug-related hepatic disorders – severe events SMQ). None of the liver-related TEAEs were SAEs.

The following results apply to the DB pools. There were no discontinuations in perampanel subjects in the epilepsy Phase 2 and 3 DB pools due to liver related TEAEs. There were 5 discontinuations due to ALT, AST, or GGT increased in the Nonepilepsy DB pool for perampanel vs none for placebo, and 1 each for ALT increased and hepatic enzyme increased for perampanel in the Phase 1 multiple dose pool (and none in placebo). In terms of outlier results, elevations in each of the liver tests occurred in very few perampanel subjects (generally < 0.5%). In the epilepsy and Nonepilepsy DB pools, the incidence of liver related lab result elevations was similar for subjects receiving perampanel and placebo. There were no cases where subjects had transaminase elevations greater than 3x upper limit of normal (ULN) associated with total bilirubin > 2x ULN.

The following results apply to the all-treated pools. In the Nonepilepsy all treated pool there were 4 subjects who discontinued due to increased hepatic enzymes (ALT or both ALT and AST) that were all reversible. There were no discontinuations due to hepatic enzymes in the Epilepsy all treated pool. In the Epilepsy and in the Nonepilepsy all treated pool, in terms of outlier results, elevations in each of the liver tests occurred in very few perampanel subjects (generally ≤ 0.6%). Perampanel subjects with elevated liver labs in the all treated epilepsy pool either had elevated pretreatment values (n=4), high baseline values (n=4), elevated values with subsequent normal values (n= 6), other medical diagnoses (1 subject with viral hepatitis A and 1 subject with viral infection), or developed elevations in Alt and AST with normal bilirubin after prolonged perampanel treatment (n=2, study day 733 and study day 584). Perampanel subjects with elevated liver labs in the all treated Nonepilepsy pool had an elevation in 1 liver parameter only (n=1, bilirubin > 2X ULN), had high baseline values (n=3), or a single elevated post-baseline value (n=7). There were no cases where subjects had transaminase elevations greater than 3x upper limit of normal (ULN) associated with total bilirubin > 2x ULN.

In the Phase 1 single dose study pool, no subjects had values for bilirubin that were > 2x ULN. Elevations of Alt or AST > 5X ULN occurred in 2 subjects, one with isolated elevation of AST followed by normal values, and another with elevated levels of AST and ALT at several evaluations., decreased toward normal by the final evaluation. No placebo subject had ALT or AST elevations > 5 X ULN in this pool. In the Phase 1 multiple dose study pool, no subjects had values for AST > 5X ULN. There was a perampanel subject with ALT > 5X ULN with elevated AST values, and both resolved during the study. Four (1.2%) perampanel subjects and one (0.9%) placebo subject had bilirubin values > 2X ULN, but in all 5 cases the subjects had bilirubin elevations at screening and throughout treatment. No placebo subjects had ALT or AST > 5X ULN.

Two subjects in Phase 1 studies discontinued due to hepatic enzyme increases. Subject 029-1001-1139 was a 41 y.o. female with increases in ALT > 3X ULN, increases in AST < 2X ULN on Days 13 to post-dose Day 3, and no increase in alkaline phosphatase. Bilirubin was not available on Day 14 during the period of maximum elevation of the transaminases but was not elevated on Day 13 or Post-dose Day 3. Other than lethargy, the subject did not report liver related AEs such as nausea, vomiting, abdominal pain, jaundice, or anorexia. Subject 013-1001-0303 was a 54 y.o. female who experienced increased liver enzymes beginning on Study Day 7. ON Day 14, AST was > 2x ULN and ALT was > 3.5x ULN. Bilirubin and alkaline phosphatase were not reported on Day 14, but were not elevated greater than 1X ULN on Day 13 or Post-dose day 1. Perampanel was discontinued and transaminitis resolved in 3 weeks. The subject experienced the TEAEs of dizziness, fatigue, and mental status changes.

In Phase 1 study 006 evaluating the effect of multiple doses of carbamazepine on a single dose of perampanel, 7 subjects had elevations in at least 2 transaminases (ALT, AST, or GGT). These were attributed to carbamazepine as they occurred during the carbamazepine period or in the post-study period.

I agree with Dr. Doi that the evidence does not suggest that perampanel use is associated with liver injury.

Skin and Immune System Disorders –

The percentages of subjects reporting TEAEs in the SMQs Severe cutaneous adverse reactions, Anaphylactic reaction, Angioedema, and Neuroleptic malignant syndrome in the epilepsy Phase 3 DB pool were at similar frequencies (or lower) in the perampanel subjects as placebo subjects. The same was true of the epilepsy Phase 2 DB and Nonepilepsy DB pools.

Skin and subcutaneous tissue disorders – TEAEs coded to the PTs Stevens-Johnson syndrome and toxic epidermal necrolysis were not reported in perampanel subjects in the entire safety database; there was 1 case of Stevens-Johnson syndrome reported in a placebo subject in Nonepilepsy studies.

TEAEs in this SOC occurring in perampanel more than placebo in the epilepsy Phase 3 DB pool included pruritus (1.1% vs 0.5%), acne (0.7% vs 2%), and dry skin (0.4% vs 0.2%), ecchymosis (0.2% vs 0), and skin irritation (0.2% vs 0). Rash occurred in 2.2% vs 1.6% for placebo and Rash papular occurred in 0.3% vs 0 in placebo. In the Epilepsy Phase 2 DB pool 3.3% of perampanel and 2.9% of placebo subjects experienced a rash, and 1.3% of perampanel and no placebo subjects experienced palmar erythema and skin ulcer, each. There were no SAEs related to rash in the Epilepsy DB pools. Eight perampanel subjects (0.7%) experienced a rash that led to drug discontinuation vs 0 placebo subjects. Most of these were categorized as moderate in severity by the investigators. The mean day of onset was 43 days (range 4 to 110 days). The mean dose was 8 mg. In some cases they were treated with methylprednisolone (n=2) or antihistamines (n=1). After discontinuation of perampanel,

resolution occurred after an average of 8.5 days (range 1-29 days with 2 noted as ongoing). None of the cases reported widespread, exfoliative or bullous rashes involving the mucocutaneous areas. In the Epilepsy all-treated pool, there were 4 additional perampanel subjects who developed rashes that led to discontinuation, 1 with “toxic skin eruption” that was described as a vesicular dermal rash on the upper torso and limbs that resolved 1 week after discontinuation of perampanel (while being treated with acyclovir, desloratidine, and quifenadine).

In the Nonepilepsy DB pool, skin related SAEs occurred only in the placebo group. In the Nonepilepsy all treated pool, 1 subject developed SAE of decubitus ulcer. In the Nonepilepsy DB pool, more perampanel subjects developed rashes leading to discontinuation than placebo subjects (0.3% vs 0.1%). The time course of onset and resolution was similar to that described for the Epilepsy DB pool, although 2 cases involved the mouth. An additional subject, with no other medications reported, developed symptoms that Dr. Doi believes fit EuroSCAR criteria for “possible” acute generalized exanthematous pustolosis (AGEP), but lacked criteria needed to make a definitive diagnosis.

In Phase 1 studies, there were no perampanel subjects who developed skin related SAEs. One subject discontinued due to rash Pruritic. Dr. Doi notes that one subject (Subject 17 in Study 002) developed erythema multiforme on Day 12 confirmed by a dermatologist, thought most likely due to an infectious etiology and treated with acyclovir. The subject completed the study, receiving the last dose of perampanel on Day 14 and the event resolved 1 week later. I have reviewed the description of that case that refers to “a few erythematous papules on the backs of both hands...the next day the rash was also present on the elbows where it looked like erythema multiforme. The subject was reviewed by a consultant dermatologist who confirmed this diagnosis. He also noted that the subject had a small cold sore on his lip that was the most likely cause of the erythema multiforme.” Notes in the subject data listing state that the most likely etiology was herpes simplex infection as the subject had developed a cold sore on his lip.

Although the risk of rash appears to be similar between perampanel and placebo, I agree with Dr. Doi that the risk of discontinuation due to rash was greater in the perampanel group, and I agree that there were no definitive cases of severe cutaneous adverse reactions associated with perampanel use.

Photosensitivity – Because nonclinical studies indicated that perampanel has the potential to cause phototoxicity, a photosensitivity questionnaire was added to the Epilepsy Phase 3 DB studies after enrollment had been ongoing for more than 6 months, and was therefore only administered to half of the study pool. In those subjects, more perampanel subjects (2%) vs placebo subjects (1%) responded that they had a skin rash/reaction/change in pigmentation/skin complaint, and more perampanel subjects (1%) than placebo subjects (0.4%) responded that skin reacted to sunlight more than expected. Of those who responded positively to the first item, all of the placebo subjects and 82% of perampanel subjects had one or more skin-related

TEAEs such as rash sunburn, or dermatitis of which none were SAEs or led to dose adjustment or discontinuation. I agree that there are limitations of these findings due to the subjective nature of the questionnaire and the administration to only half of the subjects.

Dr. Doi found that in the epilepsy DB pool, there were more perampanel subjects (n=2) than placebo subjects who reported photosensitivity reactions (0.2% vs 0), but fewer perampanel subjects reporting sunburn. In the Nonepilepsy DB pool Dr. Doi reports that a similar percentage of perampanel and placebo subjects reported photosensitivity reaction, with no reports of sunburn. In the all treated pools, there were a total of 10 perampanel subjects with photosensitivity reaction (5 epilepsy, 5 Nonepilepsy). Dr. Doi also notes additional preferred terms that could be related to sun damage reported by perampanel but not placebo subjects in the Nonepilepsy DB pool including actinic keratosis, basal cell carcinoma (4) and squamous cell carcinoma. These were not reported by perampanel subjects in the epilepsy all treated pool. The difference could be due to differences in risk factors in the populations, including age and racial composition. Melanoma was also reported by perampanel subjects (discussed in section 7.6.1 of Dr. Doi's review and later in my memo).

I agree with Dr. Doi that it is difficult to draw conclusions about the role of perampanel in sun damage.

Anaphylactic reaction/Angioedema –

In the epilepsy all treated pool, there were no perampanel subjects who reported anaphylaxis, angioedema, bronchospasm, stridor, laryngeal edema, laryngospasms, or throat tightness. Perampanel subjects reported the following TEAEs: hypersensitivity (8)/ drug hypersensitivity (1) for which the verbatim terms were mostly for allergies (seasonal, environmental, or other drug); urticaria (3), 4 each of gingival swelling and face edema/swelling face, eye swelling/eye edema/eyelid edema (5), and allergic edema(1), none of which were SAEs. One subject discontinued due to face edema. No rash, fever or dyspnea were reported. In the epilepsy Phase 2/3 DB pool hypersensitivity occurred at a similar rate in perampanel (n=3, 0.3%) vs placebo (n=1, 0.2%) and drug hypersensitivity occurred only in the placebo group (0.2%).

In the Nonepilepsy all treated pool, there were no perampanel subjects who reported anaphylaxis, laryngospasms, stridor, swollen tongue, or drug hypersensitivity. Perampanel subjects reported 3 cases of bronchospasm that according to Dr. Doi did not represent anaphylaxis or angioedema and in all 3 cases perampanel was continued without recurrence. There were 2 cases of angioedema. One case of angioedema was in a subject with a past history of angioedema and who developed angioedema on study day 180 of an OLE study. One case of angioedema occurred on Day 226 and resolved within 1 day while continuing to take perampanel. It is difficult to attribute these cases to perampanel. In the Nonepilepsy DB pool, perampanel subjects did not report bronchospasm, eyelid edema, or lip swelling, and reported the following TEAEs at similar frequencies as placebo: face edema (2 cases vs 1), and urticaria (1 vs 2), and

lip edema and swelling face were reported in 1 and 4 perampanel subjects, respectively, and no placebo subjects. Hypersensitivity was reported in 2 perampanel subjects (verbatim terms of environmental allergies and allergic reaction one day after cellulitis due to insect bites) and 1 placebo subject.

In the Phase 1 studies, 2 subjects discontinued from multiple-dose studies reporting pharyngolaryngeal pain/tongue hemorrhage in 1 case and swollen tongue (and also had sore throat, swollen glands) in the other case. There is limited information in these cases.

It does not appear that perampanel is associated with anaphylaxis

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) -

The Sponsor reviewed the entire database for subjects who met the RegiSCAR search criteria for DRESS, identifying 6 possible cases (2 placebo and 4 perampanel) of which the Sponsor identified 3 meeting the specific criteria for DRESS. Dr. Doi reviewed the narratives for all 6 subjects, as well as their laboratory and vital sign parameters, as discussed on page 153 of her review. In the 3 cases that met the specific criteria, the occurrences of the supporting criteria (laboratory abnormalities) were not contemporaneous with the rash. I agree with Dr. Doi that there are no definite cases of DRESS associated with perampanel use in this database.

Cardiac Disorders –

Deaths, SAEs, and discontinuations - In the Epilepsy DB pool there were no cardiac related SAEs or TEAEs leading to discontinuation that occurred in more 2 or more perampanel subjects and greater than placebo. In the Epilepsy DB pools combined, there was only 1 cardiac-related SAE in perampanel: aortic stenosis that occurred on Day 41 of perampanel in subject with a history of hypertension, hypercholesterolemia, type 2 diabetes, and first degree AV block; the subject was medically managed and completed the study; I agree with Dr. Doi that it is unlikely related to perampanel as it was too soon after perampanel initiation. One perampanel subject discontinued due to tachycardia.

In the epilepsy all treated pool, 1 subject with cardiac risk factors died due to cardiac arrest (discussed under deaths). In the cardiac disorders SOC in this pool, there were 12 SAEs (0.7%) and discontinuations in occurred in 0.4%

In the Nonepilepsy DB pool, perampanel subjects (0.8%) had a slightly lower frequency of cardiac SAEs than placebo (1.0%). Dr. Doi notes that the ischemia-related PTs (coronary artery disease, myocardial infarction, and acute myocardial infarction) occurred less frequently in perampanel than placebo. Of the Cardiac SAEs that occurred in 2 or more subjects and greater than placebo, there were atrial fibrillation, cardiac failure, cardiac congestive failure, and tachycardia, all at 0.1% in perampanel and none in placebo.

In the epilepsy OLE studies, there were no cardiac SAEs experienced by more than 2 perampanel subjects. Narratives for cardiac SAEs in this pool are summarized by Dr. Doi on pp.160-163 of her review. Most had underlying disorders that could have contributed to the etiology, and it is difficult to determine the role of perampanel in these cases. Two SAEs were experienced by more than 1 perampanel subject – angina pectoris and atrial fibrillation in 2 subjects each. SAEs due to arrhythmias were supraventricular (2 atrial fibrillation, 1 atrial flutter, 1 sick sinus syndrome) or bradycardic (1 bradycardia, 1 atrioventricular dissociation), and there were no events of ventricular arrhythmias.

In the Nonepilepsy all treated pool, SAEs due to arrhythmias were mainly supraventricular (including 10 atrial fibrillation, 1 atrial flutter, 1 supraventricular tachycardia, 1 sick sinus syndrome) or tachycardic/bradycardic. There was 1 sudden cardiac death in a 61 y.o. with prior cardiac history. There were 5 SAEs of syncope but after review of the narratives, Dr. Doi has determined that these were not due to arrhythmias (orthostatic hypotension, dehydration, bowel obstruction, infection, and one likely due to a parasympathetic response¹³).

In the Nonepilepsy all treated pool, perampanel subjects had a higher incidence of death, SAEs, discontinuations, and TEAEs than the epilepsy all treated pool, and I agree with Dr. Doi that this is likely due to the older population with more comorbidities.

TEAEs - In the epilepsy Phase 3 DB, epilepsy Phase 2 DB, and Nonepilepsy DB pools, a lower percentage of perampanel subjects than placebo experienced cardiac-related TEAEs. A dose response was not observed for cardiac TEAEs in either of the all treated pools.

In the Epilepsy Phase 3 DB pool, there were 4 cardiac PTs identified that occurred in two or more perampanel subjects and greater than placebo: angina pectoris (0.2% vs 0), tachycardia (0.4% vs 0.2%), QT prolonged (0.3% vs 0), and syncope (0.3% vs 0). Loss of consciousness was not reported as a PT. None of the 3 cases of QT prolonged was an SAE; 2 subjects had minimal increases in QTcF¹⁴ and 1 subject was withdrawn due to a QTcF of 462 msec (an increase of 34 msec from baseline) 1 day after completing the DB treatment, with a repeat value on the same day of 442 msec. The verbatim terms for the syncope cases were vasovagal syncope, fainted, and fainting. None of these events were SAEs or resulted in discontinuations. In the Nonepilepsy DB pool, more perampanel subjects than placebo subjects experienced TEAEs in the HLG cardiac arrhythmias (each term 0.4% or less in perampanel). Dr. Doi notes that these are disparate events with both conduction disorders and supraventricular arrhythmias (with both bradycardia and tachycardia), and

¹³ Dr. Doi's review indicates that 1 episode of syncope was due to hypertension, but in an email correspondence of 9/4/12 and 9/5/12, she has clarified that it is more likely due to a parasympathetic response in a subject with a history of hypertension who experienced syncope after waking up feeling sick with diaphoresis and "40 mm Hg of systolic arterial tension". The investigator considered the SAE related to the "increase in peristaltic bowel movements" due to the subject taking a laxative for constipation.

¹⁴ One subject had 1 single value of QTcF = 451 msec and a change of 33 msec from baseline; the other had a QTcF of 441 msec, a change of 14 msec from baseline.

ventricular extrasystoles. In this pool, syncope was experienced in a lower percentage of perampanel subjects vs placebo and was an SAE in the same percentage of perampanel and placebo subjects. Loss of consciousness was reported at the same frequency in perampanel and placebo subjects in this group (0.1%).

In the Phase 1 single dose studies, a lower percentage of perampanel experienced cardiac TEAEs than placebo, but in multiple dose studies, the incidence was higher in the total perampanel group (3.2%) vs placebo (0%). Events that occurred in 2 or more subjects were palpitations (n=4) cyanosis (n=2; one of which occurred prior to study drug administration and the other considered to be a vasovagal reaction due to manipulation of indwelling needles¹⁵), heart rate increased (n=2) and tachycardia (n=2). None were SAEs. There was 1 discontinuation due to the TEAE electrocardiogram QT prolonged 23.5 hours after receiving 8 mg perampanel (change of 37 msec) in a patient with a history of recent use of LSD, cannabinoids, valium, and Tylenol #3 and Percodan¹⁶; perampanel was withdrawn and the QT interval resolved the following day. I agree with Dr. Doi it is difficult to determine the role of perampanel in this case (and I note the time of the event that is much later than the average tmax).

In the Epilepsy and Nonepilepsy all treated pools, there were no TEAEs coded to the PTs ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia, ventricular tachycardia, or torsades de points. Subject 206-0016-0075 experienced the TEAE ventricular arrhythmia on Day 60 while on 4 mg perampanel, although no ECG was reported on that day, but two prior ECGs were read as abnormal (with normal QTc intervals) and 7 prior ECGs were reportedly normal. Subject 302-0424-0001 developed ventricular extrasystole on OLE extension day 14 (Day 168 of perampanel exposure) which resolved 19 days later without any treatment recorded.

Finally, the QT Interdisciplinary Review Team (IRT) reviewed OLE Study 228 for which a mean change from baseline of QTcF of 12.6 msec in the highest dose group (>8-12 g/day) was observed after 12 months of treatment. The IRT concluded that it is unlikely that changes from baseline reported in that study are a QT signal, as the thorough QT study (TQT study; discussed in section 2.3.9 of this memo) did not exceed the threshold of regulatory concern after a 12 mg dose, because the controlled trials did not show clinically relevant mean QTc values at this dose, because the incidence of TEAEs of concern as per ICH E14 Guidance did not differ significantly from placebo and no dose-dependent trend in QTc prolongation was observed in any study. In addition, there was no comparator group in this study making it difficult to determine a causal relationship.

I agree with Dr. Doi that the differences observed between perampanel and placebo in cardiac TEAEs were small and difficult to attribute to perampanel.

Other Organ Systems –

¹⁵ p. 109 of Study report for Study 026.

¹⁶ The opioid morphine is associated with QT prolongation.

Renal and Urinary Disorders – Dr. Doi notes that a similar percentage of subjects in the Epilepsy Phase 3 pool had TEAEs in this SOC for perampanel (2%) vs Placebo (1%). There were no AEs of acute renal failure in perampanel subjects in the epilepsy all treated pool. TEAEs occurring in 2 or more perampanel subjects in the Phase 3 DB epilepsy pool were pollakiuria (frequent daytime urination), enuresis, and nephrolithiasis (all 0.4% or less, vs 0 placebo), and hematuria (0.3% vs 0.2% in placebo). There were 3 SAEs in this pool that occurred in perampanel subjects greater than placebo (cystitis hemorrhagic that did not recur although perampanel was continued, nephrolithiasis, and urinary incontinence that occurred on the same day as status epilepticus, occurring in 1 subject each and none in placebo). In the Epilepsy all treated pool, there were 3 subjects with the SAE of nephrolithiasis (one subject with a prior history of nephrolithiasis, 1 that occurred on Day 4 and likely too soon after initiation of perampanel; perampanel was continued in all 3 cases).

In the Nonepilepsy DB Pool TEAEs in this SOC occurred in 3% each for perampanel and placebo. In this pool, the SAEs in perampanel subjects more than placebo were renal failure acute occurring in 2 subjects and diabetic nephropathy, hematuria, nephrolithiasis, and urinary retention, all occurring in 1 subject each. One case of acute renal failure occurred in a patient with an abnormal Cr value at baseline, resolved within 1 day, and did not reoccur when perampanel was continued. The other case occurred in the setting of severe pancreatitis. In the Nonepilepsy all treated pool, 2 subjects experienced the SAE of nephrolithiasis, both with a prior history.

There were no SAEs or discontinuation TEAEs in this SOC in the epilepsy Phase 2 pool or Phase 1 studies.

The TEAE of blood creatinine increased was not considered an SAE in the entire database.

I agree with Dr. Doi that perampanel does not appear to be associated with renal or urinary disorders in this database based on a review of TEAEs in the renal and urinary SOC.

Endocrine disorders – Dr. Doi notes that a higher percentage of perampanel subject than placebo developed thyroid-related disorders in the epilepsy DB pool (5 subjects, 0.4% vs 0.2%), but this was not replicated in the Nonepilepsy DB pool where the risk was (0.3% for perampanel vs 0.6% for placebo). In the epilepsy all treated pool 0.8% (n=14) developed thyroid-related disorders: goiter (6), hypothyroidism (6), hyperthyroidism (1), thyroid neoplasm (1), and thyroid cancer (1). Five of the 14 (36%) had a past history of thyroid disorder. For the 5 SAEs or discontinuations in the Epilepsy and Nonepilepsy all treated pools, the role of perampanel was unclear, in 2 cases occurring in patients with a previous history of thyroid abnormality. I agree with Dr. Doi that perampanel does not appear to be associated with thyroid disorders in this database.

Gastrointestinal disorders – In the epilepsy Phase 3 DB pool, in the SOC Gastrointestinal disorders, the TEAEs that occurred in > 1% perampanel subjects and greater than placebo were abdominal discomfort (1.1% vs 0.2%). Dr. Doi notes that nausea occurred in 5.2% (overall) vs 4.5% and toothache in 1.4% vs 0.7%, perampanel vs placebo. I note that although these are not different for perampanel vs placebo, there was a dose response for nausea, with 6% of subjects in the perampanel 8 mg group and 8% in the 12 mg group as shown in Table 124 on page 175 of Dr. Doi's review. There were 2 SAEs in perampanel subjects: nausea (1) and omental infarction (1). The following TEAEs that led to drug discontinuation occurred more frequently in perampanel than placebo: nausea (0.4% vs 0), vomiting (0.4% vs 0.2%), constipation (0.2% vs 0), abdominal pain (0.1% vs 0), and omental infarction (0.1% vs 0). In the Epilepsy Phase 2 DB pool, the TEAEs in this SOC that occurred in > 1% of perampanel subjects and greater than placebo were constipation (2.6% vs 0), and abdominal discomfort (1.3% vs 0). Dr. Doi notes that diarrhea occurred in 4.6% of perampanel vs 4.4% of placebo in this pool. There were no SAEs, and 1 perampanel discontinuation due to dry mouth.

Dr. Doi notes that in the epilepsy OLE studies, there were young perampanel subjects (28-38 y.o.) who developed SAEs of colitis (after > 1 year of exposure; perampanel was continued), colitis collagenous (in a patient with a history of other autoimmune disease – asthma and psoriasis), and ileitis (after > 4 years of treatment and resolved with continuation of perampanel); she notes that there is a higher incidence of inflammatory bowel disease in ages 20-30 years old, with a bimodal age distribution, in the general population. Dr. Doi believes that these cases seem unlikely due to perampanel, and I agree that it is difficult to attribute them to perampanel. There was also 1 SAE of ischemic colitis in a 64 y.o. patient most likely due to hypotension from septic shock 8 days after discontinuation of perampanel, and 1 large intestinal perforation that occurred during a colonoscopy.

In the Nonepilepsy DB pool, there are no TEAEs that occurred in this SOC in > 1% of perampanel subjects and greater than placebo. Dr. Doi notes that vomiting occurred in (2% vs 1.6%) and abdominal pain upper occurred in 1.2% vs 1%, perampanel vs placebo. There were no SAEs that occurred in more than 2 perampanel subjects and greater than placebo in this pool. Nausea led to drug discontinuation more frequently in perampanel than in placebo: 0.5% vs 0.3%.

Dr. Doi suggests that perampanel use is associated with nausea, vomiting, and abdominal pain. I believe that the strongest data suggest an association with abdominal discomfort and with nausea, the latter based on the dose-response.

Respiratory disorders – In the epilepsy Phase 3 DB pool, in the SOC Respiratory, thoracic and mediastinal disorders, the only TEAE that occurred in > 1% perampanel subjects and greater than placebo was oropharyngeal pain (1.7% vs 1.4%). Epistaxis occurred in 1.1% vs 0.5%. Dyspnea was experienced by perampanel subjects less often than placebo (0.3% vs 0.5%). There were no SAEs or TEAEs that led to discontinuations in this SOC. The results were similar in the Epilepsy Phase 2 DB pool,

where the TEAEs in this SOC that occurred in > 1% of perampanel subjects and > placebo were oropharyngeal pain (4.0% vs 1.5%) and sinus congestion (3% vs 0). No subjects reported dyspnea (although 1 reported dyspnea exertional). There were no SAEs or TEAEs that led to discontinuations in this SOC in this pool. In the Nonepilepsy DB pool, there were no TEAEs in this SOC that occurred in > 1% of perampanel subjects and greater than placebo. The following SAEs were reported in 2 or more perampanel subjects and greater than placebo: dyspnea (0.2% vs 0), pulmonary embolism (0.1% vs 0). Discontinuations due to dyspnea occurred more frequently in perampanel subjects than placebo (0.5% vs 0.2%).

I agree with Dr. Doi that perampanel does not appear to be associated with important respiratory disorders in this database. There is a small signal for oropharyngeal pain in both epilepsy DB pools. I agree that it is reassuring that there was not a signal for dyspnea (or SAEs or discontinuations) in the epilepsy DB pool.

Hyperthermia – In the epilepsy DB pool, 1 perampanel subject experienced the TEAE hyperthermia vs 0 placebo subjects, and there were a total of 3 subjects who experienced this TEAE in the epilepsy all treated pool. One subject developed hyperthermia on Day 67 (although recorded temperature values were in the normal range), and 1 developed hyperthermia on Day 827 and no temperature values were recorded on that day. The third patient had an SAE of hyperthermia on OLE day 199 with temperature increased to 40 ° C despite antipyretics, and blood pressure 160/129 (from baseline of 125/80); perampanel was discontinued and events resolved 14 days later. Dr. Doi proposes that an infectious etiology (particularly viral) could have caused the same clinical syndrome. There were no AEs coded to hyperthermia in the Nonepilepsy population. I agree with Dr. Doi that perampanel is not associated with hyperthermia in this database.

2.3.6 Common Adverse Events

After adjusting for exposure, Dr. Doi finds that the incidence rate of TEAEs was 2x higher in the Nonepilepsy pool (25.0 per 1000 subject weeks) than the epilepsy pool (12.5 per 1000 subject weeks). She also notes differences in the SOC distribution between these 2 pools (shown in Table 121, p. 172 of her review), likely due to underlying diseases and comorbidities. She notes that the most commonly occurring TEAEs in the epilepsy studies also occurred in the Nonepilepsy studies.

In the Epilepsy Phase 3 DB pool, the largest differences between total perampanel and placebo groups were in the incidences of the following PTs: dizziness, somnolence, irritability, fatigue, ataxia, vertigo, balance disorder, weight increased, dysarthria, fall, anxiety hypersomnia, and gait disturbance. TEAEs occurring in 5% or greater in any perampanel dose group and greater than placebo were vertigo, nausea, fatigue, irritability, nasopharyngitis, upper respiratory tract infection, fall, ataxia, balance disorder, dizziness, headache, somnolence. Dizziness was the most common TEAE, occurring in 28% of total perampanel subjects vs 9% of placebo, with somnolence occurring in 14% of total perampanel subjects vs 7% of placebo. A dose response is

most notable at the 8 mg and 12 mg dose groups, overall, vs placebo. There is little difference in general between the low dose groups (2 and 4 mg) and placebo. Dr. Doi has provided a table of adverse reactions in the Epilepsy Phase 3 DB pool with events \geq 2% and greater than placebo in any dose group (Refer to Table 124, p. 175 in her review).

In the epilepsy all treated pool, the overall incidence of TEAEs was 91%. The most common (\geq 10%) reported for perampanel subjects were dizziness (47%), somnolence (21%), headache (18%), fatigue (13%), irritability (12%), and weight increased (11%). Dr. Doi notes that exposure adjusted rates were lower in the epilepsy all treated pool (12.5 per 1000 subject weeks) than in the epilepsy Phase 3 DB pool (44.7 per 1000 subject weeks), suggesting no increase in the incidence of these events with longer exposure to treatment.

TEAEs that occurred in \geq 2% of the total perampanel administration Phase 1 Single dose pool were dizziness, somnolence, headache, fatigue, euphoric mood, nausea, vision blurred, hypoaesthesia oral, and gait disturbance. TEAEs that occurred in \geq 5% of the Phase 1 Multiple Dose Pool included dizziness, headache, somnolence, nausea, fatigue, positive rombergism, dysarthria, feeling drunk, oropharyngeal pain, insomnia, vision blurred, ataxia, diarrhea, lethargy, balance disorder, epistaxis, fall, vomiting, asthenia, and coordination abnormal.

2.3.7 Laboratory findings

Hematology – In the Epilepsy Phase 3 DB pool, Dr. Doi shows that the incidence of PCS hematology changes (an increase in NCI grade to a \geq Grade 2 from baseline; markedly abnormal) for subjects normal at baseline were similar between placebo and perampanel groups for hemoglobin, WBC, platelets, lymphocytes, and neutrophils. Only hemoglobin had potentially clinically significant (PCS) changes greater for perampanel greater than placebo, in which 2 (0.2%) perampanel subjects and no placebo subjects had PCS changes. Both subjects had single occurrence of a PCS change followed by subsequent normal values in 1 subject and subsequent values of NCI grade 1 in the other subject that approached the normal range as perampanel was continued. The majority of subjects reporting markedly abnormal low values of hemoglobin (n=14) had abnormal baseline hemoglobin values (n=12); all 12 had an increase of 1 NCI grade from a baseline NCI Grade of 1. Mean values for hematology parameters (RBC, hematocrit, hemoglobin, WBC, and platelets) were within normal ranges at baseline and end of treatment for placebo and for perampanel, and mean changes from baseline were small and of unknown clinical significance. The incidence of shifts to low values were higher in the perampanel group than placebo for hemoglobin (5.0% vs 3.5%) and neutrophils (6.5% vs 4.4%), and slightly higher for WBC (6.9% vs 6.3%), but not for RBC, hematocrit, platelets, or lymphocytes; Dr. Doi states that there were no dose response relationships seen in the shift results.

In the Epilepsy Phase 2 DB pool, no perampanel subjects with normal baseline values of hemoglobin had a result that met the low PCS criteria. One (0.7%) perampanel

subject had a PCS low WBC result (vs none in placebo), and three (2.3%) had a PCS low neutrophil result (vs none in placebo). In this pool, mean changes were small and of unknown clinical significance, according to Dr. Doi, and the mean changes were similar in the perampanel and placebo groups. In this pool, shifts to low values were higher in the perampanel group than placebo for RBC count (7.9% vs 4.4%), hemtocrit (2.7% vs 1.5%), hemoglobin (4.0% vs 2.9%), WBC count (6.0% vs 4.4%), and neutrophils (2.9% vs 0%).

In the Epilepsy all treated pool, generally the PCS changes were similar in magnitude to those in the DB pools. However, more than 4% of the total perampanel subjects had PC changes in neutrophil counts. In this pool, only 11 subjects (0.8%) had neutrophil counts between 0.5 to $1 \times 10^9/L$ or Grade 3 toxicity, with 10 subjects having only 1 single abnormal value, and 1 subject (0.1%) had a single neutrophil count less than $0.5 \times 10^9/L$ (Grade 4 toxicity).

In the Nonepilepsy DB pool, the incidence of PCS hematology changes for subjects normal at baseline were similar between placebo and perampanel for hemoglobin, WBC, platelets, lymphocytes, and neutrophils. Mean values for hematology parameters (RBC, hematocrit, hemoglobin, WBC, and platelets) were within normal ranges at baseline and end of treatment for placebo and for perampanel, and mean changes from baseline were small and of unknown clinical significance. However, I note that the values were increased for perampanel and decreased for placebo. In this pool, shifts to low values were similar in the perampanel and placebo groups for all of the hematology parameters except for lymphocytes low (4.9% for perampanel, 3.4% for placebo).

In the Nonepilepsy all treated pool, generally the PCS changes were similar in magnitude to those in the DB pool. However, 4.2% of the total perampanel subjects had PC changes in lymphocytes.

In Phase 1 single dose studies, markedly abnormal low leukocytes occurred in 5 (0.7%) of the perampanel administrations along with 9 low neutrophils (1.5%) and 3 low lymphocytes (0.5%). In the phase 1 multiple dose studies 1(0.3%) and 4 (1.6%) perampanel subjects developed markedly abnormal low leukocytes and low neutrophils, respectively. There were no markedly abnormal values reported for any of the other hematology parameters, and no placebo subjects developed treatment-emergent markedly abnormal values.

Incidences of hematology-related TEAEs were < 3% in both the perampanel and placebo groups in the Blood and lymphatic system disorders SOC. Anemia occurred more frequently in perampanel subjects than placebo subjects in both DB pools (0.8% in perampanel vs 0.2% for placebo in the Epilepsy DB Pools combined and 0.8% for perampanel vs 0.5% for placebo in the Nonepilepsy DB pool). Neutropenia and leukopenia occurred in 0.6% and 0.5%, respectively, of perampanel treated subjects in the combined epilepsy DB pools vs none in placebo.¹⁷ Of the 7 subjects with

¹⁷ The text of Dr. Doi's review incorrectly states this occurs in 0.7% and 0.6%, respectively, although Table 131 on p. 182 of her review has the correct calculations.

neutropenia, 5 had baseline abnormalities, 1 had an associated bronchitis (and a recurrence with another episode of bronchitis after perampanel had been discontinued), and 1 had single post baseline markedly abnormal values with subsequent normal values. Of the 6 subjects with leukopenia, 2 had baseline abnormalities (one of whom had a single markedly abnormal value with subsequent normal values). None of the hematology related AEs resulted in death or was considered a SAE in perampanel subjects. Two events in the perampanel group led to discontinuation; I agree with Dr. Doi that neutropenia in the setting of bronchitis described above was not likely due to perampanel. The other was thrombocytopenia beginning on Study Day 99 of perampanel 2 mg/day in a patient with abnormally low values of platelets at screening and baseline and concomitant use of oxcarbazepine, levetiracetam, and clobazam that have been associated with thrombocytopenia; it is difficult to determine the role of perampanel in this case. In the epilepsy Phase 2 DB pool, activated PTT prolonged occurred more frequently in perampanel subjects (2...6%) vs placebo (1.5%); all 4 of the perampanel subjects had baseline values above the ULN, and the placebo subject had baseline values within the normal range. In the Nonepilepsy double-blind pool, 2 events were SAEs: anemia in 1 placebo subject and 1 perampanel subject. Anemia led to discontinuation in 1 perampanel subject in this group, while hemoglobin decreased and hematocrit decreased led to discontinuation of treatment in 1 placebo subject.

I agree with Dr. Doi that perampanel does not appear to be associated with changes in hematology parameters or with AEs related to such changes in this database.

Chemistry – Evaluation of PCS chemistry changes (for subjects with normal values at baseline) in the Epilepsy Phase 3 and Phase 2 DB pools, showed a PCS change in 2% of perampanel subjects and greater than placebo only in *high CPK* (4.1% vs 0) in the Phase 2 DB pool. Smaller differences are noted for PCS *high potassium* in both pools, *low calcium* in both pools, and *low glucose* in the Phase 3 DB pool. In the Nonepilepsy DB pool PCS changes that occurred in at least 2% of perampanel subjects and greater than placebo included *high potassium* (2.6% vs 1.7%) and *high glucose* (7.0 vs 2.7%). In the Phase 1 studies, treatment emergent markedly abnormal lab results occurred in at least 2% of the perampanel group only for *high potassium* (in the multiple dose subjects).

In the Epilepsy Phase 3 DB pool and the Epilepsy Phase 2 DB pool, the mean values for lab parameters were within normal ranges at baseline and end of treatment for all treatment groups. The mean changes were small and of unknown clinical significance. In the Nonepilepsy DB pool, mean changes were also small and of unknown clinical significance, and similar in perampanel and placebo groups.

In the Epilepsy Phase 3 DB pool, the incidences of shifts were higher in perampanel than placebo for *high CPK* (6.9% vs 4.2%) and *phosphate* (1.7% vs 0.7%). In the Epilepsy Phase 2 DB pool, shifts in at least 2% of the perampanel group and twice that of placebo occurred for *high potassium* (4.0% vs 1.5%), *low calcium* (4.6% vs 1.5%), *high cholesterol* (8.6% vs 2.9%), and *high CPK* (14.4% vs 1.6%). In the Nonepilepsy DB pool, shifts in at least 2% of the perampanel group and greater than placebo

occurred for *high CPK* (8.3% vs 5.9%) and *high LDH* (2.7% vs 0.8%). For hepatobiliary parameters, shifts to high values generally occurred less frequently in perampanel than placebo in any treatment pool. In Phase 1 studies, shifts in at least 2% of perampanel group occurred for high ALT (2.3% single dose and 2.4% multiple dose) and bilirubin (4.5% multiple dose). However, as previously discussed, it does not appear that perampanel is associated with hepatotoxicity.

In the Epilepsy and Nonepilepsy all treated pools, PCS changes in chemistry parameters occurred in 1.5% or less. However, $\geq 2\%$ of perampanel subjects had PCS outliers of *high potassium*, *high CPK*, *low glucose*, high *glucose* (only in the Nonepilepsy pool) and *low sodium* (only in the epilepsy pool)

Creatine Phosphokinase (CPK) – As noted above, PCS changes in high CPK were observed in the Epilepsy Phase 2 DB pool, as well as shifts to high CPK in the Epilepsy Phase 2 DB pool, the Nonepilepsy DB pool, and the all treated pools (but not in the Epilepsy Phase 3 DB pool). However, in the Epilepsy DB pool, a lower percentage of perampanel subjects than placebo developed extremely high CPK values (3-5 X ULN or >5X ULN), and in the Nonepilepsy DB pool a similar percentage of perampanel and placebo subjects developed extremely high CPK values. In both pools, a similar percentage of perampanel and placebo subjects experienced TEAEs in the SMQ Rhabdomyolysis and Myopathy, and there was only 1 subject coded to the PT rhabdomyolysis in the entire safety database (and that case was most likely due to immobility due to a “frozen state”). I agree with Dr. Doi that perampanel does not appear to be associated with significant elevations in creatine phosphokinase in this database.

Hyponatremia – As noted above, PCS outliers of low sodium (2.4%) were noted in the epilepsy all treated pool (but not any other pool). The Sponsor performed an analysis of PCS sodium values (< 130 mmol/L and < 125 mmol/L), shifts to low values, and consecutively low sodium values in the Epilepsy Phase 3 DB Pool, the Epilepsy Phase 2 DB Pool, and the Nonepilepsy DB pool. Dr. Doi notes that there were only 4 subjects (all perampanel subjects) in these pools with sodium < 125 mmol/L. She notes that these subjects were on concomitant therapy known to cause hyponatremia (either carbamazepine or oxcarbazepine) except for the 1 subject in the Nonepilepsy DB pool. In the Epilepsy all treated pool, there were 36 perampanel subjects (2.4%) who developed sodium values < 130 mmol/L, but only 8 (0.5%) who developed sodium values < 125 mmol/L. There were 3 subjects in the entire safety population with SAEs of hyponatremia; all were in the epilepsy studies and concomitantly on oxcarbazepine or carbamazepine. I agree with Dr. Doi that it is difficult to ascertain a causal role of perampanel for hyponatremia.

Hyperkalemia – As noted above, PCS changes for high potassium (> 5.5 mmol/L) were observed in all pools, shifts for high potassium occurred in the Epilepsy Phase 2 DB pool, and $\geq 2\%$ of perampanel subjects had PCS outliers of high potassium in the all treated pools. In the epilepsy population, the elevated values were mostly between 5.5-5.9 mmol/L (n=114) and 6.0-6.4 mmol/L (n=12). There were 12 values between 6.5-8.5

mmol/L but these were either elevated at baseline or screening, 30 days after the last dose or on study days > 300 days. Although a higher percentage of perampanel subjects than placebo developed markedly abnormal high potassium values in all of the double blind pools, in the epilepsy studies there was no dose response observed and very few subjects (n=3) developed high values on 2 or more consecutive visits. Dr. Doi notes that there were no SAEs or discontinuations due to hyperkalemia in the entire safety database. I agree with Dr. Doi that perampanel dose not appear to be associated with hyperkalemia in this database.

Hypocalcemia – A signal for low calcium (either PCS low calcium or shifts to low calcium) was not replicated in all databases. There were no SAEs or discontinuations due to hypocalcaemia in the entire safety database. There does not appear to be a signal for hypocalcemia in this database.

Hypoglycemia – A higher percentage of perampanel subjects than placebo developed PCS low glucose in the Epilepsy Phase 3 DB pool. Dr. Doi finds that 88% were single, nonconsecutive low values with subsequent normal values while continuing on perampanel; none were above toxicity Grade 2. One perampanel subject had a history of diabetes mellitus. This signal was not replicated in the other DB pools and there were no SAEs of hypoglycemia in the epilepsy studies. In the Nonepilepsy studies, there was 1 hypoglycemia SAE in a subject with a history of Type 1 diabetes when the subject was “sick with a cold” and had blood glucose fluctuations. It does not appear that there is a strong association of perampanel with clinically important hypoglycemia.

Urinalysis – Dr. Doi reports that in the Epilepsy Phase 3 DB pool, shifts from normal at baseline to abnormal for urine parameters (pH and specific gravity) were infrequent and occurred at similar frequencies between perampanel and placebo groups. The shift from normal to high for urine protein was slightly higher for perampanel (8.5%) vs placebo (7.2%), but no dose response relationship was observed. Mean changes from baseline to final for pH and specific gravity were similar for perampanel and placebo subjects.

2.3.8 Vital Signs

Effects of perampanel on weight, along with other metabolic parameters were discussed in section 7.3.4.3 of Dr. Doi’s review and previously in my memo.

In the Epilepsy Phase 3 pool, similar percentages of perampanel and placebo subjects had clinically notable values and changes relative to baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR). In the Epilepsy Phase 2 DB pool, higher percentages of perampanel subjects than placebo had both increases and decreases in SBP and in DBP. Mean changes from baseline to end of treatment for SBP, DBP, and HR were within the normal range at baseline and end of treatment in all groups. Alost all of the mean changes were small and clinically insignificant, except for some of the dose groups in the Epilepsy Phase 2 DB pool with larger increases in HR and BP. However, Dr. Doi notes that the baseline values for SBP and DBP in Study

203 were lower than the values measured at screening, and if the screening values, and that if the screening values had been used, the mean changes observed in the < 4 mg dose group would be negligible. Similarly, the 38 subjects in the > 8-12 mg dose group came from Study 208, in which the baseline values for BP and HR were lower than the values measured in the screening period, so that if the screening values had been used, the mean changes in SBP and HR would have been smaller (0.8 mm Hg vs 2.8 mm Hg and 1.0 bpm vs 2.0 bpm). From this analysis of SBP, DBP, and Heart rate, there seems to be little effect of perampanel, although as discussed under “Metabolic effects”, a shift toward high blood pressure categories observed in the perampanel group vs placebo in the epilepsy Phase 3 DB pool, most evident in shifts from normal (< 120/80 mmHg) to Stage 2 hypertension ($\geq 160/100$ mm Hg).

Orthostatic Changes – Vital signs were measured in both supine and standing positions in the epilepsy Phase 2 studies and Nonepilepsy studies. The mean changes from baseline to end of treatment for orthostatic vital signs were similar in the placebo group and the total perampanel group. In the epilepsy Phase 2 DB pool and the Nonepilepsy DB pool, the incidences of concurrent orthostatic vital sign changes (SBP decrement ≥ 20 mm Hg or ≥ 40 mm Hg concurrently with HR increase of ≥ 15 or ≥ 30) were similar in the placebo and perampanel groups, as shown in Table 146, p. 197 of Dr. Doi’s review.

No TEAEs related to orthostatic changes were reported in any epilepsy study. In Nonepilepsy DB studies, a similar percentage of perampanel subjects (1.6%) reported orthostatic hypotension TEAEs compared with placebo subjects (1.5%). There was 1 orthostatic hypotension SAE in the total perampanel group that occurred after 82 days of 2 mg perampanel exposure; the event resolved the next day and the subject was continued on perampanel for another 4 months without recurrence. A lower percentage of perampanel subjects discontinued due to orthostatic hypotension than placebo (0.1% vs 0.2%).

In Phase 1 single dose studies, perampanel subjects had a lower incidence of concurrent orthostatic vital sign measurements than placebo. In multiple dose studies, perampanel subjects had lower (or similar incidence) of concurrent orthostatic vital sign measurements than placebo. In single dose studies, 1 orthostatic hypotension TEAE occurred in the perampanel group (vs 0 placebo) and in multiple dose studies a similar percentage of perampanel subjects reported such TEAEs compared with placebo (2.9% vs 2.6%). There were no SAEs or discontinuations due to orthostatic hypotension in these studies. Dr. Doi notes 2 potentially clinically significant AEs were reported following administration of 2 mg perampanel in Study 001, and although the timing corresponded to perampanel exposure, she proposes that the events could have been vasovagal episodes (possibly due to study measurements such as blood draws, but such potential causes were not identified in the narratives). In 1 case the subject reported dizziness when standing up at 4 hours for measurement of standing blood pressure with no loss of consciousness; he was laid flat and his BP was recorded as 85/28 mm Hg and pulse 66 bpm; he made a rapid recovery. The second case was a subject who became pale, bradycardic (sinus bradycardia with 1st degree AV block, pulse 35 bpm, and BP 86/31 mm Hg) at 30 minutes post-dose. At 1 hour post-dose, HR

decreased when he sat up and blood pressure remained low (89/44 mm Hg). Vital signs gradually improved with complete resolution by 4 hours.

There does not appear to be a signal for orthostatic hypotension.

2.3.9 Electrocardiograms

ECG data come from the thorough QT trial Study 013 and from ECGs performed during the epilepsy, Nonepilepsy, and Phase 1 trials. The FDA QT IRT reviewed the results of Stud 013 in a review dated December 6, 2011 and reported no significant QTc prolongation effect of perampanel 6 mg and 12 mg from the TQT study, in an assay that was sensitive based on moxifloxacin effect. However, the IRT noted that the 12 mg dose would not cover predicted exposures for subject with mild or moderate hepatic impairment receiving ≥ 6 mg/day. The IRT has recommended labeling language.

The relationship between perampanel plasma concentrations and QT interval duration was evaluated based on the epilepsy Phase 3 DB pool and the results, shown on p. 200 of Dr. Doi's review do not suggest a relationship between placebo-corrected QTcF and perampanel concentration. In the epilepsy studies, no subject had a maximum QTcF of > 500 msec, and the percentages of subjects with QTcF > 450 msec or an increase of 30-60 msec were similar (or less) with perampanel than with placebo. Percentages of subjects with QTcF increases from baseline of > 60 msec were $< 1\%$ for perampanel, and comparable with placebo. Mean changes in the Epilepsy DB pools for ECG parameters (QT, HR, PR, QRS, RR) were small and of unknown clinical significance. In the Nonepilepsy DB studies, ECGs were not performed in all of the studies, but in those studies with ECG data outlier analysis was similar in perampanel and placebo. In Phase 1 studies with ECG data, no subject had a maximum QTcF > 500 msec. In single dose studies, a maximum QTc F > 450 occurred in fewer perampanel than placebo subjects, and no subject had an increase in QTcF > 60 msec, although placebo subjects had fewer QTcF increases of 30-60 msec than perampanel subjects (4.5% vs 8.4%). In multiple dose Phase 1 studies, 1 perampanel subject had maximum QTcF > 450 and QTcF increase > 60 msec (vs 0 placebo). Perampanel subjects had fewer QTcF increases of 30-60 msec than placebo.

In general, incidences of shifts in ECG interpretation and incidences of treatment emergent ECG abnormalities (regardless of baseline ECG) were less in the perampanel group than in the placebo group (or similar to placebo), except for *sinus bradycardia* that occurred slightly more in perampanel vs placebo (28.1% vs 26.5%) in the Phase 3 pool and to a greater extent (50.4% vs 38.7%) in the Phase 2 pool. For details, please refer to table 149 on page 202 of Dr. Doi's review. In the Nonepilepsy DB pool the incidences of shifts in ECG interpretation and abnormal ECGs were similar in placebo and perampanel. In Phase 1 studies, the Sponsor reported that all of the placebo and perampanel subjects had interpretations of "no clinically significant abnormalities" both at baseline and end of study. Sinus tachycardia was detected in 3.4% of ECGs in perampanel (0 in placebo) in the multiple dose studies and not detected in the single dose studies. In the single dose studies, bradycardia was more likely to be detected in the perampanel group vs placebo (87.5% vs 71.9%), and this was not the case with the

multiple dose studies where bradycardia was less in perampanel vs placebo (74.4% vs 80.8%). First degree AV block was detected in slightly more ECGs in the perampanel group than placebo in both the single dose (9.9% vs 9.0%) and multiple dose studies (10.3% vs 7.7%). Intraventricular block was detected only in the perampanel group (1% of single dose and 3.4% of multiple dose).

I agree with Dr. Di that there is no evidence of QT prolongation with perampanel. Based on these results and the results reviewed in Section 2.3.5 (p. 26) of this memo, it does not appear that there is a signal for cardiac findings from perampanel.

2.3.10 Dose-Dependency for Adverse Events

Dr. Doi notes that generally there was a dose response observed for safety issues. Dr. Doi notes the difficulties in interpreting dose response in the controlled trials given that the subjects were titrated to the target dose and any AE occurring during titration may have occurred at a dose lower than the final target dose. I agree that differences in the safety profile among dose groups may reflect differences in the demographics of the studies that the dose groups represent.

Dr. Doi notes that the randomized, double-blind placebo controlled Study 218 in neuropathic pain investigated different titration intervals for perampanel. Up-titration in the perampanel arm in Cohort 1 occurred at 3-week intervals, where as in Cohort 2 it occurred at 1-week or 2-week intervals. The 1 week titration group had the highest incidence of neurologic-related TEAEs of dizziness, fall, gait disturbance, vision blurred, fatigue, dysarthria, balance disorder, headache, and confusional state. Study related TEAEs and withdrawals due to TEAEs were also most common in the 1 week titration group. The safety profiles in the 2-week and 3-week titration groups were similar to each other. Please refer to Table 150 on p. 204 of Dr. Doi's review for a comparison. Dr. Doi recommends for subgroups at higher risk for neurologic related AEs, a slower titration interval should be recommended. I agree that this should be considered, particularly for the elderly.

2.3.11 Time-Dependency for Adverse Events

Dr. Doi has reviewed distribution of TEAEs by time of onset in appropriate sections of her review. For 21 commonly occurring TEAEs in the epilepsy all treated pool the sponsor has analyzed the time to first occurrence, and find that for at least half of the subjects, the first occurrence was within 6 weeks of beginning treatment (dizziness, fatigue, gait disturbance, increased appetite, somnolence, vertigo, vision blurred), the first 10-14 weeks of treatment (anger, ataxia, balance disorder, confusional state, decreased appetite, dysarthria, fall, irritability, nausea), the first 18-20 weeks of treatment (aggression, diplopia, weight increased), or after 6 months or more (anxiety, back pain). Subjects continued to have first occurrences of all ADRs during treatment.

2.3.12 Drug Interactions

Drug-Demographic Interactions – Dr. Doi notes that a total of 104 pediatric subjects (12 to ≤ 16 y.o. were exposed to perampanel in the epilepsy clinical trial development

program. She believes that this NDA did not provide enough information regarding the safety profile of perampanel in adolescent subjects. She notes that the Sponsor has recently initiated Study 235, a randomized, double-blind, placebo controlled study of the effects of adjunctive therapy with perampanel on cognition growth, safety, tolerability, and PK in adolescents (12 to 18 y.o.). The enrolment goal is 132 subjects and as of October 1, 2011, 39 subjects had been enrolled. Five SAEs have been reported (including increased aggressive behavior in a perampanel subject). Dr. Doi recommends waiting until the results of Study 235 are available before approving perampanel for use in adolescent pediatric subjects. Because of the concern of aggression, I agree that this approach should be considered.

Geriatric subjects - Dr. Doi notes that the sponsor reports no significant effect of age on perampanel clearance based on a population PK analysis of patients ranging in age from 12 to 74 years. She notes that the number of elderly patients in the NDA is small: 32 subjects in phase 1 studies (age range 65-79 y.o.) and 31 subjects in the epilepsy Phase 2/3 DB studies. (The Nonepilepsy studies included 1209 elderly subjects, although these subjects were given lower doses than for the epilepsy studies). Dr. Doi notes that in the epilepsy studies, elderly subjects had lower duration of exposure at higher doses. She also notes that the safety profile of elderly subjects was different from adult subjects. Elderly subjects in the epilepsy Phase 3 DB pool had a higher rate of discontinuation in the perampanel group (28.6%, 8/28) than placebo (0/8), with most discontinuing to AEs (4) and subject choice (3), while the overall incidences of discontinuations in the pool were 14.6% and 11.3%, respectively. She discusses age related neurologic concerns on pp. 118-119 of her review and finds that the elderly population is at the highest risk compared to adults < 65 y.o. and adolescents for dizziness/coordination group terms and somnolence/fatigue group terms that occurred in 55% and 35% of the elderly, respectively, and in no elderly placebo patients. I agree with Dr. Doi's concern in elderly subjects. She recommends a slower titration (than the recommended weekly titration) in elderly patients and although this has not been evaluated specifically in the elderly, it is reasonable to consider.

Sex – Dr. Doi refers to the Clinical Pharmacology review for analyses of sex differences in pharmacokinetics in which either small decreases (< 20%) or no change in clearance was found in females on average, although outliers have not been discussed. Differences between males and females especially with respect to aggression are discussed on pp. 105-106 of Dr. Doi's review and earlier in my memo.

Race – Dr. Doi notes that the sponsor reports no significant effect of race on perampanel clearance. In the epilepsy Phase 3 DB pool and Nonepilepsy pool, the subjects were predominantly white (75% and 92%, respectively) and I agree with Dr. Doi that with small sample sizes in other racial groups (Asians and Blacks < 10%), it is difficult to make conclusions regarding racial differences in the safety profile.

Drug-disease interactions (hepatic impairment and renal impairment) were evaluated in Clinical Pharmacology studies. These are summarized in Dr. Doi's review. Please refer to p. 207 of her review and to the Clinical Pharmacology review for details. Of note,

because of the longer half-life in mild and moderate hepatic impairment compared to healthy subjects, the Sponsor recommends that dose increases should occur no more frequently than every 2 weeks in that population, compared to the recommendation of dose titration weekly in patients without hepatic impairment.

Drug-Drug Interactions were evaluated in *in vitro* studies, studies in healthy volunteers, and in a population PK analysis based on the pooled Phase 3 DB studies. Please refer to Dr. Doi's summary of the findings on p. 208 of her review. Of note, the clearance of perampanel is increased 2-3 fold by CYP3A inducers. Also of note, dosing was not stratified in the clinical studies based on exposure to enzyme inducers or non-inducers. In studies 304 +304 combined, as previously noted, more than half of the subjects were taking an enzyme inducing AED concomitantly. SAEs and discontinuations for patients on non-enzyme inducing AEDs were approximately 2x the rate in patients on enzyme inducing AEDs at the 12 mg dose.¹⁸ The broad hostility SMQ as well as the modified hostility SMQ had 2x and 1.7x, respectively, greater rates in subjects on nonenzyme inducing AEDs than in patients on enzyme inducing AEDs, and although there little difference for patients taking placebo, these findings may be confounded by the presence of non-inducing AEDs that may contribute to these events. It would be useful to know to what perampanel is metabolized in the presence of inducers, and whether the metabolite is active with respect to either efficacy or safety.

2.3.13 Human Carcinogenicity

Dr. Doi's evaluation of deaths, serious AEs, discontinuations due to AE and common AEs under the MedDRA SCO Neoplasm benign, malignant, and unspecified (including cysts and polyps) in the perampanel clinical program did not suggest an increased risk of malignancy in subjects taking perampanel.

In the Phase 2/3 DB studies, none of the perampanel subjects developed malignant neoplasm (1 benign lung neoplasm and 1 lipoma). Dr. Doi's discussion focuses on the all treated groups and this seems appropriate due to the longer duration of exposure. In the epilepsy all treated pool, there were benign conditions (3 lipoma, 3 uterine leiomyoma, 2 skin papilloma, 1 acrochordon (skin tag), 1 benign breast neoplasm, 1 benign lung neoplasm) as well as breast cancer (1), breast cancer in situ(1), breast cancer metastatic(1), breast cancer recurrent(1), colon cancer (1), colon neoplasm/hepatic neoplasm (1), prostate cancer (1), thyroid cancer (1), and thyroid neoplasm (1), glioma (1) and 1 case of malignant melanoma. Eleven were SAEs, and of those, benign lung neoplasm occurred early (DB day 12) as did uterine leiomyoma (Day 80), but the others without a previous history occurred more than 1 year into treatment. In the absence of a control group, it is difficult to determine the role of perampanel.¹⁹

¹⁸ Email from Dr. Doi on 9/7/12.

¹⁹ In the epilepsy (n=1651) and nonepilepsy (n=2717) all treated pools, after excluding the 1 perampanel subject with recurrent breast cancer, there was 1 (0.023%) perampanel subject (52 yo WF) with breast cancer in situ (vs 0.071% SEER for breast cancer in situ for 50-54 year old white females). There were 2 (0.046%) perampanel subjects (45 yo and 60 yo WF) with breast cancer metastatic and breast cancer, respectively (vs 0.19% SEER for breast cancer for 45-49 yo WF or 0.37% for 60-64 yo WF).

In the Nonepilepsy DB studies, the only neoplasm that occurred in 2 or more subjects and greater than placebo was basal cell carcinoma. In the Nonepilepsy OLE studies, the following additional neoplasm were reported in perampanel subjects: metastatic bronchial carcinoma (1), lung neoplasm (1), lung neoplasm malignant (2), breast cancer (1), thyroid neoplasm (1), colon cancer (1), rectal cancer (1), pancreatic cancer (1), gastric neoplasm (1), endometrial cancer (1), uterine cancer (1), prostate cancer (1), squamous cell carcinomas (4), adenocarcinoma (1), chondrosarcoma (1), basal cell carcinomas (10), lentigo maligna stage unspecified (1), malignant melanoma (2), both subjects newly diagnosed (Day 33 and Day 96), malignant melanoma in situ (2), one subject with history of melanoma and one subject newly diagnosed on Day 69, melanoma recurrent (1) in a subject with history of melanoma.

I agree that the assessment of a relationship between perampanel exposure and neoplasms is difficult. Dr. Doi suggests that the higher number of neoplasms in the Nonepilepsy all treated pool (0.7 per 1000 subject-weeks) than in the Nonepilepsy all treated pool (0.2 per 1000 subject weeks) is expected due to the older population, and that the number and types of neoplasm is similar to what is expected in that population. She notes that the 4 cases of lung neoplasm in the Nonepilepsy population are consistent with the background rate. She notes that there is 1 case of malignant melanoma in the epilepsy population (in a 49 y.o. white male without a prior history of melanoma and after 4.7 years of perampanel exposure) and 5 in the Nonepilepsy population (2 with a prior history, and 3 diagnosed within 3 months of initiation of perampanel that is likely to be too soon for carcinogenicity due to perampanel). According to SEER, the incidence of melanoma of the skin in a cohort of white, males, 45-49 y.o. is 27.9 per 100,000 subjects. In the epilepsy population in this database, the incidence rate of melanoma is 60.6 per 100,000 subjects (1/1651), twice the SEER rate. I agree that with only 1 case in the epilepsy population, it is difficult to distinguish a drug-related effect from chance alone. Melanoma should be followed in post-marketing surveillance.

2.3.14 Human Reproduction and Pregnancy Data

Dr. Doi notes that the Sponsor proposes classification as Pregnancy Category C as reproductive toxicity studies demonstrate adverse effects on fetal development but there are no data from adequate and well controlled trials in humans or reliable post-marketing data that allow evaluation of effects on reproduction and fetal development.

As of the cutoff date for the 120 day Safety Update, there were a total of 16 pregnancies in 14 subjects in the entire dataset, all on perampanel. Fourteen of the pregnancies were in OLE studies. The 16 pregnancies resulted in the following outcomes: 8 induced abortions, 4 spontaneous abortions, 2 healthy births (with no congenital abnormalities reported), 1 neonatal death (neonatal aspiration of fluid during birth), and 1 ongoing. In the cases of the spontaneous abortions, 2 were taking known teratogenic drugs (carbamazepine or valproic acid) and 1 was taking oxcarbazepine. I agree with Dr Doi that the assessment of the causal relationship between perampanel exposure and spontaneous abortions is difficult, particularly in absence of a control group.

2.3.15 Pediatrics and Assessment of Effects on Growth

As previously noted, the effect of perampanel on growth and development parameters in pediatric subjects is under ongoing evaluation in Study 235. Dr. Doi also mentions Study 307, the OLE of Studies 304, 305, and 306 in subjects aged 12 years and older.

2.3.16 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Sponsor reported no fatal overdoses. Dr. Doi notes that the AE most frequently associated with overdose was dizziness, reported as an overdose-associated TEAE in 8 (0.8%) of the 1038 subjects who received perampanel in the epilepsy Phase 3 DB pool. Other over-dose associated TEAEs reported for more than 1 subject were nausea (n=3), somnolence (n=2), vomiting (n=2), and accidental overdose (n=2). In the Phase 3 OLE study, the event most frequently associated with overdose was dizziness.

2.3.17 Postmarket Experience

The European Commission issued marketing authorization for the use of Fycompa in July 2012. Postmarketing data from Europe was not available for FDA review during the review of this NDA.

2.3.18 Summary of Significant Safety Concerns:

Dr. Doi has not identified safety issues that would preclude the approval of perampanel. *I agree with her assessment.*

Among the primary safety concerns identified in her review are severe psychiatric events (hostility and aggression), dizziness and coordination, somnolence and fatigue, falls and injuries, and metabolic effects (increases in weight, total cholesterol, and blood pressure).

The rate of titration may be important in the appearance of AEs, and I agree that labeling recommending slower titration than the weekly proposed schedule should be considered in the elderly.

Dr. Doi recommends that approval in the pediatric population be postponed pending completion and review of the ongoing trials in pediatrics that will provide more information on safety and PK in 132 adolescents. Based on the risk for hostility and aggression, and the small number of pediatric subjects in each dose group, I agree that this should be considered.

2.3.19 Postmarketing Risk Management Plan

A REMS has not been proposed by the Sponsor and I agree that a REMS is not necessary. Dr. Doi does not recommend any postmarketing requirements, and I agree. She does recommend postmarketing surveillance for cholelithiasis/choledocholithiasis and for tendon/ligament ruptures.

2.3.20 Conclusions

Safety Team Leader Memo
NDA 202834

Dr. Doi has reviewed the safety issues associated with perampanel use. There are no safety issues that would preclude approval. I agree with her assessment. She will recommend some modifications to the labeling.

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

/s/

SALLY U YASUDA
10/01/2012

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202-834
Priority or Standard	Standard
Submit Date(s)	December 22, 2011
Received Date(s)	December 22, 2011
PDUFA Goal Date	October 22, 2012
Division / Office	Division of Neurology Products Office of New Drugs
Reviewer Name(s)	Mary Doi, M.D., M.S.
Review Completion Date	August 22, 2012
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 partial-onset seizures with or without secondary generalization
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 NDA 202-834 (perampanel) as of August 22, 2012. The efficacy of perampanel in the adjunctive therapy of partial-onset seizures with or without secondary generalization is being reviewed by Dr. Martin Rusinowitz. Final recommendations on approval of this application will be provided by Drs. Rusinowitz (primary reviewer) and Hershkowitz (CDTL).

1.2 Risk Benefit Assessment

There are many FDA-approved medications for partial-onset seizures with or without secondary generalization, but none of these treatments are completely efficacious in all patients. In addition, the adverse reactions (hepatic, hematologic, dermatologic, teratogenic, etc.) of these approved treatments can limit their use. For these reasons, additional treatments are needed for partial-onset seizures.

An important consideration in the evaluation of this drug is that it is a first in class molecule that targets the AMPA receptors among other yet unknown functions. It is anticipated that toxicities that have not been observed in the premarketing database might be identified once the drug is used in the postmarketing setting, particularly in patients who are not as healthy as those included in the clinical trials.

Several safety issues have been identified in this application with evidence of a dose response between perampanel 2 mg and 12 mg daily. Given the need for additional efficacious therapies for this devastating disease, the safety of perampanel appears to be acceptable once safety concerns are mitigated by the strategies outlined below.

If approved, perampanel should be recommended for doses from 4 mg/day to 8 mg/day and only in adults (patients >16 years old).

Furthermore, I recommend that the following information be incorporated into the prescribing information for perampanel:

- Boxed Warning for Severe Neuropsychiatric Events (Hostility and Aggression)
- Indications and Usage: Adult patients with epilepsy (>16 years old)
- Warnings and Precautions for the following serious adverse reactions:
 - Dizziness and Coordination
 - Somnolence and Fatigue
 - Falls and Injuries
 - Metabolic Effects (increases in weight, total cholesterol, blood pressure)

- Dosage and Administration:
 - Maximum recommended daily dose is 8 mg
 - Slower titration for elderly subjects (with dosage increases no more frequently than every two weeks)
- Medication Guide because of the Suicidality warning required by the Division for all antiepileptic medications

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommendations for any postmarket requirements or commitments. Postmarketing surveillance is recommended for cholelithiasis/choledocholithiasis and tendon/ligament ruptures.

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)benzotrile. The Sponsor 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.

Clinical trials using perampanel have also been performed for other patient populations such as patients with Parkinson's disease, multiple sclerosis, migraine, and neuropathic pain.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are many currently available drugs approved for the adjunctive therapy of partial-onset seizures with or without secondary generalization. Please see the list provided in the efficacy review performed by Dr. Rusinowitz.

2.3 Availability of Proposed Active Ingredient in the United States

None.

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 selective AMPA antagonist is currently approved for any indication.

A literature review identified several publications discussing the safety profile of other AMPA receptor antagonists. The AMPA receptor antagonist, NS1209, when given as an intravenous treatment for chronic neuropathic pain reportedly had the adverse events of headache, dizziness, somnolence, fatigue, feeling abnormal, dry mouth, and nausea which were experienced slightly more frequently in the NS1209 group than placebo.¹

The most frequent reported adverse events with another AMPA receptor antagonist, talampanel (LK300164), were dizziness, unsteadiness, headache, ataxia, urinary tract infection, drowsiness, fall, and slurred speech.² Another study that investigated the use of talampanel in amyotrophic lateral sclerosis (ALS) patients reported mortality rates in talampanel subjects of 8% and placebo of 5%.³ Dizziness and somnolence occurred more frequently in talampanel subjects than placebo subjects.

A Phase 2 study using intravenous ZK200775, another AMPA receptor antagonist, for neuroprotection in acute ischemic stroke was stopped prematurely for safety reasons (severe reduction in level of consciousness).⁴

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The original IND for perampanel (IND 68,368) for the treatment of refractory partial onset epilepsy was opened on October 7, 2003. (b) (4)



On May 25, 2011, Eisai, Inc. submitted a New Drug Application (NDA 202-534) for perampanel to the FDA for the proposed indication of adjunctive treatment of patients

1 Gormsen L, et al. The Efficacy of the AMPA Receptor Antagonist NS1209 and Lidocaine in Nerve Injury Pain: A Randomized, Double-Blind, Placebo-Controlled, Three-Way Crossover Study. *Anesth Analg*, 2009; 108: 1311-9.

2 Langan YM, et al. Talampanel, a New Antiepileptic Drug: Single- and Multiple-dose Pharmacokinetics and Initial 1-Week Experience in Patients with Chronic Intractable Epilepsy. *Epilepsia*. 2003; 44(1): 46-53.

3 Pascuzzi RM et al. A Phase II Trial of Talampanel in Subjects with Amyotrophic Lateral Sclerosis. *Amyotrophic Lateral Sclerosis*. 2010; 11: 266-271.

4 Walters MR et al. The AMPA Antagonist ZK 200775 in Patients with Acute Ischaemic Stroke: A Double-Blind, Multicentre, Placebo-Controlled Safety and Tolerability Study. *Cerebrovasc Dis*. 2005; 20: 304-309.

with partial-onset epilepsy. Eisai received a Refuse to File (RTF) letter for NDA 202-534 from the FDA on July 21, 2011 primarily due to missing safety datasets and analyses (21 CFR § 314.50 (d)(5)(vi)(a)). On September 26, 2011, Eisai and the Division met to discuss a plan to address the deficiencies outlined in the RTF letter. The NDA application was resubmitted on December 22, 2011 for the same proposed indication. The new PDUFA goal date is October 22, 2012.

2.6 Other Relevant Background Information

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

Overall, the submission was acceptable for review. However, on inspection of the case report forms, there were many discrepancies between the CRFs and other portions of the NDA (narratives and integrated summary of safety, ISS). In response to the Division's information request, the Sponsor stated that there were "CRF pages that were inadvertently excluded from the published CRF in the NDA." Additionally, some of the SAE narratives only included information regarding other AEs and not the events surrounding the actual SAE. The Sponsor stated that these narratives that had been updated for the NDA resubmission were "inadvertently not included" in the respective Clinical Study Report Addendums. Furthermore, some analyses for a few of the laboratory parameters were not included in the ISS (lactate dehydrogenase, creatine kinase, magnesium, and urinalysis results). Finally, some pregnancies were not included in ISS Section 15, Effects During Pregnancy. The Sponsor stated that these pregnancies were "inadvertently missed in the manual tabulation provided in the original table."

3.2 Compliance with Good Clinical Practices

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

3.3 Financial Disclosures

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

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The reader is referred to the Chemistry, Manufacturing and Controls (CMC) review.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

The reader is referred to the Pharmacology/Toxicology review by Dr. Toscano.

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 in the clinical overview and from the proposed Prescribing Information.

The proposed dose is 4-12 mg per day, given as a single daily dose before bedtime in patients aged 12 years and older. The sponsor proposes treatment initiation with a dose of 2 mg/day, increasing in increments of 2 mg/day at intervals no more frequently than weekly.

4.4.1 Mechanism of Action

Please see Section 2.1 of this review.

4.4.2 Pharmacodynamics

From the pharmacodynamic analysis based on the pooled data from the 3 efficacy trials for partial-onset seizures, perampanel exposure has been correlated with efficacy in the reduction of seizure frequency.

Other important pharmacodynamic findings are as follows:

- Impairment in psychomotor performance with single and multiple doses of 8 mg and 12 mg with performance testing returning to baseline within 2 weeks of cessation of perampanel dosing.
- Impairment of car handling ability after doses of 12 mg.

- No impairment of psychomotor tasks, driving performance or sensori-motor coordination with single and multiple daily doses of 4 mg.
- Impairment of psychomotor performance after single doses of 4 to 12 mg, and after 21 days of multiple 12 mg/day doses when administered to healthy subjects receiving alcohol to achieve a blood concentration of 80-100mg/100mL.
- Additive or supra-additive effects on complex tasks (such as driving ability) to the impairment effects of alcohol.
- Decreases in levels of alertness in healthy subjects dosed from 4 to 12 mg/day.
- Small decreases in mood following dosing of only 12 mg/day.
- Enhancements in the effects of alcohol on vigilance and alertness, and increases in the levels of anger, confusion, and depression with multiple dosing of 12 mg/day.
- Increases in the occurrence of the adverse events of fatigue, somnolence, gait disturbances, dizziness, weight increase, irritability, dysarthria, and euphoric mood with increasing average plasma concentration of perampanel.
- No effects on cognitive function following single and multiple doses up to 12 mg/day in healthy subjects.
- No prolongations of the QTc interval (or effects on QRS duration) with daily doses of up to 12 mg/day administered for 7 days in a double-blind, randomized, placebo- and moxifloxacin-controlled clinical pharmacology trial in healthy subjects.

4.4.3 Pharmacokinetics

Absorption

Following oral administration of perampanel, perampanel is rapidly and completely absorbed (absolute bioavailability approximately 100%). Mean time of maximum concentration (t_{max}) ranged from 0.5 to 4.0 hours. When administered with food, the peak plasma concentrations of perampanel were reduced and delayed by 2 hours, while the extent of absorption was not affected.

Dose Proportionality

In healthy subjects, plasma concentrations of perampanel increased in direct proportion to administered doses over the range of 2 to 12 mg. In a population PK analysis of patients with partial-onset seizures receiving perampanel up to 12 mg/day, a linear relationship was found between dose and perampanel plasma concentrations.

Distribution

In vitro studies show that perampanel is approximately 95% bound to plasma proteins. Steady state was typically achieved by Day 14 of repeated dosing in healthy subjects and Day 21 of dosing in patients. Drug accumulation was evident with repeated administration of perampanel. In studies of healthy subjects who received daily perampanel doses ranging from 1 mg to 6 mg, mean AUC accumulation ratios varied between 3.40 and 4.88.

Metabolism

Perampanel is metabolized via primary oxidation and sequential glucuronidation. Based on the results of *in vitro* studies, the primary oxidative metabolism is mediated by CYP3A4 and/or CYP3A5. Following administration of radiolabeled perampanel, most of the drug-related material in plasma is perampanel with only trace amounts of perampanel metabolites.

Elimination

In a population PK analysis of pooled data (19 Phase 1 studies), the mean half-life ($t_{1/2}$) of perampanel was 105 hours (longer in patients with mild or moderate hepatic impairment). In clinical studies, CYP3A4 inducers carbamazepine, oxcarbazepine, and phenytoin caused large and statistically significant increases in perampanel clearance. Renal clearance is a minor route of elimination of perampanel. Following administration of a radiolabeled perampanel dose to 8 healthy elderly subjects, 30% of recovered radioactivity was found in the urine and 70% in the feces.

5 Sources of Clinical Data

NDA 202-834 was submitted on December 22, 2011. 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 NDA 202-834 up to August 20, 2012.

Safety Information Amendments were submitted by the Sponsor on the following dates in 2012: February 6, March 23 and 30, April 20 and 30, May 10 and 21, June 7, July 5, 16, and 27, and August 6, 2012.

The integrated summary of safety (ISS) for perampanel includes data from 10 studies performed in the primary indication of epilepsy, 15 studies performed in other non-epilepsy indications (Parkinson's Disease, neuropathic pain, migraine, and multiple sclerosis), and 27 Phase 1 studies.

5.1 Tables of Studies/Clinical Trials

The three tables in Appendix 1 list all of the completed and ongoing studies (both double-blind, randomized, placebo-controlled and open-label extension studies) in the epilepsy population (Table 155), the DB and OLE studies in the non-epilepsy population (Table 156), and the Phase 1 studies in healthy volunteers (Table 157).

5.2 Review Strategy

This review focuses on the safety of oral perampanel in the epilepsy population, non-epilepsy population (Parkinson's disease, migraine, multiple sclerosis, and neuropathic pain), and clinical pharmacology studies. Safety will be presented for Deaths, Serious

AEs, Discontinuations due to AEs, AEs of interest, common AEs, laboratory and ECG evaluations, and vital signs. The efficacy of oral perampanel as adjunctive therapy in the treatment of partial-onset seizures was evaluated by Dr. Rusinowitz.

5.3 Discussion of Individual Studies/Clinical Trials

The detailed characteristics of the studies have been presented in the tables in Appendix 1 of this review. A summary of the studies is provided below.

The epilepsy development program included the following studies (Table 1):

- Three double-blind (DB), Phase 3 studies:
 - Studies 304, 305, and 306 conducted globally to investigate the efficacy, safety, and tolerability of a range of doses of perampanel (2, 4, 8, and 12 mg) given as adjunctive treatment to subjects 12 years or older with partial-onset seizures.
- Five Phase 2 studies:
 - Study 203 (DB) to assess initial tolerability and PK in the target population
 - Study 206 (DB) to establish proof of concept and provide information on the dose regimen
 - Study 208 (DB) and Study 231 (OLE) to evaluate the safety and tolerability of doses up to 12 mg/day
 - Study 235 (DB) to evaluate effects on cognition, growth, safety, tolerability, and PK in adolescents (12 to <18 years of age). Of note, this study had limited enrollment at the time of this submission, and a report of this study was not included in the submission. However, deaths and SAEs as of January 15, 2012 were included in the 120-day Safety Update.
- Three open-label extension (OLE) studies for long-term safety and efficacy data:
 - Study 207 (OLE of Studies 206 and 208) in adult subjects
 - Study 233 (OLE of Study 231) in Japanese subjects 20 years or older
 - Study 307 (OLE of Studies 304, 305, and 306) utilized a blinded conversion period in subjects aged 12 years or older

The following studies evaluated perampanel for other indications:

- Parkinson's disease:
 - 7 double-blind studies (202, 204, 214, 226, 301, 302, 309).
 - 4 OLE studies (205, 220, 303, 318).
 - Of note, the single subject who participated in Study 226 before it was terminated was not included in the ISS.
- Neuropathic pain (diabetic or postherpetic neuropathy):
 - 2 double-blind studies (218, 227)
 - 1 OLE study (228)
- Multiple sclerosis: 1 double-blind study (201)
- Migraine headache: 1 double-blind study (210)

The following 27 Phase 1 studies evaluated single (0.2 to 36 mg) or multiple doses (1 to 12 mg) of perampanel administered to healthy male and female volunteers:

- Bioavailability and bioequivalence (Studies 003, 008, 016, 017, 037, 039, 040)
- PK and initial tolerability (Studies 001, 002, 010)
- Effects of intrinsic factors on PK (Studies 004, 007, 015, 026)
- Effects of extrinsic factors on PK (Studies 005, 006, 014, 019, 025, 029, 030)
- PK and PD (Studies 009, 013, 020, 023, 024)
- Relative bioavailability of a suspension formulation (Study 028)

Table 1. Summary of Epilepsy Studies

Study number (population)	Treatment duration	Treatment groups
Epilepsy double-blind placebo controlled short-term studies:		
G000-304 (Epilepsy – refractory partial seizures)	19 weeks (subjects will be up-titrated weekly in 2 mg increments to their randomized dose)	E2007 8 mg
		E2007 12 mg
		Placebo
G000-305 (Epilepsy – refractory partial seizures)	19 weeks (subjects will be up-titrated weekly in 2 mg increments to their randomized dose)	E2007 8 mg
		E2007 12 mg
		Placebo
G000-306 (Epilepsy – refractory partial seizures)	19 weeks (subjects will be up-titrated weekly in 2 mg increments to their randomized dose)	E2007 2 mg
		E2007 4 mg
		E2007 8 mg
		Placebo
Epilepsy double-blind placebo controlled short-term studies:		
E049-203 (Epilepsy - epileptic subjects with partial and generalized seizures)	4 weeks	E2007 1 mg
		E2007 2 mg
		Placebo
A001-206 (Epilepsy - refractory partial seizures)	14 weeks (dose will be increased every 2 weeks by 1 mg up to 4 mg/day or the MTD)	E2007 MTD up to 4 mg given BID
		E2007 MTD up to 4 mg given QD
		Placebo
G000-208 (Epilepsy - refractory partial seizures)	16 weeks (dose will be increased every 2 weeks by 2 mg up to 12 mg/day or the MTD)	E2007 MTD up to 12 mg
		Placebo
Epilepsy open-label uncontrolled short-term study:		
J081-231 (Epilepsy - refractory partial seizures)	10 weeks (dose will be increased every week by 2 mg up to 12 mg/day or the MTD)	E2007 MTD up to 12 mg
Epilepsy uncontrolled open-label long-term studies:		
A001-207 (Epilepsy - refractory partial seizures)	212 weeks (from 206) or 220 weeks (from 208) (dose will be increased every 2 weeks by 2 mg up to 12 mg/day or the MTD)	E2007 MTD up to 12 mg
J081-233 (Epilepsy - refractory partial seizures)	112 weeks (same dose as used in the maintenance period in study 231)	E2007 MTD up to 12 mg
G000-307 (Epilepsy - refractory partial seizures)	104 weeks (titration will be made based on previous dose in 2 mg increments up to 12 mg/day or MTD in the first 12+/-6 weeks conversion period)	E2007 MTD up to 12 mg

Source: Meeting package for request for pre-NDA meeting September 2, 2010 (page 6)

6 Review of Efficacy

The reader is referred to Dr. Martin Rusinowitz’s review of efficacy.

7 Review of Safety

Safety Summary

The perampanel NDA submission summarizes the safety data of 5284 perampanel-exposed subjects from 52 trials conducted in healthy volunteers (n=916), subjects with

partial-onset seizures (n=1651), and in subjects with nonepilepsy indications (n=2717) such as Parkinson's disease, neuropathic pain, multiple sclerosis, and migraine.

The Sponsor reported a total of 30 deaths in perampanel exposed subjects (8 deaths in the epilepsy studies and 22 deaths in the nonepilepsy studies). All of the epilepsy deaths occurred in open-label extension studies. The deaths that occurred in the nonepilepsy population occurred in both the double-blind studies (with a lower mortality rate in perampanel subjects than placebo) and open label extension trials. The deaths occurred in subjects with either significant comorbidities or underlying risk factors or were due to disparate events or lacked enough detail to make definitive conclusions regarding the causal role of perampanel.

The Sponsor proposed a Warnings and Precautions statement for the perampanel prescribing information for the following three adverse reactions:

- Suicidal Behavior and Ideation (as required by the Division for all antiepileptic medications)
- Dizziness and Somnolence
- Withdrawal of Antiepileptic Drugs

I have identified several areas of safety concerns with perampanel in this review (listed below). I recommend that these adverse reactions also be added to the prescribing information for perampanel. There was reasonable evidence of a causal association between perampanel and these adverse reactions (associated with a higher incidence in perampanel subjects than placebo with evidence of a dose response relationship). Furthermore, all of these safety issues resulted in serious (or otherwise clinically significant), life-threatening, or lethal outcomes.

- Hostility, aggression, and changes in mood, behavior, and personality
- Dizziness and coordination
- Somnolence and fatigue
- Falls and Injuries
- Metabolic effects (increases in weight, total cholesterol, blood pressure)

Additionally, there were other adverse effects of concern. I recommend postmarketing surveillance to further investigate the potential safety issue of tendon and ligament ruptures. For the potential safety issue of cholelithiasis and choledocholithiasis, I also recommend close monitoring in the postmarketing period.

Finally, there was no definitive evidence of any perampanel-related cases of blood dyscrasias, serious skin rashes, drug reaction with eosinophilia and systemic symptoms (DRESS), anaphylaxis, drug-induced liver injury, renal failure, or other laboratory abnormalities. Furthermore, a formal QT study did not find evidence of QT prolongation in subjects exposed to perampanel.

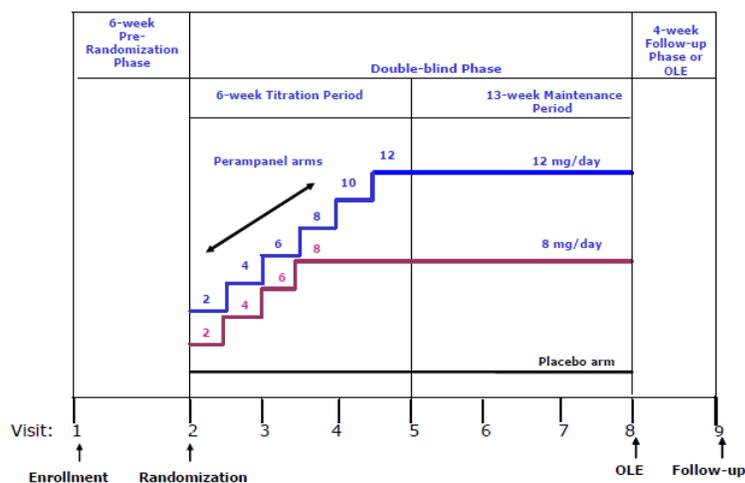
7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In their ISS, the Sponsor summarized safety data from 52 perampanel clinical trials (both completed and ongoing studies). The safety data from these trials were divided into the following categories: Phase I trials (n=27), Phase 2 DB studies (n=3), Phase 3 DB studies (n=3), epilepsy open-label studies (n=4), and nonepilepsy studies (n=15 for indications of Parkinson’s disease, neuropathic pain, migraine, and multiple sclerosis). These trials are described in Section 5.1 of this review and listed in Table 1 of the ISS (and in Appendix 1 of this review).

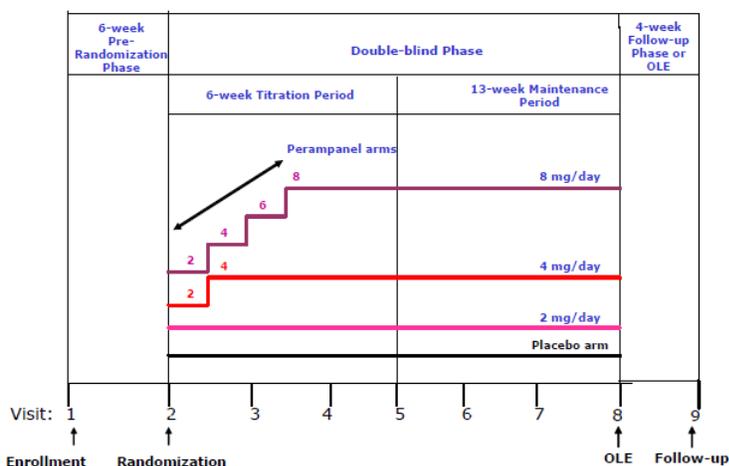
The focus of this safety review is pooled data from the three Phase 3 DB clinical trials performed in subjects with partial-onset seizures. Studies 304, 305, and 306 were randomized, double-blind, placebo-controlled, dose-escalation, parallel-group studies to evaluate the efficacy and safety of perampanel given as adjunctive therapy in subjects with refractory partial seizures aged 12 years and older. The three phases of the studies were the prerandomization, double-blind (with a 6-week titration period followed by a 13-week maintenance period), and follow-up phase. The following two figures illustrate the study diagrams for the Phase 3 DB studies.

Figure 1. Study Diagram: Epilepsy Phase 3 Study 304 and 305



Source: Figure 9.1 in both the Clinical Study Reports for Studies 304 and 305

Figure 2. Study Diagram: Epilepsy Phase 3 Study 306



Source: Figure 9.1, Clinical Study Report for Study 306

The key inclusion and exclusion criteria for the Phase 3 DB studies are listed below (Source: Clinical Study Reports 304, 305, 306).

Key Inclusion Criteria

1. Male or female and **≥ 12 years** of age (except for sites in Bulgaria, China, France, Germany, India, Lithuania, the Netherlands, and Portugal, subjects **≥18 yrs** 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).
3. Diagnosis of **epilepsy with partial seizures +/-** secondarily generalized seizures.
4. Computed tomography or magnetic resonance **imaging** within the last 10 years that ruled out a progressive cause of epilepsy.
5. **Uncontrolled partial seizures** despite having been treated with **≥2** different AEDs within the last 2 years.
6. During the 6-week Prerandomization Phase, subjects must have had **≥ 5 partial seizures** (with **≥2** partial seizures per each 3-week period) and no 25-day seizure-free period in the 6-week period, as documented via a valid seizure diary.
7. On stable doses of **1, 2 or a maximum of 3 approved AEDs**. Only 1 inducer AED (defined as carbamazepine, phenytoin, phenobarbital, or primidone) was allowed.
8. On a **stable dose** of the same concomitant AED(s) for 1 month prior to Visit 1.
9. If on a stable dose (other than intermittent rescue use) of **benzodiazepines** for epilepsy (or for anxiety or sleep disorders), the prescribed dose was stable for 1 month prior to Visit 1. Benzodiazepines were counted as one AED.
10. A **vagal nerve stimulator** was allowed but it must have been implanted **≥ 5 months** prior to Visit 1. Stimulator parameters could not be changed.

Key Exclusion Criteria

1. **Pregnant** and/or lactating women.
2. Presence of **nonmotor simple partial seizures only**.

3. Presence of **primary generalized epilepsies** or seizures.
4. Presence or previous history of **Lennox-Gastaut syndrome**.
5. History of **status epilepticus** within approximately 12 months prior to Visit 1.
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).
9. Scheduled and/or confirmed to have **epilepsy surgery** within 6 months after Visit 1; however those with previously documented “failed” epilepsy surgery were allowed.
10. 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).
11. Significant **active hematological disease**; WBC count $\leq 2500/\mu\text{L}$ or an absolute neutrophil count $\leq 1000/\mu\text{L}$.
12. Clinically significant **ECG abnormality**, including prolonged QTc (>450 msec).
13. Suffering from **psychotic disorder(s)** and/or unstable recurrent **affective disorder(s)** with use of antipsychotics or who had a suicide attempt(s) ≤ 2 years.
14. **Progressive central nervous system disease**, including degenerative CNS diseases and progressive tumors.
15. **Drug or alcohol dependency** or abuse within approximately the last 2 years.
16. Multiple drug allergies or a **severe drug reaction** to an AED(s), including dermatological, hematological, or organ toxicity reactions.
17. 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.
18. Concomitant use of **vigabatrin**.
19. Concomitant use of **barbiturates** (except for seizure control indication).
20. Use of intermittent rescue **benzodiazepines** ≥ 2 times in one month prior to Visit 1.

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 hematological disease, psychotic disorders, significant ECG abnormality). Of note, the exclusion criteria in some of the nonepilepsy studies were less restrictive (in Study 301, subjects were excluded only if they had any “unstable” abnormalities of the hepatic, renal, cardiovascular, respiratory, gastrointestinal, hematological, endocrine or metabolic systems.)

Data Cutoff Dates

At the time of the NDA submission, except for the ongoing open-label extension studies (OLE Studies 207, 233, and 307), the perampanel clinical trials were finished and the safety data was complete. In the NDA, the Sponsor identified December 1, 2010 as the cutoff date for the majority of safety data for these ongoing studies and identified July 1, 2011 as the cutoff date for information regarding additional deaths and SAEs.

In the 120-day Safety Update, the Sponsor identified October 1, 2011 as the cutoff date for the majority of the safety data and identified January 15, 2012 as the cutoff date for information regarding additional deaths and SAEs from these 3 OLE studies.

Furthermore, as of the 120-day Safety Update, there were 3 recently initiated, ongoing studies (Studies 232, 235, and 332). The Sponsor provided information regarding only deaths and SAEs in these 3 new studies through January 15, 2012 (clinical study reports were not provided).

Comment: Updated results for Study 233 based on the data cutoff date of January 15, 2012 were provided by the Sponsor in a stand-alone interim clinical study report instead of integrated within the 120-day Safety Update Report due to operational difficulties and delays at the sites in Japan (due to the 2011 tsunami).

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. Of note, for the Phase 1 study analyses, adults with hepatic impairment in the Study 015 (PK study in subjects with reduced hepatic function) were excluded from the safety analysis set. Healthy controls from Study 015 were included in the pooling for the ISS.

An adverse event (AE) was defined as any untoward medical occurrence in a clinical investigation subject administered an investigational product. Adverse events included any change in the subject's condition (symptoms, physical findings, or clinical syndromes). An abnormal laboratory test result was considered an AE if the identified laboratory abnormality led to any type of intervention. 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) that the subjects experienced from the time of signing the informed consent form to the last visit (most Phase 2 and 3 studies) and for 14 days after study drug discontinuation (Phase 3 epilepsy studies). Some investigators continued to record spontaneously reported AEs for more than 14 days after study drug discontinuation. Any AE that were recorded on the CRF from 15 to 30 days after study drug discontinuation were also included in the safety analyses.

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 during the treatment period.

The adverse event verbatim terms from the 52 trials were originally coded using different versions of the Medical Dictionary for Regulatory Activities (MedDRA), ranging from version 3.1 to 13.1 (ISS Table 20.26). To allow pooling of the AE data, the Sponsor recoded all of the AEs from the individual Clinical Study Reports (CSRs) to MedDRA Version 13.1.

Comment: In the safety information amendment dated April 20, 2012, the Sponsor provided information regarding the coding differences between the preferred terms in the ISS MedDRA Version 13.1 relative to the versions of MedDRA originally used in the individual CSRs (Tables 20.27, 20.28, and 20.29). After reviewing the recoded preferred terms alongside the original verbatim terms, the recoding process seemed appropriate. Oftentimes, the recoded preferred terms in the ISS more accurately captured the meaning of the verbatim terms than the preferred terms in the original CSRs. Other coding differences were minor (e.g., pharyngolaryngeal pain to oropharyngeal pain, vision disturbance NOS to visual impairment). There were only a few coding differences for the Phase 3 epilepsy studies because the original coding dictionaries were either MedDRA Version 13.0 or 13.1.

After reviewing the AE dataset 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 rare cases of miscoding. For example, for subject 013-1001-0463, the verbatim term, "giddy," was coded to the MedDRA PT, "dizziness." For subject 208-3004-1038, "metastatic polyp" was coded to colonic polyp (under the HLT benign neoplasms gastrointestinal in the GI disorders SOC) instead of being coded to gastrointestinal cancer metastatic (under the HLT gastrointestinal neoplasms malignant NEC in the Neoplasms benign, malignant and unspecified SOC).

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. In the NDA, the preferred terms were mapped only to primary SOCs instead of both primary and secondary SOCs (datasets with secondary SOCs were provided upon our request on May 21, 2012). For example, the MedDRA PT, gait disturbance, was coded under the primary SOC of General disorders, administration site conditions which provided less precise information than the secondary SOC of Nervous system disorders.

Other preferred terms that described similar symptoms were also coded to other primary SOCs instead of grouped together within the SOC Nervous system disorders. Confusional state and disorientation were coded to the SOC Psychiatric disorders whereas the PTs mental impairment and cognitive disorder were coded to SOC

Nervous system disorders. Vertigo was coded to the SOC Ear/labyrinth disorders (whereas ataxia and dizziness were coded to SOC Nervous system disorders).

Furthermore, on a subject level, for subject 302-0428-0006, “worsened sleep fragmentation” was coded to poor quality sleep (under the HLT sleep disturbances NEC in the Nervous system disorders SOC). However, for subject 302-0428-0003, “sleep fragmentation (waking up several times during the night, unable to get back to sleep)” was coded to insomnia (under the HLT disturbances in initiating and maintaining sleep in the Psychiatric disorders SOC).

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 pooled into 3 different groups. Safety data in the Nonepilepsy studies (Parkinson’s disease, neuropathic pain, multiple sclerosis, and migraine) were pooled into 4 different groups (as requested by the Division in the Refuse to File letter). Safety data in the Phase 1 studies were pooled into single-dose and multiple-dose groups. The following table summarizes the integrated analysis pools.

Table 2. Overview of Integrated Analysis Pools

Pool	Pool definition	Trials included
Subjects with partial-onset seizures*		
Epilepsy All Treated Pool (10 studies)	All treated subjects with epilepsy (including OLE studies)	Studies 304, 305, 306 Studies 203*, 206, 208 Studies 207, 231, 233, 307
Epilepsy Phase 3 Double-blind Pool	All treated subjects with epilepsy from phase 3, DB studies	Study 304 Study 305 Study 306
Epilepsy Phase 2 Double-blind Pool	All treated subjects with epilepsy from phase 2, DB studies	Study 203* Study 206 Study 208
Subjects with non-epilepsy indications		
Nonepilepsy All Treated Pool (15 studies)	All treated subjects with PD, MS, neuropathy, migraine (including OLE studies)^	Studies 202, 204, 214, 301, 302, 309 Studies 218, 227 Studies 201, 210 Studies 205, 220, 228, 303, 318
Nonepilepsy Double-blind Pool	All treated subjects from DB trials (PD, MS, neuropathy, migraine)^	Studies 202, 204, 214, 301, 302, 309 Studies 218, 227 Studies 201, 210
Parkinson's Disease Double-blind Pool	All treated subjects with PD from DB trials	Studies 202, 204, 214, 301, 302, 309
Neuropathic Pain Double-blind Pool	All treated subjects with diabetic or post-herpetic neuropathy from DB trials	Study 218 Study 227
Healthy subjects		
Phase I study pool (27 studies)	Subjects who received ≥ 1 dose of perampanel	Studies 003, 008, 016, 017, 037, 039, 040 Studies 001, 002, 010, 028 Studies 004, 007, 015, 026 Studies 005, 006, 014, 019, 025, 029, 030 Studies 009, 013, 020, 023, 024

Source: FDA RTF letter, Table 1 (7/21/11)

*16 subjects enrolled in Study 203 had generalized seizures, not partial-onset seizures

^ Subjects treated with entacapone from Study 309 were not included in the DB phase analysis. However, the information after they rolled over to the extension and started taking perampanel was summarized under perampanel groups in the Nonepilepsy All Treated Pool.

The following tables summarize the number of subjects from each study (by randomized dose group) in the different double-blind pooled groups. For the Epilepsy Phase 3 DB pool, each of the doses was not evaluated in every study, resulting in an uneven number of subjects across the dose groups. Doses of 2 and 4 mg were only evaluated in Study 306, while the dose of 8 mg was evaluated in all three studies. In the placebo group, 85.5% (378) subsequently enrolled in the OLE Study 307. In the perampanel group, 80.7% (838) subsequently enrolled in the OLE Study 307 (ISS Table 5).

Table 3. Number of Subjects from each Study in the Epilepsy Phase 3 DB Pool

	Placebo	Daily Dose of Perampanel			
		2 mg	4 mg	8 mg	12 mg
Study 304	121			133	134
Study 305	136			129	121
Study 306	185	180	172	169	
TOTAL	442	180	172	431	255

Source: ISS Table 3

For the Epilepsy Phase 2 DB pool, the perampanel dose groups in this pool each represent the results of a single study. Study 203 evaluated doses of 1 and 2 mg/d. Study 206 evaluated doses of 4 mg/d (or the maximum tolerated dose, MTD). Study 208 evaluated doses of 12 mg/d or the MTD, and all subjects from that study were included in the >8-12 mg/d group in the pool. In the placebo group (of Study 206/208), 69.4% (43/62) subsequently enrolled in the OLE Study 207. In the perampanel group (of Study 206/208), 68.3% (95/139) subsequently enrolled in the OLE Study 207 (ISS Table 5).

Table 4. Number of Subjects from each Study in the Epilepsy Phase 2 DB Pool

	Placebo	Daily Dose of Perampanel			
		<4 mg	4 mg	>4-8 mg	>8-12 mg
Study 203	6	12			
Study 206	52 ^a		101 ^a		
Study 208	10				38
TOTAL	68	12	101	0	38

Source: ISS Table 4

a: One subject randomly assigned to the perampanel group mistakenly received placebo for the entire duration of treatment. In this pool, that subject was included in the placebo group; in the CSR, that subject was included in the perampanel group in the analyses of safety.

The nonepilepsy Parkinson's disease DB pool included safety data from six Phase 2 and Phase 3 DB studies in PD. Almost all of the studies evaluated doses \leq 4 mg. Only one study (Study 214) evaluated doses >4-8mg. [Of note, the single subject who participated in Study 226 before it was terminated was not included in this pool.] In the placebo group, 61.0% (512/839) subsequently enrolled in their respective OLE studies (205, 220, 303, and 318). In the perampanel group, 60.6% (912/1504) subsequently enrolled in their respective OLE studies. In the entacapone group, 46.2% (108/234) subsequently enrolled in OLE Study 318 and treated with perampanel (ISS Table 9).

Table 5. Number of Subjects from each Study, Parkinson's Disease DB Pool

	Placebo	Entacapone	Daily Dose of Perampanel		
			<4 mg	4 mg	>4-8 mg
Study 202	6		13		
Study 204	66		197		
Study 214	20				55
Study 301	255		256	253	
Study 302	251		251	250	
Study 309	247	234		242	
TOTAL	845	234	717	745	55

Source: ISS Table 6

The nonepilepsy Neuropathic pain DB pool included safety data from two Phase 2 studies. In the placebo group, 69.4% (84) subsequently enrolled in the OLE Study 228. In the perampanel group, 47.2% (178) subsequently enrolled in the OLE Study 228 (ISS Table 9).

Table 6. Number of Subjects from each Study, Neuropathic Pain DB Pool

	Placebo	Daily Dose of Perampanel		
		<4 mg	4 mg	>4-8 mg
Study 218	48			98
Study 227	73	72	69	138
TOTAL	121	72	69	236

Source: ISS Table 7

Note: 7 subjects who were not included in the Safety Analysis Sets in the CSRs for Studies 218 and 227 were included in the Safety Analysis Set within this document. These seven subjects received at least one dose of study drug, and the only subsequent data they had were the end-of-study records (completion or discontinuation). In accord with the sponsor's current safety standards, such records were considered safety assessments in the ISS. Such records were not considered safety assessments when the CSRs were written.

In the Nonepilepsy DB pool, two additional Phase 2 DB Studies (201 and 210) were combined with the Parkinson's disease DB pool and Neuropathic pain DB pool. These two studies contributed an extra 113 subjects to the placebo group and 119 patients in the <4mg group.

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

Overall Exposure

The exposure to perampanel in subjects with epilepsy meets the minimum ICH guidance recommendations (minimum 1500 total, 300 subjects for 6 months and 100 for one year at clinically relevant doses). As of the 120-day Safety Update cutoff date of October 1, 2011, 1651 subjects with epilepsy had received perampanel in the double-blind, placebo-controlled trials (Phase 2 and 3), Phase 2 open-label study, and open-label extension studies. A total of 1231 subjects and 996 subjects were exposed for greater than 6 months and 1 year, respectively. There were 453 subjects who had received perampanel for greater than 2 years. The 1038 perampanel subjects in the Phase 3 double-blind trials comprise 62.9% of the total epilepsy perampanel population (and 15.0% of the total exposure in subject-weeks to perampanel). The 151 perampanel subjects in the Phase 2 double-blind trials comprise 9.1% of the total epilepsy perampanel population (and 1.7% of the total exposure to perampanel). All of the long-term safety data (> 6 months of exposure) was collected from the open-label extension studies.

An additional 2717 subjects received perampanel in studies performed for nonepilepsy indications. A total of 1251 subjects and 556 subjects were exposed for at least 6 months and one year, respectively. The 2013 perampanel subjects in the double-blind trials comprise 74.1% of the total nonepilepsy perampanel population (and 38.9% of the total exposure to perampanel in subject-weeks). The overall extent of exposure to perampanel in this pool (86176.1 subject-weeks) was less than the overall extent of exposure to perampanel in the epilepsy all treated pool (118920.0 subject-weeks).

In the Phase 1 studies, a total of 916 healthy subjects received perampanel in single- and multiple-dose studies.

A total of 104 pediatric subjects (12 to ≤16 years-old) were exposed to perampanel in the epilepsy clinical development program with 82 subjects and 65 subjects exposed to perampanel for greater than 6 months and 1 year, respectively. There were no pediatric subjects in the Phase 1, epilepsy Phase 2, or nonepilepsy trials.

Comment: Of note, the Sponsor has recently initiated Study 235 which is a randomized, double-blind, placebo-controlled study of the effects of adjunctive therapy with perampanel on the cognition, growth, safety, tolerability, and PK in adolescents (from 12 to <18 years of age). As of October 1, 2011, 39 subjects have been enrolled with an enrollment goal of 132 subjects. Only information regarding deaths and SAEs from this study was included in the ISS and the 120-day Safety Update.

Table 7. Perampanel Exposure by Duration and Study Pool

Exposure to Perampanel	TOTAL	Epilepsy			Nonepilepsy		Phase 1
		Phase 3 DB	Phase 2 DB	All (DB+OLE)	DB Pool	All	
≥ 1 dose*	5284	1038	151	1651	2013	2717	916
> 6 months	2482	NA	NA	1231	369	1251	NA
> 12 months	1552	NA	NA	996	NA	556	NA
> 24 months	519	NA	NA	453	NA	66	NA
Subject-weeks	206014	17862.6	2001.0	118920.0	33510.1	86176.1	917.9

Source: ISS Tables 39, 40, 20.4-4, 44, 22.3-13 and 120-day Safety Update Table 7

*≥ 1 dose along with ≥ 1 safety assessment

Even after restricting the epilepsy population to subjects who received maximum daily doses at or above the proposed dose for marketing (b) (4) the number of subjects still meets the minimum ICH guidance recommendations with a total of 1573 subjects.

Epilepsy Phase 3 Double-blind Pool

The double-blind phases of these 3 studies were all 19 weeks in duration (comprised of a titration period of ≤ 6 weeks and a maintenance period of 13 weeks). During the titration period, doses were increased in 2 mg increments on a weekly basis until the randomly assigned dose was attained. Down-titration of the dose was also permitted for subjects experiencing intolerable AEs anytime during the double-blind phase.

The following table summarizes extent of exposure by randomized dose for the Phase 3 DB Pool. Fewer subjects completed the trial in the higher dose groups. However, the percentages of subjects who received treatment for more than 18 weeks were similar between the placebo group and the lower dose groups. Specifically, more than 18 weeks of treatment was received by 81.9% of the subjects in the placebo group and 80.0%, 86.0%, 78.7%, and 67.8% of those in the 2, 4, 8, and 12 mg/d groups, respectively. Furthermore, the mean duration of exposure in the 12 mg group was lower (16.00 weeks versus 17.48-17.95 weeks for the other dose groups). These discontinuations in the higher dose groups (8 and 12 mg) occurred more often during the titration period (weeks 1-6).

Table 8. Extent of Exposure by Randomized Dose, Epilepsy Phase 3 DB Pool

Extent of Exposure	Placebo n (%)	Perampanel n (%) ^a				Total
		2 mg	4 mg	8 mg	12 mg	
Any exposure, n (%)	442	180	172	431	255	1038
0-1 week	4 (0.9)	1 (0.6)	3 (1.7)	2 (0.5)	4 (1.6)	10 (1.0)
> 1 to 2 weeks	4 (0.9)	2 (1.1)	1 (0.6)	5 (1.2)	4 (1.6)	12 (1.2)
> 2 to 4 weeks	11 (2.5)	3 (1.7)	3 (1.7)	10 (2.3)	9 (3.5)	25 (2.4)
> 4 to 6 weeks	7 (1.6)	3 (1.7)	1 (0.6)	14 (3.2)	15 (5.9)	33 (3.2)
> 6 to 8 weeks	3 (0.7)	2 (1.1)	2 (1.2)	7 (1.6)	14 (5.5)	25 (2.4)
> 8 to 10 weeks	6 (1.4)	5 (2.8)	1 (0.6)	6 (1.4)	7 (2.7)	19 (1.8)
> 10 to 12 weeks	2 (0.5)	2 (1.1)	1 (0.6)	2 (0.5)	1 (0.4)	6 (0.6)
> 12 to 14 weeks	7 (1.6)	4 (2.2)	2 (1.2)	5 (1.2)	2 (0.8)	13 (1.3)
> 14 to 16 weeks	2 (0.5)	2 (1.1)	0	6 (1.4)	6 (2.4)	14 (1.3)
> 16 to 18 weeks	34 (7.7)	12 (6.7)	10 (5.8)	35 (8.1)	20 (7.8)	77 (7.4)
> 18 weeks	362(81.9)	144 (80)	148 (86)	339 (78.7)	173 (67.8)	804(77.5)
> 20 weeks	13 (2.9)	7 (3.9)	6 (3.5)	15 (3.5)	9 (3.5)	37 (3.6)
Duration of exposure(wks) ^b						
n	442	180	172	431	255	1038
Mean	17.75	17.55	17.95	17.48	16.00	17.21
Median	19	19	19	19	18.86	19
Number of subject-weeks ^c	7844.7	3158.7	3088.1	7534.9	4080.9	17862.6

Source: ISS Table 20.4-46, 20.4-2

a: Subjects treated during the double-blind study. Dose is the randomized treatment groups.

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, subjects were unable to reach and maintain the higher dose groups of perampanel. The target dose was the last dose taken by 98.3%, 93.6%, 81.0%, and 61.2% of the subjects in the 2mg, 4mg, 8mg, and 12mg dose groups, respectively (ISS Table 20.4-55). After comparing the number of subjects in the modal dose groups with the randomized dose groups, the modal dose groups have fewer subjects in the highest dose group (>8-12 mg) and more subjects in the lower dose groups than the randomized dose groups. The following table summarizes the number of subjects in each group by modal versus randomized dose groups.

Table 9. Number of Subjects by Dose Group, Epilepsy Phase 3 DB Pool

Randomized Dose Groups	2 mg	4 mg	8 mg	12 mg
# subjects in each group	180	172	431	255
Modal Dose Groups	<4 mg	4 mg	>4-8 mg	>8-12 mg
# subjects in each group	210	190	450	188
difference in n from randomized dose groups	+16.7%	+10.5%	+4.4%	-26.2%

Source: ISS Tables 39, 20.4-46

The following table provides further evidence that down-titrating or discontinuations occurred more frequently in the higher dose groups. Of those randomized to the 12 mg group, 72.5% (n=185) reached the assigned dose. However, of these subjects, 24.3%

later down-titrated or discontinued (twice the rate of placebo 11.3%). Of those randomized to the 8 mg group, a larger percentage of subjects (96%, n=414) reached the assigned dose. However, a similar percentage of subjects (25.1%) later down-titrated or discontinued (twice the rate of placebo 11.3%). A high percentage of the subjects in the 2 mg and 4 mg dose groups reached their assigned doses (99% and 98%, respectively) and down-titrated or discontinued at rates similar to placebo.

Table 10. Subjects who Down-titrated or Discontinued, Epilepsy Phase 3 DB Pool

Daily Dose	Placebo n/m (%)	Perampanel n/m (%) ^a			
		2 mg (n=180)	4 mg (n=172)	8 mg (n=431)	12 mg (n=255)
0 mg	50/442 (11.3)	0	0	0	0
2 mg		26/179 (14.5)	3/3 (100)	2/2 (100)	4/4 (100)
4 mg		1/1 (100)	17/169 (10.1)	6/6 (100)	7/7 (100)
6 mg				7/9 (77.8)	6/7 (85.7)
8 mg				104/414 (25.1)	19/25 (76.0)
10 mg					18/27 (66.7)
12 mg					45/185 (24.3)

Source: ISS Table 20.4-13

a: Subjects treated during the double-blind study. Dose groups are based on the actual treatment groups.

n=number of subjects who down-titrated or discontinued study

m=number of subjects with highest dose at the particular dose.

Down-titrated: A subject is said to have needed down-titration at a particular dose if he/she was exposed to this dose and his/her dose was reduced and stayed reduced during the rest of the Dosing Period for any reason. Each subject is counted only once, namely, at the highest dose she/he was exposed to.

Concomitant AEDs affected the subjects' ability to reach and maintain the higher dose groups of perampanel. Fewer subjects receiving non-enzyme inducing AEDs could reach and maintain higher doses of 8-12 mg for the entire double-blind treatment phase when compared to subjects receiving enzyme-inducing AEDs (e.g., carbamazepine, oxcarbazepine, or phenytoin). In subjects who received a baseline AED shown to have an inducing effect on the plasma clearance of perampanel (carbamazepine, oxcarbazepine and phenytoin), 75% of those in the 8 mg/d group, and 62% of those in the 12 mg/d group reached the target randomized dose and maintained that dose for the entire double-blind treatment phase (ISS Table 20.4-13.1). For subjects who received only non-enzyme inducing AEDs, the values were lower at 67%, and 42%, respectively (ISS Table 20.4-13.2). However, for the lower perampanel dose groups, the percentages were similar between the subjects with and without concomitant inducer AEDs (83% of those in the 2 mg/d group, 90% of those in the 4 mg/d group versus 88% and 86%, respectively).

Additionally, the subjects' ability to tolerate the higher dose groups of perampanel was affected by age. As age increased, fewer subjects randomized to the 12 mg group remained in the study. The mean duration of exposure in the 12 mg group was 17.61 weeks, 16.04 weeks, and 10.55 weeks for the age categories of <17 years, >=17 to <65 years, >=65 years, respectively (ISS Table 20.4-46.1).

Epilepsy Phase 2 Double-blind Pool

The median duration of exposure in each dose group reflected the maximum duration of exposure in the studies that the dose groups correspond to (4 weeks for the < 4 mg group in Study 203, 14 weeks for the 4 mg group in Study 206, and 16 weeks for the >4-8 and >8-12 mg/d groups in Study 208). In each dose group, a majority of the subjects received perampanel for the expected duration.

Table 11. Extent of Exposure by Modal Dose, Epilepsy Phase 2 DB Pool

	Placebo	Perampanel ^a				Total
		<4 mg	4 mg	>4-8 mg	>8-12 mg	
Duration of exposure(wks) ^b						
n	68	34	89	15	13	151
Mean	11.0	7.2	14.1	18.1	17.6	13.3
Median	12.0	4.0	14.0	16.4	16.7	14.1
Number of subject-weeks ^c	749.0	244.7	1256.0	271.1	229.1	2001.0

Source: ISS Table 40

The exposure to perampanel is defined as the exposure during the double-blind and open-label studies except for subjects with gap in perampanel exposure from the double-blind study to the open-label study of > 14 days, in this case only the longer exposure out of the two studies is counted.

a: Subjects treated during the double-blind study. Dose is the modal dose received.

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

Epilepsy All Treated Pool

The mean duration of exposure for the highest modal dose group >8-12 mg/day was 89.1 weeks (over 1½ years). Most of the subjects (77.7%) in the highest modal dose group were treated for >51 to 102 weeks or >102 to 153 weeks. This reflects the designs of the OLE studies, in which the dose is titrated upward to a maximum of 12 mg (or to the maximum tolerated dose). Only 3.9% (n=65) of the subjects had exposures >3 years and 0.8% (n=14) with exposures >5 years as of the data cut-off date (October 1, 2011) for the 120-day Safety Update. This is likely because subjects (n=1216) recently entered OLE Study 307 (from Phase 3 DB Study 304 which ended November 2010, 305 ended January 2011, and 306 ended July 2010). Subjects (n=138) entered OLE Study 207 earlier (from Phase 2 DB Study 206 which ended in 2007 and Study 208 ended in 2008).

Table 12. Extent of Exposure by Modal Dose, Epilepsy All Treated Pool

	Perampanel				Total
	<4 mg	4 mg	>4-8 mg	>8-12 mg	
Duration of exposure(wks)					
n	153	192	354	952	1651
Mean	28.1	50.8	56.6	89.1	72.0
Median	10.6	24.4	37.1	91.7	70.9
Number of subject-weeks ^a	4296	9756	20045.9	84822	118920

Source: 120-day Safety Update Table 7

The exposure to perampanel is defined as the exposure during the double-blind and open-label studies except for subjects with gap in perampanel exposure from the double-blind study to the open-label study of > 14 days, in this case only the longer exposure out of the two studies is counted.

a: Number of subject-weeks = summation over all subjects' exposure durations

Nonepilepsy Pools

The studies included in the nonepilepsy pools differed in duration, doses evaluated, and region performed. In the neuropathic pain DB pool, the treatment duration specified by the protocols for both studies was 15 weeks. In the Parkinson's DB pool, the treatment durations specified by the protocols for the six studies ranged from 4 to 30 weeks.

Therefore, in the nonepilepsy DB pool, the protocol-specified durations of treatment in the 10 studies included in this pool ranged from 4 to 30 weeks. Only 3 studies (PD Study 214 and neuropathic pain Studies 218 and 227) evaluated perampanel doses >4 mg/day. The study with the longest duration and largest number of subjects (PD Study 301) was performed in Europe and South Africa resulting in differences in exposure in subgroups of the subjects based on region.

Compared to the epilepsy studies, subjects were exposed to lower doses (and shorter duration) of perampanel in the nonepilepsy studies.

In the nonepilepsy DB pool, the highest dose group studied (>4-8 mg) had the shortest mean duration of exposure (10.8 weeks). The >8-12 mg dose group was not evaluated in these studies. In the placebo and total perampanel groups, the mean duration of exposure was similar at 17.5 and 16.7 weeks, respectively.

In the nonepilepsy all treated pool, the highest dose group (>8-12 mg) had the longest mean duration of exposure (49.4 weeks) due to the design of the OLE studies. However, only 40 subjects were included in this dose group. The majority (91%) of the exposure (subject-weeks) occurred in the lower dose groups (<4 mg and 4 mg). Furthermore, the mean duration of exposure (31.7 weeks) for the total perampanel group in the nonepilepsy all treated pool was less than half that of the epilepsy all treated pool (72.0 weeks).

Table 13. Extent of Exposure by Modal Dose, Nonepilepsy Pools

	Placebo	Perampanel				Total
		<4 mg	4 mg	>4-8 mg	>8-12 mg	
Nonepilepsy DB Pool						
Duration of exposure(wks)		Randomized Dose Groups				
n	1079	908	814	291		2013
Mean	17.5	17.0	18.3	10.8		16.7
Median	17.9	15.0	18.7	11.9		15.3
Number of subject-weeks ^a	18930.3	15468.7	14912.9	3128.6		33510.1
Nonepilepsy All Treated						
Duration of exposure(wks)		Modal Dose Groups				
n		1048	1441	188	40	2717
Mean		25.7	36.0	28.6	49.4	31.7
Median		14.2	30.0	15.7	49.3	21.0
Number of subject-weeks ^a		26950.6	51884.3	5366.7	1974.6	86176.1

Source: ISS Tables 44, 45

The exposure to perampanel is defined as the exposure during the double-blind and open-label studies except for subjects with gap in perampanel exposure from the double-blind study to the open-label study of > 14 days, in this case only the longer exposure out of the two studies is counted.

a: Number of subject-weeks = summation over all subjects' exposure durations

Phase 1 Studies

In the Phase 1 single-dose studies, doses of perampanel ranged from 0.20 mg to 36 mg. The mean duration of exposure to study drug was 1 day in the placebo group and 1.6 days in the perampanel group. In the Phase 1 multiple-dose studies, doses of perampanel ranged from 1 mg to 12 mg. The mean duration of exposure was 2.3 weeks in the placebo group and 2.7 weeks in the perampanel group.

Median Values for Modal Dose in the Pooled Groups

The following table summarizes the median values for the modal dose groups for each of the study pools. In the Phase 2 DB Pool, subjects in the highest dose group (>8-12 mg) were taking lower doses (median 6.0 mg, mean 7.5 mg). Therefore, these subjects (taking doses more appropriately classified as >4-8 mg) will likely not have the same AE profile as other subjects in the highest dose group.

In the nonepilepsy pools, the studies evaluated lower doses than the epilepsy studies. The highest dose group (>8-12 mg) was not evaluated in the DB studies (and in only 40 subjects in the OLE studies). Additionally, within the two highest dose groups, the median doses were 2.0 mg lower than that of the epilepsy studies.

Table 14. Median Values for the Modal Dose Groups by Study Pools

Pooled Groups	Perampanel Median Modal Dose				
	<4 mg	4 mg	>4-8 mg	>8-12 mg	Total
Epilepsy					
Epilepsy Phase 3 DB Pool	2.0	4.0	8.0	12.0	8.0
Epilepsy Phase 2 DB Pool	1.5	4.0		6.0	4.0
Epilepsy All Treated Pool	2.0	4.0	8.0	12.0	10.0
Nonepilepsy					
Parkinson's DB Pool	2.0	4.0	4.0		2.0
Neuropathic pain DB Pool	2.0	4.0	6.0		4.0
Nonepilepsy DB Pool	2.0	4.0	6.0		2.0
Nonepilepsy All Treated	2.0	4.0	6.0	10.0	4.0

Source: ISS Tables 20.4-1, 20.4-15, 20.4-18, 20.4-20, 20.4-28, 20.4-30, 20.4-32

7.2.1.2 Demographics

The Sponsor categorized the demographic characteristics into the following population subgroups: age group (<17 years, ≥17 to <65 years, ≥65 years), sex (male, female), race (white, black/African American, Asian/Pacific, other), and region (Europe, North America, Asia-Pacific, Central/South America, other).

Epilepsy Pools

The demographic characteristics of the different safety pools for the epilepsy population are listed in the following table. In the epilepsy Phase 3 pool, the subjects were young (mean age 34.9 years) predominantly white (75%) or Asian (19%) with mean BMI (25.0 kg/m²) in the overweight category (≥25 kg/m²). The subjects were enrolled in sites worldwide: Europe (44%), North America (22%), Asia-Pacific (18%), Central/South America (11%). [Of note, although females had a lower mean weight (64.9 kg) than males (75.4 kg), the mean BMIs were similar (24.9 kg/m² and 25.1 kg/m², respectively) (ISS Table 20.2-1.2)].

Pediatric subjects (<17 years) were only enrolled in the epilepsy Phase 3 studies. Pediatric subjects had a mean age of 14.3 years and were mostly male (61.1%), white (82%), with a mean weight of 54.6 kg and BMI 20.9 kg/m² (ISS Table 20.2-1.1). About half (47%) were ages 15 and 16, while approximately one-third (36%) were ages 12 and 13.

Among the by-region subgroups, there were differences in the demographic and baseline characteristics. While the racial distribution for subjects at sites in North America contained some diversity (81.4% white, 9.4% black/African American, 1.3% Asian), the subjects from sites in Central/South America and Europe were mostly white (94.4% and 99.2%, respectively), and subjects at sites in Asia-Pacific were all either Asian (61.2%) or Chinese (38.8%). The subjects from North America were the oldest (mean age 37.6 years) with the highest BMI (mean 26.8 kg/m²) while the subjects from

Asia were the youngest (mean age 31.1 years) with the lowest BMI (mean 22.5 kg/m²) (ISS Table 20.2-1.5).

Comment: When considering the dose-response relationship for adverse events (discussed in subsequent sections of this review), it is important to keep in mind the differences in the demographics among the dose groups. These differences in demographics may change the baseline risk factors for AEs (particularly AEs associated with BMI, age, and race). The highest dose group (12 mg from Studies 304 and 305) also contains the highest percentages of subjects from North America and Central/South America, resulting in the oldest (mean 36.1 years), predominantly white (85%) cohort with the highest BMI (26.0 kg/m²). Conversely, the lowest dose groups (2 and 4 mg from Study 306) contain the highest percentage of subjects from Asia and Europe, resulting in the youngest (mean 33.7 years) cohort with the highest percentage of Asian subjects (35%) and with the lowest BMI (24.0 kg/m²). The 8 mg dose group (from all 3 studies) may have an intermediate baseline risk profile.

Table 15. Baseline Demographic Characteristics of Epilepsy Pools

	AGE	SEX	RACE				REGION					Wt (kg)	BMI
	mean	male	W	B	A	O	Eur	NA	Asia	CA	O	mean	mean
Epilepsy Phase 3 Double Blind Pool (by Randomized Treatment Group)													
Placebo n=442	34.3	50%	76%	3%	17%	3%	43%	24%	17%	11%	5%	70.2	25.0
Treated n=1038	35.1	48%	75%	2%	20%	3%	44%	21%	19%	11%	5%	70.0	25.0
2 mg n=180	33.8	47%	66%	0	33%	1%	60%	0	33%	0	7%	65.4	23.5
4 mg n=172	33.6	51%	61%	0	38%	1%	55%	0	36%	0	9%	69.5	24.5
8 mg n=431	35.6	48%	78%	2%	16%	4%	42%	24%	15%	14%	5%	70.3	25.2
12 mg n=255	36.1	47%	85%	4%	7%	5%	29%	42%	6%	21%	2%	72.9	26.0
Epilepsy Phase 2 Double Blind Pool													
Placebo n=68	38.9	46%	93%	4%	1%	1%	53%	37%	0	0	10%	75.5	25.8
Treated n=151	40.8	46%	90%	7%	2%	1%	58%	38%	0	0	5%	77.8	27.3
Epilepsy All Treated Pool													
Treated n=1651	35.6	49%	76%	2%	19%	3%	45%	23%	18%	9%	5%	70.8	25.2

Sources: ISS (Tables 30, 31, 32, 20.2-10), 120-day Safety Update (Table 20.2-41.1)

Treated = Total Perampanel Group

Race Categories: White, Black, Asian (includes Chinese), Other (includes American Indian/Alaska Native)

Region Categories: Europe, North America, Asia, Central/South America, Other (Australia/South Africa)

Nonepilepsy Pools

There were many differences between the demographic characteristics of the subjects enrolled in the epilepsy and nonepilepsy studies. Compared to the epilepsy Phase 3 pool, the nonepilepsy DB subjects were older (mean age 61.8 years) and predominantly white (92%) males (57%) with higher weight and BMI (mean wt 77.5 kg, BMI 27.1 kg/m²). Fewer subjects were from Asia (4%) or Central/South America (5%).

Within the nonepilepsy DB pool, the demographics between the placebo and total perampanel groups were similar. However, there were differences among the dose groups, reflecting the demographics in the studies that the dose groups represented. The lower dose groups (<4 mg and 4 mg) correspond to the PD studies while the highest dose group (>4-8 mg) corresponds mostly (81%) to the neuropathic pain studies (majority from North America with mean BMI in the obese, ≥ 30 kg/m², category).

Phase 1 Study Pools

The healthy subjects were slightly younger (mean age 31.1 years) than the epilepsy Phase 3 population (34.9 years). Many of the studies enrolled only male subjects, so the percentage of males (65.9%) was approximately twice that of females (34.1%). Most subjects were also white (76.2%) and from North America (42.5%) or Europe (50.1%). The mean BMI (24.5 kg/m²) was similar to the epilepsy population (25.0 kg/m²) even though the mean weight was higher (73.1 kg versus 70.1 kg, respectively) (ISS Table 38).

Baseline Disease characteristics

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

Baseline AEDs

Subjects enrolled in the epilepsy Phase 3 studies were being treated with 1, 2, or a maximum of 3 approved AEDs at stable doses for ≥ 3 weeks prior to the first visit. Only 1 enzyme-inducing AED (defined as carbamazepine, phenytoin, phenobarbital, or primidone) was allowed. Most of the total perampanel group was being treated at baseline with 2 AEDs (51.3%), fewer with 3 AEDs (34.5%) and fewest with only 1 AED (14.1%) (ISS Table 20.2-3). More than half of the total perampanel group was taking an enzyme-inducing AED (58.8%), and most was taking a non-enzyme inducing AED (93.3%). A similar pattern was seen in the placebo group. The most common AEDs, (taken by $\geq 10\%$ of the subjects in any group), were carbamazepine, valproic acid, lamotrigine, levetiracetam, topiramate, oxcarbazepine, clobazam, and clonazepam (in order of decreasing frequency in the total population) (ISS Table 20.2-4).

Comment: Upon further review of Tables 20.2-3 and 20.2-4, there were differences among the dose groups, likely corresponding to regional differences in AED use. In the 12 mg dose group (from North America and Central/South America), a higher percentage of subjects took an enzyme-inducing AED (63.5%), specifically

carbamazepine (37.6%) at baseline. Also, in the 12 mg group, a higher percentage of subjects took levetiracetam (34.1% vs 26.5% in the 2 and 4 mg dose group). Conversely, in the 2 and 4 mg dose group (from Asia and Europe), a higher percentage of the subjects took valproic acid (44% vs 24.7% of 12 mg group), lamotrigine (35.2% vs 24.7%), and topiramate (22.2% vs 17.6%).

Concomitant Medications and Diseases

Concomitant non-AED medications included medications started before the first dose of study drug and were continuing at the time of first dose of study drug or started on or after the first dose of study drug. Concomitant diseases included medical conditions present at screening.

In the epilepsy Phase 3 pool, the AED regimen that subjects were taking upon entering one of the Phase 3 epilepsy studies could not be changed during treatment with study drug. Therefore, the list of most common concomitant AEDs was similar to the AEDs at baseline (ISS Table 33). The most commonly taken concomitant non-AEDs were paracetamol, ibuprofen, and lorazepam (used for any indication) (ISS Table 20.3-3). Concomitant diseases occurred in 72.2% of those in the placebo group and 71.1% of those in the total perampanel group (ISS Table 20.2-27). The only medical condition present at screening in $\geq 10\%$ of the 1480 subjects was headache (13.0%). There were no significant differences in concomitant diseases between the placebo and total perampanel groups.

Comment: Upon further review of Tables 20.3-3 and 20.2-27, there were differences among the dose groups, likely corresponding to regional differences in concomitant medications and diseases. In the 12 mg dose group (from North America and Central/South America), a higher percentage of subjects were taking concomitant medications (73.3% vs 69.2% in placebo). Most of the medications listed in Table 20.3-3 were taken more frequently by the subjects in the 12 mg dose group than placebo. Notably, the use of the following medications was higher (12 mg group vs placebo): lorazepam (10.2% vs 5.0%), diazepam (6.3% vs 5.0%), levothyroxine (7.5% vs 2.9%), citalopram (3.9% vs 2.5%), sertraline (3.1% vs 2.5%), paroxetine (1.6% vs 0.5%), risperidone (2.0% vs 0.5%), and vicodin (2.7% vs 0.9%).

Furthermore, in the 12 mg dose group, a higher percentage of subjects had concomitant diseases (82.4% vs 72.2% in placebo). Most of the disease SOCs were more prevalent in the 12 mg dose group than placebo. Notably, the prevalence of the following concomitant diseases was higher in the 12 mg group than placebo:

- *Congenital, familial and genetic disorders (15.3 vs 7.0%) driven by cerebral palsy*
- *Endocrine disorders (10.6% vs 3.6%) driven by hypothyroidism*
- *Gastrointestinal disorders (25.9% vs 15.6%) driven by constipation and GERD*
- *Immune system disorders (20.4% vs 14.0%)- drug hypersensitivity, seasonal allergy*
- *Nervous system disorders (51.0% vs 42.8%) driven by headache and migraine*
- *Psychiatric disorders (32.2% vs 22.4%) driven by depression, insomnia, and anxiety*

- *Vascular disorders (12.9% vs 8.1%) driven by hypertension*

Conversely, in the 2 and 4 mg dose group (from Asia and Europe), a much lower percentage of the subjects were taking concomitant medications (49% vs 69.2 in placebo) and had concomitant disease (59.4% vs 72.2% in placebo).

In the epilepsy Phase 2 studies, similar to the findings at baseline, the most common concomitant AEDs were carbamazepine, lamotrigine, valproic acid, levetiracetam, oxcarbazepine, topiramate, and phenytoin (ISS Table 34). The only medical condition present at screening in $\geq 10\%$ of the 219 subjects was headache (18.3%). There were no significant differences in concomitant diseases between the placebo and total perampanel groups (ISS Table 20.2-27).

In the nonepilepsy Parkinson's disease pool, the most commonly taken anti-Parkinson's medications, (taken by $\geq 10\%$ of the subjects in the placebo, entacapone, or total perampanel group), were Sinemet, Madopar, pramipexole, ropinirole, entacapone, amantadine, Stalevo, and selegiline (ISS Table 20.3-25). The only non-anti-Parkinson's medication taken by $\geq 10\%$ of the subjects was acetylsalicylic acid (ISS Table 20.3-26). The most common concomitant diseases were hypertension, insomnia, depression, constipation, back pain, and anxiety (in order of decreasing frequency) (ISS Table 20.2-34). A similar pattern was seen between the placebo group and treatment groups.

In the nonepilepsy neuropathic pain pool, the most commonly taken pain medications were gabapentin and pregabalin (ISS Table 20.3-28). The most commonly taken nonpain medications were acetylsalicylic acid, metformin, paracetamol, lisinopril, simvastatin, insulin glargine, multivitamins, atorvastatin, hydrochlorothiazide, metoprolol, furosemide, levothyroxine, and atenolol (ISS Table 20.3-29). The most common concomitant diseases/conditions were hypertension, type 2 diabetes mellitus, hypercholesterolemia, drug hypersensitivity, osteoarthritis, hyperlipidemia, gastroesophageal reflux disease, insomnia, depression, back pain, and hypothyroidism (in order of decreasing frequency) (ISS Table 20.2-35). The types of concomitant diseases and medications were consistent with subjects with concurrent diagnoses of diabetic or postherpetic neuropathy.

7.2.2 Explorations for Dose Response

The reader is referred to Dr. Martin Rusinowitz's review of efficacy for explorations of dose-response with respect to efficacy. Analyses of safety stratified by perampanel dose were performed and are discussed in this review.

7.2.3 Special Animal and/or In Vitro Testing

The reader is referred to the Pharmacology/Toxicology Review by Dr. Christopher Toscano.

7.2.4 Routine Clinical Testing

In all of the populations (epilepsy, nonepilepsy, and Phase 1), safety was evaluated using the following parameters: AEs, clinical laboratory tests, physical examinations, and vital signs. The epilepsy and nonepilepsy trials also evaluated body weight. ECGs were performed in all of the epilepsy studies and in most of the non-epilepsy and Phase 1 studies. The Phase 3 epilepsy studies also evaluated photosensitivity and potential withdrawal symptoms (photosensitivity and withdrawal questionnaires that were added to each study by protocol amendment after enrollment had been ongoing for more than 6 months). The number and timing of data measurements were dependent on trial design and duration.

An independent Data Monitoring Committee monitored the safety data of the Phase 3 DB studies (Studies 304, 305, and 306).

The clinical testing in the Phase 3 trial protocols 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 after Visit 2 and before Visit 8.

Table 16. Schedule of Assessments, Epilepsy Phase 3 DB Studies

Phase Period	Pre-randomization ^a	Double-blind Phase							Follow up ^b
		Titration ^a			Maintenance ^b				
Week	Week -6	0	2	4	6	10	14	19	23
Day	Day -42	0	14	28	42	70	98	133	161
Visit	Visit 1	2	3	4	5	6	7	8	9
Assessment									
Adverse events		X	X	X	X	X	X	X	X
Vitals and weight ^c	X	X	X	X	X	X	X	X	X
Laboratory evaluation	X	X			X	X	X	X	X
12-lead ECG ^d	X	X			X		X	X	X
Physical examination ^e	X	X						X	X
Neurological exam ^e	X	X						X	X
Photosensitivity questionnaire								X	
Withdrawal questionnaire ^f		X						X	X

Source: Clinical Study Report Study 304, Table 9.2

^a All visits were to be done within ± 3 days of the schedule.

^b Visit was to be done within ± 7 days of the schedule. Note the follow-up visit only applied to the subjects who completed the study (or who discontinued the study early), but did not enroll into the OLE Study 307.

^c Height (without shoes) was to be measured only at Visit 1.

^d If subject had a normal ECG baseline reading, but during any visit thereafter the QTc was measured as > 450 msec, three consecutive ECGs separated by 5-10 minutes were to be performed to confirm the abnormality.

^e All findings from the physical exam and the neurological exam at Visit 1 were documented and only changes from baseline were documented at Visit 2, Visit 8, and Visit 9 or Early Discontinuation Visit (if applicable). For any other clinic visits during the study, the physical exam and the neurological exam were only performed when there was a complaint from the subject. Clinically significant abnormal findings from the physical exam or the neurological exam were to be reported as an AE. The Phase 2 DB Study 206 also performed ophthalmological examinations.

^f Administered to all subjects at Visit 2 to obtain a baseline. In addition, those subjects not rolling over into the OLE study and those subjects who discontinued between Visit 2 and Visit 8 were administered Withdrawal Questionnaire 2 at the end of therapy or Early Discontinuation Visit, Withdrawal Questionnaire 3 by phone 8 (±2) days after the last dose of study drug and Withdrawal Questionnaire 4 in person at the Follow-Up Visit.

The following table summarizes the laboratory data captured during the epilepsy trials.

Table 17. Laboratory Assessments, Epilepsy DB Studies

Hematology	hematocrit, hemoglobin, red blood cell count, platelet count, bands, white blood cell count with differential (Phase 2 DB Study 206 also collected PT, PTT, thrombin time)
Chemistry	
Electrolytes	sodium, potassium, chloride, calcium, bicarbonate, magnesium, phosphorus
Liver function tests	alkaline phosphatase, ALT, AST, GGT, total bilirubin
Renal function tests	blood urea nitrogen and creatinine
Other	albumin, total cholesterol, creatine phosphokinase, glucose, LDH, uric acid, triglycerides, total protein
Urinalysis	pH, ketones, leukocytes, protein, urine glucose, urine microscopy

Source: Clinical Study Report Study 304, Table 9.3

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. Narratives were written for subjects with selected markedly abnormal laboratory values. The following table summarizes the modified NCI-CTC grades and criteria used by the Sponsor.

Table 18. 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) ^d	< LLN - 3.0 x 10 ⁹ /L or < 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	< LLN – 800/mm ³ < LLN - 0.8 x 10 ⁹ /L	<800/ - 500mm ³ <0.8 – 0.5 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
Neutrophils/granulocytes (ANC/AGC)	< 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 ^e	< 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)	<LLN – 3 g/dl <LLN – 30 g/L	2 - < 3 g/dl 20 – 30 g /L	< 2 g/dl < 20 g /L	-
Alkaline phosphatase	> ULN – 3.0 x ULN ^b	> 3.0 - 5.0 x ULN ^b	> 5.0 - 20.0 x ULN	> 20.0 x ULN
ALT, SGPT (serum glutamic pyruvic transaminase) ^{c,e}	> ULN - 3.0 x ULN ^b	> 3.0 - 5.0 x ULN ^b	> 5.0 - 20.0 x ULN	> 20.0 x ULN
AST, SGOT (serum glutamic oxaloacetic transaminase) ^{c,e}	> ULN – 3.0 x ULN ^b	> 3.0 - 5.0 x ULN ^b	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Bicarbonate, serum-low	< LLN - 16 mEq/dl	11 - 15 mEq/dl	8 - 10 mEq/dl	< 8 mEq/dl
Bilirubin (hyperbilirubinemia) ^{c,e}	> 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	7.0 - < 8.0 mg/dl 1.75 - < 2.0 mmol/L	6.0 - < 7.0 mg/dl 1.5 - < 1.75 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 ^e	> 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 ^b	> 3.0 - 5.0 x ULN ^b	> 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 – 3.0mmol/L	40 - < 55 mg/dl 2.2 - < 3.0 mmol/L	30 - < 40 mg/dl 1.7 - < 2.2 mmol/L	< 30 mg/dl < 1.7 mmol/L
Phosphate, serum-low (hypophosphatemia)		2.0 - <minimum of (2.5 mg/dl, LLN) 0.6 - <minimum of (0.8 mmol/L, LLN)	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	-	2.5 - <3.0 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	-	120 - <130 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	-	> ULN - 10 mg/dl <=0.59 mmol/L with physiologic consequences	> 10 mg/dl > 0.59 mmol/L

AGC = absolute granulocyte count, ALT = alanine aminotransferase, ANC = absolute neutrophil count, AST = aspartate aminotransferase, GGT = gamma-glutamyl transpeptidase, LLN = lower limit of normal, SGOT = serum glutamic oxaloacetic transaminase, SGPT = serum glutamic pyruvic transaminase, ULN = upper limit of normal, WBC = white blood cell
 Source: ISS Table 20.15

Comment: I compared the modified NCI-CTC grades and criteria used by the Sponsor 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).⁵ 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 Sponsor. Additionally, more severe cases of hypertriglyceridemia were categorized in each Grade by the Sponsor when compared to CTCAE Version 4.03 (e.g., Grade 4 included triglyceride levels >10 xULN by the Sponsor, 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 Sponsor).

Vital signs measurements included systolic blood pressure, diastolic blood pressure, pulse, and weight. Criteria for identifying clinically notable values and abnormal changes in blood pressure and pulse are listed in the following tables.

Table 19. 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 Module 2.7.4, Table 11, page 42

Table 20. Criteria for Identifying Abnormal Changes in Blood Pressure and Pulse

Variable	Increment	Decrement
Systolic Blood Pressure	≥ 20 mmHg	≥ 20 mmHg
	≥ 40 mmHg	≥ 40 mmHg
Diastolic Blood Pressure	≥ 10 mmHg	≥ 10 mmHg
	≥ 20 mmHg	≥ 20 mmHg
Pulse	≥ 15 bpm	≥ 15 bpm
	≥ 30 bpm	≥ 30 bpm

The same criteria were used to summarize orthostatic changes.

Source: Summary of Clinical Safety Module 2.7.4, Table 12, page 43

Orthostatic changes in vital signs were measured in several perampanel studies. Different criteria were used to determine clinically significant values (Table 21). In some

⁵ 5 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 March 29, 2012. http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf

studies, a standard definition of orthostatic hypotension (decrease in systolic blood pressure of ≥ 20 mmHg on standing or decrease in diastolic blood pressure of ≥ 10 mmHg on standing) was used. A subset of these studies also added a criterion of clinical significance based on the investigator's judgment. There were other studies that did not specify the criteria that were used. Of note, orthostatic changes were not measured in the three epilepsy Phase 3 trials.

Table 21. Clinical Studies that Measured Orthostatic Changes in Vital Signs

Indication	Study	Orthostatic Change	Criteria for Clinically Significant Values	
			Standard Criteria	Investigator's Judgement
Epilepsy	203	X		
	206	X		
	208	X		
	207	X		
Parkinson's Disease	202	X		
	204	X		
	214	X		
	301	X	X	X
	302	X	X	X
	309	X	X	X
	205	X	X	
	220	X		
Neuropathic Pain	303	X	X	X
	318	X	X	
	227	X	X	
	218	X	X	
Migraine Headache	228	X	X	
	210	X	X	
Multiple Sclerosis	201	X		

Source: Summary of Clinical Safety Module 2.7.4, Table 13, page 43

Each ECG was interpreted by a central ECG laboratory cardiologist who was blinded to the treatment. For electrocardiogram parameters, treatment-emergent ECG abnormalities were determined by the following criteria: rate (HR < 60 and HR > 100 bpm), atrial-related conduction (PR interval > 200 ms), ventricular-related conduction (QRS > 120 ms), repolarization-related (prolonged QT), and ischemia/infarction. To assess prolonged QT, both QTcB and QTcF were calculated. To identify ischemia and infarction events, the ECG comments were reviewed by the Sponsor's Clinical/Medical group and all abnormalities related to ischemia and infarction were flagged.

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 drugs in this class are currently approved for clinical use.

7.3 Major Safety Results

7.3.1 Deaths

In the epilepsy studies, there were a total of 9 deaths at the time of the data collection cut off of January 15, 2012. Eight deaths occurred in subjects receiving perampanel (12 mg) in the open-label extension studies. One death (subject 5110-4010) occurred during the prerandomization phase of the double-blind Study 304 (did not receive study drug and will not be included in the subsequent analyses). Excluding this last death, the mortality rate for perampanel-exposed subjects in the epilepsy studies is 0.5% (8/1651) or 0.07 per 1000 subject-weeks of exposure (8/118920.0 subject-weeks) or 3.51 per 1000 subject-years of exposure (8/2280.7 subject-years). None of the deaths were considered by the investigators to be related to perampanel.

Comment: Treatment-emergent deaths in the epilepsy studies were defined in the ISS as deaths that occurred within 30 days after the last dose of treatment. In a safety information amendment dated March 23, 2012, the Sponsor responded to our request to provide information regarding all deaths that occurred in the epilepsy studies up to 60 days after the last dose of treatment. The Sponsor stated that after conducting a search of their Pharmacovigilance product safety surveillance database, no additional unreported deaths from epilepsy studies occurred up to the NDA resubmission data cut-off for deaths/SAEs of July 1, 2011. The Sponsor stated that the epilepsy study protocols had consistent instructions for the investigators “to report any death/SAE for a period of 30 days after study discontinuation, and any death/SAE judged by the investigator to be related to study treatment regardless of the length of time since study completion.” The exceptions were Studies 231 and 233 which instructed investigators to only report deaths/SAEs for up to 28 days after study discontinuation.

In terms of sudden, unexplained death in epilepsy (SUDEP) cases, there was only one case classified as SUDEP (subject 306-1502-6004). The incidence rate of SUDEP in the epilepsy population is 0.44 per 1000 subject-years of exposure (1/2280.7 subject-years). However, if the other subject who died suddenly (subject 2802-5014) is included, the incidence rate could increase to 0.88 per 1000 subject-years. This incidence rate remains low compared to rates reported in the literature of 3.5-9.3 per 1000 person-years in subjects with refractory epilepsy.⁶

In the nonepilepsy studies, there were a total of 32 deaths (26 in the Parkinson's disease studies and 6 in the neuropathic pain studies). In the Parkinson's disease studies, most of these deaths occurred in the double-blind studies (17 deaths) with a higher rate in the placebo group, 0.8% (7/845), than either the total perampanel group,

6 Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. *Lancet Neurol*. 2008; 7: 1021–31.

0.6% (9/1517), or the entacapone group, 0.4% (1/234). In the neuropathic pain studies, most of the deaths occurred in the double-blind studies (4 deaths) with a much higher rate in the placebo group, 1.7% (2/121), than the total perampanel group, 0.5% (2/377).

In the nonepilepsy population, the mortality rate for perampanel-exposed subjects is 0.8% (22/2717) or 0.26 per 1000 subject-weeks of exposure (22/86176.1 subject-weeks) or 13.2 per 1000 subject-years of exposure (22/1652.7 subject-years).

Table 22. Mortality for Perampanel-Exposed Subjects by Indication

Indication	Total # Subjects	Total # Deaths	Crude Mortality	Subject-weeks Exposure	Subject-years Exposure	Mortality per 1000 Subject-years
Epilepsy	1651	8	0.5%	118920.0	2280.7	3.51
Nonepilepsy	2717	22	0.8%	86176.1	1652.7	13.2

Comment: The mortality rate in the nonepilepsy population is higher than that of the epilepsy population (or almost 4 times that of the epilepsy population after adjusting for the duration of exposure). This increased mortality in the nonepilepsy population is likely due to the older population (mean age 62.3 years) when compared to the epilepsy population (mean age 35.6 years). Additionally, more subjects with comorbidities entered the nonepilepsy trials due to the less restrictive exclusion criteria than the epilepsy trials.

There were no deaths in the Phase 1 trials. The following table summarizes the relative risk between perampanel and placebo subjects of mortality by indication in the DB pooled groups. There is a trend towards a lower risk of death in the perampanel-treated subjects when compared to the placebo subjects. However, none of the values was statistically significant.

Table 23. Relative Risk of Mortality by Treatment Group

Double-Blind Pool	Perampanel		Placebo		Relative Risk (95% C.I.)
	Deaths	n	Deaths	n	
Epilepsy DB Pool	0	1189	0	510	NA
Nonepilepsy DB Pool	11	2013	9	1079	0.66 (0.27-1.58)
Parkinson's DB Pool	9	1517	7	845	0.72 (0.27-1.92)
Neuropathic Pain DB Pool	2	377	2	121	0.32 (0.05-2.25)
All studies	11	3202	9	1589	0.61 (0.25-1.46)

For the deaths in the epilepsy trials, the mean age was 43.5 (compared to 35.6 years for the entire epilepsy population). The 12 mg dose of perampanel was taken by all of these subjects. Most were male (62.5%) and white (75%). The total exposure to perampanel ranged from 172 days to greater than 600 days.

For the deaths in the nonepilepsy trials, the mean age was 68.9 (compared to 62.3 years for the entire nonepilepsy population). The mean dose of perampanel was 3.66 mg (dose range 0.5 mg to 8 mg). Three-fourths were male (compared to 59% of the entire nonepilepsy population). Almost all of the deaths occurred in whites (97%).

For all deaths combined, the AEs leading to death were coded most often to the MedDRA SOC, Cardiac disorders (n=14) and Neoplasms benign, malignant and unspecified (incl cysts and polyps) (n=7). After stratifying by treatment group in the nonepilepsy double-blind trials, AEs leading to death in these two SOCs were more common in the placebo group than the perampanel subjects. The incidence of AEs coded to the Neoplasms SOC for the placebo subjects (0.28%, 3/1079) is greater than for the perampanel subjects (0.05%, 1/2013). The incidence of AEs coded to cardiac disorders SOC for the placebo subjects (0.37%, 4/1079) is greater than for the perampanel subjects (0.25%, 5/2013).

The following table summarizes all of the deaths in both the epilepsy and nonepilepsy trials. Additionally, in the following paragraphs, the available clinical details for the 30 deaths in patients treated with perampanel (8 epilepsy, 22 nonepilepsy) are summarized.

Table 24. Summary of All Deaths in Epilepsy and Nonepilepsy Trials

Subject	Study	Age*/sex/race /country	Last treatment	Last dose	Preferred Term(s)
Epilepsy Open-Label Extension Studies					
0009-0176	207	48/F/W/USA	Perampanel	12 mg	Cardiac arrest
2704-5006	307	23/M/A/Ind	Perampanel	12 mg	Road traffic accident
1502-6004	307	54/M/W/Bgr	Perampanel	12 mg	Death (SUDEP)
3101-6002	307	53/M/W/Ltu	Perampanel	12 mg	Cerebral haemorrhage
2802-5014	307	28/F/W/Isr	Perampanel	12 mg	Sudden death
5128-4011	307	73/M/W/USA	Perampanel	12 mg	Pneumonia
1007-4009	307	50/M/W/Arg	Perampanel	12 mg	Head injury, hydrocephalus
2760-6003	307	20/F/A/Ind	Perampanel	12 mg	Death neonatal
Parkinson's Disease Double-Blind Studies					
0112-0002	204	65/M/W/Deu	Perampanel	0.5 mg	†Lung neoplasm, tachycardia, dyspnoea, cardiac failure
0175-0007	301	65/M/W/Hun	Perampanel	2 mg	Left ventricular failure
0201-0004	301	67/M/W/Ltu	Perampanel	2 mg	Sick sinus syndrome
0129-0012	301	84/M/W/Cze	Perampanel	4 mg	Broncho-pneumonia
0165-0006	301	81/F/W/Deu	Perampanel	4 mg	Circulatory collapse
0132-0008	301	68/M/W/Est	Perampanel	4 mg	Cardiac failure
0102-0003	301	63/M/W/Aut	Placebo		†Acute myocardial infarction
0571-0002	302	63/M/W/Arg	Perampanel	4 mg	‡Sepsis
0584-0021	302	57/M/W/Bra	Placebo		Bile duct cancer
0408-0002	302	78/M/W/USA	Placebo		Prostate cancer
0447-0013	302	69/M/W/USA	Placebo		†Cardio-respiratory arrest
0466-0001	302	80/M/W/USA	Placebo		Pneumonia
0476-0004	302	68/F/W/USA	Placebo		Myocardial infarction (MI), femur fracture (18 days prior to MI)
0128-0003	309	78/M/W/Cze	Perampanel	4 mg	‡Sepsis
0752-0004	309	77/M/W/Lva	Perampanel	4 mg	Hip fracture
0203-0002	309	75/M/W/Ltu	Placebo		Coronary artery disease
0210-0002	309	56/M/W/Pol	Entacapone	200 mg	†Psychotic disorder, cardiopulmonary failure

Parkinson's Disease Open-Label Extension Studies					
0407-0015	205	71/M/W/Ita	Perampanel	2 mg	†Back pain, hypotension
0122-0004	205	72/M/W/Deu	Perampanel	4 mg	General health deterioration
0604-0009	205	53/M/W/Scg	Perampanel	4 mg	Sudden death
0239-0008	303	79/M/W/Zaf	Perampanel	4 mg	Cardiac failure
0176-0001	303	65/F/W/Hun	Perampanel	4 mg	Sepsis
0178-0005	303	77/M/W/Hun	Perampanel	4 mg	Cardiopulmonary failure
0178-0013	303	58/F/W/Hun	Perampanel	2 mg	Metastatic bronchial carcinoma
0215-0002	303	68/M/W/Pol	Perampanel	4 mg	Lung neoplasm malignant
0132-0005	318	77/M/W/Est	Perampanel	4 mg	‡Cardiopulmonary failure
Neuropathic Pain Double-Blind Studies					
1301-1002	227	67/M/W/USA	Perampanel	8 mg	Acute pancreatitis
1324-1004	227	73/F/W/USA	Perampanel	2 mg	Multi-organ failure
1007-1002	227	60/F/W/Gbr	Placebo		Lung neoplasm malignant
1318-1018	227	61/F/A/USA	Placebo		†(No cause of death available)
Neuropathic Pain Open-Label Extension					
1407-1002	228	61/F/W/Can	Perampanel	4 mg	Arrhythmia
1321-1010	228	68/M/W/USA	Perampanel	6 mg	Adenocarcinoma

Source: ISS Tables 115 and 116

A=Asian/Pacific, ARG=Argentina, AUT=Austria, BGR=Bulgaria, BRA=Brazil, CAN=Canada, CZE=Czech Republic, DEU=Germany, EST=Estonia, F=Female, GBR=Great Britain, HUN=Hungary, IND=India, ISR=Israel, ITA=Italy, LTU=Lithuania, LVA=Latvia, M=Male, POL=Poland, SCG=Serbia, USA=United States of America, W=White, ZAF=South Africa

*Age (years) is calculated at baseline.

†Reported by the investigators as possibly related to study drug.

‡Event was not treatment-emergent (the start date was > 30 days after the last dose of study drug).

Comment: In a safety information amendment on March 23, 2012, in response to the Division's request, the Sponsor submitted a revised ISS Table 116 that corrected the various discrepancies between the numbers reported in the table and the narratives/CRFs. The Sponsor reported that the discrepancies between individual CRFs and narratives were a result of "queries of those CRF pages that were inadvertently excluded from the published CRF in the NDA."

Epilepsy population:

Comment: After reviewing the available clinical details for the 8 deaths, it is difficult to draw any definitive conclusions about the causal role of perampanel in these deaths that all occurred in the OLE studies. Three of the deaths were sudden deaths: 1 SUDEP, 1 cardiac arrest (on OLE Day 705 in a subject with history of morbid obesity and other cardiac risk factors), and 1 cause unknown (27 year-old who died suddenly on OLE Day 173 after a fall with ventricular fibrillation noted by EMS without any significant previous history of abnormalities on ECG or electrolytes).

The other 5 deaths were due to disparate events: car accident (passenger), cerebral hemorrhage, pneumonia (73 year-old), head injury/hydrocephalus due to a seizure, and a neonatal death (maternal concomitant use of Pregnancy Class D medications,

carbamazepine and clobazam). Of note, human pregnancy data is discussed further in Section 7.6.2.

Subject 0009-0176, a 48 year-old white female treated with perampanel for 705 days in OLE Study 207 (in addition to 92 days in DB Study 206), who died unexpectedly. Subject had a history of hypoxic brain injury (with “limited insight, calculations”) with complex partial and secondarily generalized seizures, localized to temporal lobe, and treated at baseline with Dilantin (500 mg total daily dose) and Kepra (3000 mg total daily dose). Seizure diary entries for the 2 months prior to study entry recorded 1 to 9 complex partial seizures per day (and no secondary generalized seizures). Baseline medical/surgical history included vagal nerve stimulation implantation, hypertension, hypercholesterolemia, hypothyroidism, morbid obesity (148 kg), post menopausal, abdominal ascites, edema, hyponatremia, mild depression, and acid reflux. Other concomitant medications included levothyroxine, olmesartan, omeprazole, ibuprofen, loperamide, rosuvastatin, metoclopramide, ranitidine, paroxetine, and vitamin D.

The subject was randomized to the perampanel bid treatment group in the DB Study 206 (dose titrated up to 2 mg bid) which the subject completed without any significant events and entered the OLE Study 207. On OLE Day 2 ((b) (6)), the subject experienced dizziness. Perampanel was continued. Later, the Dilantin dose was decreased to 400 mg/day ((b) (6)). There was a recurrence of dizziness on Day 156 ((b) (6)) when the perampanel dosage was titrated to 6 mg. Later, the Dilantin dose was decreased to 300 mg/day ((b) (6)).

Between Study Day 270 ((b) (6)) and Study Day 533 ((b) (6)) the subject experienced several episodes of falls (in 1 instance with a seizure recorded in the diary) sustaining neck/head pain, left shin laceration, and bruises. The subject also experienced several episodes of seizures while on the maintenance dosage of 12 mg. Vitals performed within a month of these events were not different from baseline (and were without orthostasis) On ((b) (6)) EKG was noted to have a “t wave abnormality”, similar to the baseline EKG. On ((b) (6)) EKG was noted to have a “high QRS voltage.” The study drug was continued. The Dilantin dose was decreased to 200 mg/day and later increased to 400 mg/day ((b) (6)). *(Of note, the CRF did not include the seizure diary pages from ((b) (6)) The Sponsor provided these pages upon our request in a safety information amendment on March 23, 2012).*

On Study Day 677 ((b) (6)) during visit 11, the subject’s vitals and labs were checked and were at baseline (afebrile, weight 148.6 kg, BP 134/88, HR 90). The only notable labs were an elevated alkaline phosphatase (237 U/L) and gamma glutamyl transferase (123 U/L). However, these were consistent with the subject’s baseline values. EKG was reported as a borderline ECG with a high QRS voltage. It was recorded that “a cardiologist was subsequently contacted for a second opinion and the ECG was ruled not clinically significant.” The last seizure diary entry was recorded on ((b) (6)) (13 simple partial and 2 complex partial seizures were recorded and similar to previous entries).

On Study Day 705 ((b) (6)) the subject experienced a fatal “cardiac arrest.” The subject was found dead. The subject’s mother reported that the subject looked “more fatigued and weaker the previous day.” No hospitalization dates were reported. **Myocardial infarction** was the cause of death listed on the death certificate. No autopsy was conducted. The subject received her last dose of perampanel on Day 705 (day of fatal event).

Subject 2704-5006, a 23 year-old Asian male treated with perampanel for 55 days who died in an automobile crash. The subject had a history of complex partial seizures with secondary generalization and was being treated with carbamazepine, valproic acid, and clobazam. No comorbidities or other concomitant medications were reported. The subject was randomized to the placebo group in the DB Study 305 which the subject completed and subsequently entered OLE Study 307. The patient was started on perampanel 2 mg per day and completed the titration to 12 mg per day. On OLE Day 56, the

subject sustained a fatal “road traffic accident” in which he was reportedly a passenger (not the driver). The death certificate was not available. An autopsy was performed but the results were not available. The subject received his last dose of perampanel on Day 55.

Subject 1502-6004, a 54 year-old white male treated with perampanel for 55 days who died unexpectedly. The subject had a history of complex partial seizures with and without secondary generalization and was being treated with topiramate and oxcarbazepine. No comorbidities or other concomitant medications were reported. The subject was randomized to the placebo group in the DB Study 306 which the subject completed and subsequently entered OLE Study 307. The patient was started on perampanel 2 mg per day and completed the titration to 12 mg per day. On OLE Day 56 (b) (6) the subject died during his sleep and was found by his wife in the morning. The wife reported no changes in the subject’s condition in the previous days. No autopsy was conducted. The event was reported as a **SUDEP** (sudden, unexplained death in epilepsy). The subject received his last dose of perampanel on Day 55. In the seizure diary, it is recorded that the subject did not have any seizures from (b) (6). The last entry in the seizure diary was on (b) (6) (the family did not return the last seizure diary containing information until (b) (6) “despite several phone requests”). The baseline ECG on Study Day 1 was reported as “abnormal but not clinically significant” (no follow-up ECGs were performed according to the CRF).

Subject 3101-6002, a 53 year-old white male treated with perampanel for 174 days in OLE Study 307 (in addition to 133 days in DB Study 306), who died after a **cerebral hemorrhage**. The subject had a history of complex partial seizures with and without secondary generalization and was being treated with topiramate and carbamazepine. Comorbidities included gastritis. No other concomitant medications were reported. The subject was randomized to the perampanel 8 mg treatment group in the DB Study 306 which the subject completed without any significant events reported and subsequently entered the OLE Study 307. The patient continued on perampanel 8 mg per day and completed the titration to 12 mg per day. On OLE Day 174 (b) (6) the subject developed a severe headache along with nausea, vomiting, and loss of consciousness. The subject was hospitalized and vitals revealed a BP of 220/110 and CT scan revealed an intracranial hemorrhage with hematoma in the thalamus and hemorrhage into the cerebral ventricles. On Study Day 176, the patient died. No autopsy was conducted. The subject received his last dose of perampanel on Day 174. In the seizure diary, it is recorded that the subject had only one seizure (complex partial without secondary generalization) from (b) (6). The last vitals checked during the study (on February 3, 2010) revealed a BP of 132/90 and HR of 68. The last labs checked on January 6, 2010 were at baseline (including platelet count). (The hematology parameters, PT and PTT, were not analyzed in this trial).

Subject 2802-5014, a 27 year-old white female treated with perampanel for 172 days in OLE Study 307 who died suddenly. The subject had a history of complex partial seizures with and without secondary generalization and was being treated with phenobarbital, carbamazepine, and levetiracetam. Past medical history included encephalitis and hypotension. The subject was randomized to the placebo group in the DB Study 305 which the subject completed and subsequently entered OLE Study 307. The subject started the titration of perampanel at 2 mg and on OLE Day 149, the subject started the maintenance period at 12 mg of perampanel. On OLE Day 173, the subject died suddenly. The subject’s father reported that the subject fell in the kitchen (subject did not have a seizure). The subject was noted with ventricular fibrillation on ECG unresponsive to cardioversion performed by EMS. Electrolyte changes were suspected, but lab tests were not performed (prior labs did not reveal any electrolyte abnormalities). Prior ECGs revealed sinus bradycardia and left ventricular hypertrophy with repolarization changes and a normal QTc interval. Seizure diary did not reveal any entries for 10 months. The cause of death was “**sudden death, cause unknown.**” The subject received her last dose of perampanel presumably on Study Day 172. No autopsy was performed.

Subject 5128-4011, a 73 year-old white male treated with perampanel for 616 days in OLE Study 307 who died from pneumonia. The subject had a history of simple and complex partial seizures with and

without secondary generalization and was being treated with levetiracetam, zonisamide, and oxcarbazepine. Comorbidities included melanoma, squamous cell carcinoma, hip fracture, chronic falls/balance impairment. The subject was randomized to the placebo group in the DB Study 304 and on Study Day 128, the subject experienced a seizure and a fall resulting in a subdural hematoma and intracerebral hemorrhage. The subject completed the study and entered the OLE Study 307. On OLE Day 1, the subject's labs revealed a low sodium value of 128 mmol/L (baseline 136, reference range 135-148 mmol/L). The investigator stopped the concomitant drug, oxcarbazepine, with resolution of the hyponatremia. On Study Day 201, while on the maintenance dose of 12 mg perampanel, the subject experienced the AE of anger. On Study Day 604, the subject experienced pneumonia and was hospitalized. One week later, the subject was transferred to hospice. On Study Day 616, the subject died with the cause of death listed as **pneumonia**. No autopsy was performed. The subject received the last dose of perampanel on Study Day 611.

Subject 1007-4009, a 50 year-old white male treated with perampanel for 537 days in OLE Study 307 (in addition to 133 days in DB Study 304), who died from a head injury. The subject had a history of traumatic brain injury, subarachnoid hemorrhage, mild cognitive impairment, pancreatitis, seizure disorder. Concomitant medications included oxcarbazepine, phenobarbital, fenofibrate, sertraline, clobazam, and omeprazole. On OLE Day 416, while on the maintenance dose of 12 mg perampanel, the subject experienced a seizure and traumatic intracranial hemorrhage with subdural hygroma. On Study Day 530, the subject experienced another seizure resulting in a temporal bone fracture and fronto-parietal hematoma. The hospital course was complicated by pneumonia requiring IV antibiotics and mechanical ventilation. The subject received his last dose of perampanel on Study Day 537. The subject later developed a urinary tract infection, device related infection, meningitis, and hydrocephalus requiring catheter drainage. On Study Day 593, the subject died (56 days after the last dose of perampanel) because of "dysfunction of the catheter" and worsening hydrocephalus. The cause of death was described as non-traumatic cardiac arrest secondary to **hydrocephalus** caused by the event of head injury.

Subject 2760-6003, a 20 year-old Asian female treated with perampanel for 197 days in OLE Study 307 (in addition to 138 days in DB Study 306), who delivered a male infant who died shortly after birth. Medical history included pyrexia of unknown origin. Concomitant medications included clobazam, domperidone, carbamazepine, paracetamol, pantoprazole. On OLE Day 198, the subject's pregnancy test was positive. The subject had received her last dose of perampanel one day prior on Study Day 197 (the subject received perampanel for 54 days since her last menstrual period). On Study Day 415 (39 weeks gestation), the subject delivered a male neonate who died within 6 hours of birth. An autopsy was performed but the results were not available. The cause of death was listed as **neonatal aspiration** of fluid during birth.

Nonepilepsy population: 22 deaths in patients treated with perampanel. The first 2 cases were considered possibly related to study drug by the investigators. None of the other 20 deaths were considered related to perampanel by the Sponsor. Summaries of the Sponsor's narratives of these deaths are provided in the following paragraphs.

Comment: After reviewing the details for the first 2 cases, these deaths were unlikely related to perampanel (see my comments following each of these 2 cases). After reviewing the available clinical details for the other 20 deaths, it is difficult to draw any definitive conclusions about the causal role of perampanel in these deaths. Most of these deaths occurred in subjects at high risk (n=13) due to their older age and significant comorbidities (diabetes mellitus, coronary artery disease, arrhythmias, aortic stenosis, and other cardiovascular risk factors). Other deaths were due to malignancies

(n=3) that are more common in this older age cohort. One death was due to acute pancreatitis (cholelithiasis and pancreatitis are discussed further in Section 7.3.5.1 Hepatobiliary Disorders).

Finally, there were 3 deaths in the Parkinson's disease studies resulting from complications related to injuries (cervical hematoma, hip fracture, femoral neck fracture). Two of these occurred in the DB studies (0.13% compared to 0.12% in placebo, n=1 femur fracture prior to MI). These types of injuries are more common in this older age cohort particularly with gait disturbances related to Parkinson's disease. However, there is also an association between perampanel and an increased incidence of falls and somnolence (please see Section 7.3.4.2 Nervous System Disorders). Therefore, it is important to note that the subject who sustained the cervical hematoma had also reported the AE of somnolence prior to the fall that led to a complicated surgical and hospital course, ultimately resulting in death.

[Of note, there were discrepancies in the Study Day numbers between the narratives and the CRFs. Therefore, the days listed in the narratives below are approximate].

Subject 0112-0002, a 65 year-old white male treated with perampanel for 14 days in DB Study 204 who died from severe cardiac failure. The subject had a primary diagnosis of Parkinson's disease on multiple medications (not translated in CRF). Comorbidities included chronic obstructive pulmonary disease and hypertension. No other concomitant medications other than for Parkinson's disease were reported. The subject was started on 0.5 mg of perampanel on (b) (6). On Study Day 9, he experienced the SAEs of severe dyspnoea and tachycardia. Vitals revealed a BP of 120/80 (lower than baseline BP 140/95) and HR of 88. EKG revealed "S1-Q3 type" but was reportedly "lost at site." Labs were notable for a high potassium value of 5.4 mmol/L (prestudy values ranged from 4.3 to 5.3). The study drug was continued. On Day 14, the subject was hospitalized for mild, peripheral edema. The subject received his last dose of perampanel on Day 14. Vitals revealed a BP of 115/90 and HR of 92 (weight increased 4 kg from baseline). EKG revealed "tachycardia, S1-Q3-type." During the hospitalization, he was diagnosed with lung cancer. On Day 35, the subject developed severe "cardiac failure" and died from "multiple organ insufficiency." It was not reported whether an autopsy was conducted.

Comment: This case was considered "possibly related" by the investigators. However, the subject most likely sustained a pulmonary embolism (the "S1-Q3-type" on ECG can be indicative of right heart strain due to pulmonary emboli). The patient had risk factors of developing a PE from the hypercoagulable state due to the underlying undiagnosed malignancy. Furthermore, the subject was on a low dose of perampanel.

Subject 0407-0015, a 71 year-old white male treated with perampanel for 258 days in OLE Study 205 who died from **hypotension**. The subject had a primary diagnosis of Parkinson's disease on pramipexole, amantadine, and levodopa/benserazide. Comorbidities included hypertension, cerebral vasculopathy, right sciatic pain, and cardiac conduction disorders ("right branch block and right anterior block"). Other concomitant medications included acetylsalicylic acid. The subject was randomized to the placebo group in the DB Study 204 which the subject completed without any events and subsequently entered OLE Study 205. The subject was started on 1 mg of perampanel on (b) (6) which was titrated to 2 mg on Study Day 29 (b) (6). Hypertension was recorded as an AE (BP 155/95 – 150/100). Five months later (b) (6) blood pressure was recorded as 130/90 - 140/95 and EKG was reported as having no clinically significant abnormalities (earlier blood pressure readings in 2004 were as high as 170/100). Labs were within normal limits and at baseline (including complete blood

count). “Worsening of trunk flexion” was reported as an AE by the subject. The study drug was continued, and the patient was referred to neuro-rehabilitation.

On Study Day 258 [REDACTED] (b) (6) the subject started to feel “unwell” along with back pain. He was evaluated by his family doctor who found that the BP was 80/50. Midodrine hydrochloride was administered. However, the weakness and hypotension persisted. On Day 259 [REDACTED] the subject woke up and went to the bathroom. Soon afterwards, his wife found him unresponsive on the floor. The subject was pronounced dead when EMS arrived. The subject received his last dose of perampanel on Day 258. An autopsy was not conducted.

Comment: This case was considered “possibly related” by the investigators. However, the hypotension and back pain may have been a result of an aortic aneurysm rupture. The subject had many risk factors for vasculopathy such as hypertension, “cerebral vasculopathy,” and age/sex. It is reassuring that the subject was on a low dose of perampanel and was tolerating it well for approximately 8 months.

Nonepilepsy Double-blind Trials:

Subject 0175-0007, a 66 year-old white male treated with perampanel for 53 days in DB Study 301 who died from left ventricular failure and pulmonary embolism. The subject had a primary diagnosis of Parkinson’s disease on ropinirole and levodopa/benserazide. Comorbidities included hypertension, diabetes mellitus, atherosclerosis (lower), stroke, anemia, hyperuricaemia, and incontinence. Other concomitant medications included metformin, acetylsalicylic acid, vaseretic, allopurinol, and famotidine. The subject was randomized to the 2 mg perampanel group. On [REDACTED] (b) (6) vitals were normal (BP 120/80, HR 70). On Study Day 50 [REDACTED] (b) (6) the subject developed “tracheobronchitis” and was treated with theophylline, amoxicillin-clavulanate, and bromhexine. On Day 54, he developed “**left ventricular failure and pulmonary embolism**” and died. The subject received his last dose of perampanel on Day 53. It was not reported whether an autopsy was conducted. Baseline labs revealed a mild anemia and mildly elevated eosinophil count (no follow-up labs were reported).

Subject 0201-0004, a 67 year-old white male treated with perampanel for 41 days in DB Study 301 who died from sick sinus syndrome. The subject had a primary diagnosis of Parkinson’s disease on ropinirole, entacapone, and levodopa/benserazide. Past medical history included bradycardia, angina pectoris, “extrasystoles”, stroke, and prostate hyperplasia. Other concomitant medications included bisacodyl and finasteride. The subject was randomized to the 2 mg perampanel group. On [REDACTED] (b) (6), blood pressure (115/60, HR 68) was slightly lower than baseline (baseline BP 130/80, HR 72). On Study Day 41 [REDACTED] (b) (6) the subject developed **sick sinus syndrome** (treated with amiodarone and glyceryl trinitrate) and died. The subject received his last dose of perampanel on Day 41. It was not reported whether an autopsy was conducted. Baseline labs revealed a mildly elevated creatinine (no follow-up labs were reported).

Subject 0129-0012, an 84 year-old white male treated with perampanel for 161 days in DB Study 301 who died from respiratory failure. The subject had a primary diagnosis of Parkinson’s disease on levodopa/carbidopa/entacapone. Past medical history included stroke, diabetes mellitus, supraventricular arrhythmia, ischemic heart disease, hypertension, and benign prostatic hyperplasia. Other concomitant medications included acetylsalicylic acid, amlodipine, ramipril, nimesulide, furosemide, isosorbide, and propafenone. The subject was randomized to the 4 mg perampanel group. On Study Day 146 [REDACTED] (b) (6) the subject was hospitalized for “idiopathic colitis” and was treated with mesalazine and famotidine. On Study Day 156, while in the hospital, the subject developed severe “bronchopneumonia” and was treated with multiple antibiotics (meropenem, cefoperazone, cefotaxime sodium), spironolactone, digoxin, ipratropium bromide, and enoxaparin. The subject received his last dose of perampanel on Day 161. On Study Day 177 [REDACTED] (b) (6) the subject died due to **acute respiratory distress syndrome**. It was not reported whether an autopsy was conducted. Last labs [REDACTED] (b) (6) were within normal limits (including WBC).

Subject 0165-0006, an 81 year-old white female treated with perampanel for 128 days in DB Study 301 who died from “circulatory collapse.” Along with a primary diagnosis of Parkinson’s disease, the subject’s medical history included aortic stenosis. The subject was randomized to the 4 mg perampanel group. After 128 days of exposure to the study medication, the subject underwent **elective heart surgery**. On Study Day 130, the subject developed post-surgical complications and had an SAE of “circulatory collapse” and died. The subject received her last dose of perampanel on Day 128.

Subject 0132-0008, a 68 year-old white male treated with perampanel for 196 days in DB Study 301 who died from cardiac failure. Along with a primary diagnosis of Parkinson’s disease, the subject’s medical history included hypertension and prostatic hyperplasia. The subject was randomized to the 4 mg perampanel group. On Study Day 100, the subject developed unstable angina, pulmonary edema, and cardiac failure. These events resolved after treatment with ramipril, enoxaparin, nitrates, and diuretics. On Study Day 190, the subject experienced **cardiac failure**. On Study Day 196, the subject died. The subject received his last dose of perampanel on Day 196.

Subject 0571-0002, a 63 year-old white male treated with perampanel for 64 days in DB Study 302 who died from sepsis. Along with a primary diagnosis of Parkinson’s disease, the subject’s medical history included diminished vision and left knee arthrosis. The subject was randomized to the 4 mg perampanel group. On Study Day 10, the subject reported the AE of somnolence. On Study Day 52, the subject fell in the bathroom and was later hospitalized for an SAE of quadriparesis. A cervical spine MRI revealed a possible hematoma due to the fall. On Study Day 64, the subject underwent a C1-2 laminectomy and immobilization surgery. On Day 64, perampanel was discontinued and dexamethasone was initiated. Post-operative course was complicated by a gastrointestinal bleed requiring gastric surgery. Approximately 2 months later, on Study Day 131, the subject experienced an SAE of **sepsis**. On Study Day 138, the subject died. Vitals signs during the study revealed borderline orthostasis similar to the subject’s baseline (Study Day 56: supine BP 125/75, HR 80 and standing 115/75, HR 85; Study Day 0: supine BP 125/70, HR 73 and standing BP 115/60, HR 78).

Subject 0128-0003, a 78 year-old white male treated with perampanel for 74 days in DB Study 309 who died from sepsis. Along with a primary diagnosis of Parkinson’s disease, the subject’s medical history included hyperuricemia and fracture of the right upper extremity. The subject was randomized to the 4 mg perampanel group. On Study Day 29, the subject experienced an SAE of **stroke** and was treated with pentoxifylline. During the hospitalization, the subject experienced the SAE of confusion (and AE of vivid dreams) which led to the discontinuation of perampanel on Day 74. More than 1 month later, on Study Day 111, the subject experienced an SAE of **sepsis**. On Study Day 112, the subject died.

Subject 0752-0004, a 77 year-old white male treated with perampanel for 58 days in DB Study 309 who died from hip fracture. Along with a primary diagnosis of Parkinson’s disease, the subject’s medical history included pneumonia, coronary heart disease, chronic heart failure, and anemia. The subject was randomized to the 4 mg perampanel group. On Study Day 52, the subject experienced an SAE of **hip fracture** and was hospitalized. The subject underwent surgical repair. On Study Day 60, the subject died. The subject received his last dose of perampanel on Day 58. Vital signs on Study Day 42 were at baseline and were negative for orthostasis.

Subject 1301-1002, a 67 year-old white male treated with perampanel for 86 days in the neuropathy DB Study 227 who died from **acute pancreatitis**. Comorbidities included hypertension and diabetes mellitus. The subject was randomized to the 8 mg perampanel group. On Study Day 84, the subject experienced the SAE of severe acute pancreatitis (with cholelithiasis). Perampanel was discontinued on Day 86. The subject’s prolonged hospital course was complicated by renal failure (requiring hemodialysis), atrial fibrillation, urinary tract infection, and blood pressure fluctuation. On Study Day 159, the subject died. An autopsy was not conducted.

Subject 1324-1004, a 73 year-old white female treated with perampanel for 3 days in the neuropathy DB Study 227 who died from “multi-organ failure.” Comorbidities included coronary artery disease, hypertension, hyperlipidemia, diabetes mellitus, anemia, and chronic renal insufficiency. The subject was randomized to the 2 mg perampanel group. On Study Day 1, the subject began experiencing shortness of breath, nausea, dizziness, incoherence, and weakness. The investigator considered these events to be probably related to the study drug and the subject was discontinued from the study. The subject received his last dose of perampanel on Day 3. Subsequently, the dizziness, incoherence, and weakness resolved. On Study Day 17, the subject experienced a **cerebrovascular accident**. Brain MRI revealed a right middle cerebral artery territory infarction with hemorrhagic transformation with mass effect and midline shift. On Study Day 28, the subject died due to multi-organ failure.

Nonepilepsy OLE Trials

Subject 0122-0004, a 72 year-old white male (Parkinson’s disease) treated with perampanel for 813 days in OLE Study 205 (in addition to 84 days in DB Study 204) who died from “general physical health deterioration.” The subject was randomized to the 1 mg perampanel group during DB Study 204 which the subject completed with the following adverse events reported: confusion, vertigo, cognitive deficit, and “amentia”. Once enrolled in OLE Study 205, the perampanel dose was titrated up to 4 mg. Subject experienced AEs of pneumonia (Day 26), vertigo and swollen feet bilateral (Day 48), joint/muscle pains (Day 65), downfall, hallucination, and gait disturbance (Day 99), dementia, cachexia, infection, and anemia (Day 811), and worsening PD (Day 814). The subject received his last dose of perampanel on Day 813. On Study Day 828, the subject experienced a SAE of **general physical health deterioration** and died due to “old age.” An autopsy was not performed.

Subject 0604-0009, a 53 year-old white male (Parkinson’s disease) treated with perampanel for 892 days in OLE Study 205 (in addition to 84 days in DB Study 204) who died unexpectedly. Past medical history included hypertension and depression. The subject was randomized to the 1 mg perampanel group during DB Study 204 which the subject completed without any significant events and subsequently entered the OLE Study 205. The patient continued on perampanel 1 mg per day and completed the titration to 4 mg. Only one adverse event was recorded (drowsiness). On Day 892, the subject had a **sudden worsening of his cardiorespiratory function** and died. An autopsy was not performed. Last EKG (on Study Day 826) was reported as normal sinus rhythm with a heart rate of 66 bpm with possible left atrial enlargement. The subject received his last dose of perampanel on Day 892.

Subject 0239-0008, a 79 year-old white male (Parkinson’s disease) treated with perampanel for 63 days in OLE Study 303 who died from **cardiac failure**. Past medical history included hypertension and arthritis. The subject was randomized to the placebo group in the DB Study 301 during which the subject developed the following adverse events: acute myocardial infarct requiring coronary artery stenting, cardiac failure, renal function impairment, confusion, weakness, hypotension, and intermittent falls. The subject subsequently entered OLE Study 303 and was started on 2 mg of perampanel which was titrated up to 4 mg. On Day 20, the subject experienced an SAE of acute left ventricular failure and was hospitalized and treated with furosemide. On Study Day 60, the subject experienced an SAE of cardiac failure. The subject received his last dose of perampanel on Day 63. On Study Day 74, the subject died.

Subject 0176-0001, a 65 year-old white female (Parkinson’s disease) treated with perampanel for 157 days in OLE Study 303 (in addition to 223 days in DB Study 301) who died from sepsis. The subject was randomized to the 4 mg perampanel group in the DB Study 301 which the subject completed without any events and subsequently entered OLE Study 303 and continued on 4 mg. On Day 119 (b) (6), the subject experienced an SAE of **femoral neck fracture** requiring surgical repair. Subsequently, the subject developed pneumonia and decubitus ulcers leading to **sepsis** and treatment with multiple antibiotics. On Study Day 158 (b) (6) the subject died. The subject received her last dose of perampanel on Day 157. The vital sign measurement on (b) (6) revealed hypotension (BP 90/70) and was lower than baseline (110/70).

Subject 0178-0005, a 77 year-old white male (Parkinson's disease) treated with perampanel for 355 days in OLE Study 303 (in addition to 218 days in DB Study 301) who died from cardiopulmonary failure. Past medical history included bronchiectasis, atherosclerosis, hypercholesteremia. The subject was randomized to the 4 mg perampanel group in the DB Study 301 which the subject completed without any events and subsequently entered OLE Study 303 and continued on 4 mg. The following adverse events were recorded: "fatigue, fainting, anxiety, dizziness, tiredness, and orthostasis-fall." On Day 356 (b) (6) the subject experienced an SAE of "**cardiopulmonary failure**" and died. The subject received his last dose of perampanel on Day 355. Vitals on the last visit (b) (6) were normal (supine BP 136/79, HR 64) along with an ECG that was reportedly without any clinically significant abnormalities.

Subject 0178-0013, a 58 year-old white female (Parkinson's disease) treated with perampanel for 319 days in OLE Study 303 (in addition to 217 days in DB Study 301) who died from "**metastatic bronchial carcinoma**." The subject was randomized to the 4 mg perampanel group in the DB Study 301 which the subject completed without any events and subsequently entered OLE Study 303 and continued on 4 mg. The following adverse events were recorded: "hypotension, hypertension, often falls." On Day 308, the subject was hospitalized for severe pneumonia and a pleural effusion. On Study Day 312, drainage of the pleural fluid was performed and was subsequently diagnosed with a "primary chest malignancy." On Study Day 322 (b) (6) the subject died from pneumothorax and respiratory failure. The subject received her last dose of perampanel on Day 319.

Subject 0215-0002, a 68 year-old white male (Parkinson's disease) treated with perampanel for 171 days in OLE Study 303 (in addition to 210 days in DB Study 301) who died from a "malignant lung neoplasm." The subject was randomized to the 4 mg perampanel group in the DB Study 301 which the subject completed and subsequently entered OLE Study 303 and continued on 4 mg. On Day 156 (b) (6) the subject was hospitalized for "breathlessness, coughing, and a feverish state." A CT scan revealed a **malignant lung neoplasm**. The subject received his last dose of perampanel on Day 171. On Study Day 189, the subject died while at home with palliative care.

Subject 0132-0005, a 77 year-old white male (Parkinson's disease) treated with perampanel for 35 days in OLE Study 318 who died from cardiopulmonary failure. Past medical history included myocardial infarction, ischemic heart disease, pneumonia. The subject was randomized to the 200 mg entacapone group in the DB Study 309 which the subject completed and subsequently entered OLE Study 318 and switched to perampanel (titrated to 4 mg). The following adverse events were recorded: atrial fibrillation (Day 0) and transient ischemic attack (Day 17). The subject received his last dose of perampanel on Day 35. More than 1 month later on Study Day 70, the subject developed hypotension, hypoxemia, and tachycardia. On Study Day 71 (b) (6) the subject died due to **cardiopulmonary failure**.

Subject 1407-1002, a 61 year-old white female (neuropathic pain) treated with perampanel for 83 days in OLE Study 228 who died unexpectedly. Past medical history included coronary artery disease. The subject was randomized to the placebo group in the DB Study 227 and subsequently entered OLE Study 303 and was started on 2 mg of perampanel which was titrated up to 4 mg. The subject received her last dose of perampanel on Day 83 (b) (6). On Day 105 (b) (6) the subject was found unresponsive by her husband. It was recorded that the subject experienced **sudden death likely from an acute malignant arrhythmia**. No autopsy was performed.

Comment: This is likely not related to perampanel as the death occurred after approximately 5 elimination half-lives of perampanel.

Subject 1321-1010, a 68 year-old white male (neuropathic pain) treated with perampanel for 273 days in OLE Study 228 who died from adenocarcinoma. The subject was randomized to the placebo group in the DB Study 227 and subsequently entered OLE Study 303 and was started on 2 mg of perampanel which was titrated up to 6 mg. On Day 147, the patient experienced a worsening of baseline congestive heart failure. On Study Day 205, the subject was hospitalized for cor pulmonale secondary to congestive heart

failure. On Study Day 273 (b) (6) the subject was hospitalized for nausea and vomiting and diagnosed with **metastatic adenocarcinoma**. The subject died on (b) (6). The subject received his last dose of perampanel on Day 273.

7.3.2 Nonfatal Serious Adverse Events

The Sponsor defined serious adverse events (SAEs) as those that result in death, are life-threatening, require hospitalization or prolonged hospitalization, or result 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 Sponsor. All SAEs were followed by the investigators until resolution or stabilization. This approach was acceptable to the reviewer.

In the Epilepsy All Treated Pool (Phase 2/3 DB and OLE trials), a total of 17.3% (285/1651) of perampanel exposed subjects experienced one or more treatment emergent SAEs as of the data cut-off date of the 120-day Safety Update. The MedDRA SOC for which most subjects had an SAE was Nervous System Disorders (6.7%, n=110), followed by Injury, Poisoning and Procedural Complications (3.9%, n=64) and Psychiatric Disorders (3.6%, n=59). The MedDRA PT for which most subjects had an SAE was Convulsion (2.7%, n=44), followed by Status Epilepticus (1.1%, n=18) and Aggression (0.8%, n=14). The following table lists the SAEs by MedDRA SOC (in descending order of frequency in the Epilepsy All Treated Pool) for both the epilepsy and nonepilepsy all treated pools.

The percentage of subjects with SAEs was higher in the epilepsy all treated pool (17.3%) than the nonepilepsy all treated pool (11.7%). However, after adjusting for differences in exposure, the incidence of SAEs in the epilepsy pool (2.40 per 1000 subject-weeks) is less than the nonepilepsy pool (3.70 per 1000 subject-weeks). There were differences in the SOC distribution between the epilepsy and nonepilepsy pools (likely due to the underlying diseases and comorbidities). The epilepsy pool had a much lower incidence rate of SAEs in the following SOCs: Cardiac, Neoplasms, Musculoskeletal, General, Renal, Respiratory, and Vascular disorders.

Table 25. Treatment-Emergent SAEs by System Organ Class

	Epilepsy All Treated Pool	Nonepilepsy All Treated Pool
Total number of subjects	1651	2717
Subjects with any Treatment-Emergent SAE	285	319
Incidence of SAEs per number of subjects	17.3%	11.7%
Total exposure (subject-weeks)	118920.0	86176.1
Incidence of SAEs per 1000 subject-weeks	2.40	3.70
MedDRA SOC	n (% , 1000 subject-wks)	
Nervous System Disorders	110 (6.7%, 0.92)	82 (3.0%, 0.95)
Injury, Poisoning and Procedural Complications	64 (3.9%, 0.54)	52 (1.9%, 0.60)
Psychiatric Disorders	59 (3.6%, 0.50)	43 (1.6%, 0.50)
Infections and Infestations	35 (2.1%, 0.29)	45 (1.7%, 0.52)
Gastrointestinal Disorders	17 (1.0%, 0.14)	31 (1.1%, 0.36)
Cardiac disorders	12 (0.7%, 0.10)	46 (1.7%, 0.53)
Neoplasms Benign, Malignant and Unspecified	11 (0.7%, 0.09)	23 (0.8%, 0.27)
Musculoskeletal and Connective Tissue Disorders	10 (0.6%, 0.08)	31 (1.1%, 0.36)
General Disorders and Administration Site	9 (0.5%, 0.07)	19 (0.7%, 0.22)
Reproductive System and Breast Disorders	7 (0.4%, 0.06)	5 (0.2%, 0.06)
Surgical and Medical Procedures	6 (0.4%, 0.05)	5 (0.2%, 0.06)
Renal and Urinary Disorders	5 (0.3%, 0.04)	7 (0.3%, 0.08)
Metabolism and Nutrition Disorders	5 (0.3%, 0.04)	6 (0.2%, 0.07)
Respiratory, Thoracic and Mediastinal Disorders	4 (0.2%, 0.03)	17 (0.6%, 0.20)
Hepatobiliary Disorders	4 (0.2%, 0.03)	4 (0.1%, 0.05)
Investigations	4 (0.2%, 0.03)	4 (0.1%, 0.05)
Pregnancy, Puerperium and Perinatal Conditions	4 (0.2%, 0.03)	0
Vascular Disorders	3 (0.2%, 0.02)	15 (0.6%, 0.17)
Eye Disorders	3 (0.2%, 0.02)	2 (0.1%, 0.02)
Blood and Lymphatic System Disorders	1 (0.1%, 0.01)	3 (0.1%, 0.03)
Ear and Labyrinth Disorders	1 (0.1%, 0.01)	2 (0.1%, 0.02)
Endocrine Disorders	1 (0.1%, 0.01)	1 (0.0%, 0.01)
Skin and Subcutaneous Tissue Disorders	1 (0.1%, 0.01)	1 (0.0%, 0.01)
Congenital, Familial and Genetic Disorders	1 (0.1%, 0.01)	0
Social circumstances	0	2 (0.1%, 0.02)

Source: ISS Tables 20.7-3 and 20.7-10 and 120-day Safety Update Table 19

Of note, there was one additional SAE in Study 233 (reported in a separate clinical study report in the 120-day Safety Update submission due to tsunami-related delays in the Japanese study), subject 1009-1001 who was hospitalized for a planned hemorrhoidectomy for chronic hemorrhoids. No other additional SAEs, deaths, or TEAEs leading to discontinuations were reported in Study 233.

In the epilepsy clinical development program, 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. There was one SAE of acute pancreatitis

in the epilepsy OLE studies (reviewed in Section 7.3.5.1 Hepatobiliary Disorders). In the nonepilepsy trials, there were SAEs coded to acute renal failure, acute pancreatitis, and rhabdomyolysis (reviewed in detail in Sections 7.3.5 and 7.4.2.3).

Epilepsy DB Pools

In the Phase 3 DB pool, the number of subjects with at least 1 SAE was lower than placebo in the two lowest dose groups (2 mg and 4 mg), similar in the 8 mg group, and higher than placebo in the 12 mg group. After stratifying by study, a dose response relationship was only seen in Studies 304 and 305. In Study 306, the three treatment groups had lower incidences of SAEs than the placebo group. After including the OLE studies, the incidence rate for the total perampanel group for the all treated pool was lower at 2.40 (285/118920 subject-weeks) than the Phase 3 DB pool at 3.19 (57/17862.6 subject-weeks).

Table 26. Incidence of SAEs by Randomized Dose, Epilepsy DB Pools

Subjects with any SAE	Placebo n (%)	Perampanel n (%)				
		2 mg	4 mg	8 mg	12 mg	Total
Epilepsy Phase 2 DB	3 (4.4)	0	2 (2.0)	NA	1 (2.6)	3 (2.0)
Epilepsy Phase 3 DB	22 (5.0)	6 (3.3)	6 (3.5)	24 (5.6)	21 (8.2)	57 (5.5)
Study 304	6 (5.0)			8 (6.0)	9 (6.7)	17 (6.4)
Study 305	7 (5.1)			10 (7.8)	12 (9.9)	22 (8.8)
Study 306	9 (4.9)	6 (3.3)	6 (3.5)	6 (3.6)		18 (3.5)

Source: ISS Tables 117, 118 and CSR 304 Table 12.4, CSR 305 Table 12.4, CSR 306 Table 12.4

Nonepilepsy DB Trials

In the nonepilepsy DB studies, the highest dose group (>4-8 mg) had a two-fold higher incidence of SAEs than the placebo group, whereas both of the lower dose groups had similar incidences of SAEs to the placebo group.

Table 27. Incidence of SAEs by Randomized Dose, Nonepilepsy DB Pools

Subjects with any SAE	Placebo n (%)	Perampanel n (%)				Total
		<4 mg	4 mg	>4-8 mg	>8-12 mg	
Nonepilepsy DB	65 (6.0)	49 (5.4)	56 (6.9)	33 (11.3)	NA	138 (6.9)
Parkinson's Disease DB	60 (7.1)	46 (6.4)	54 (7.2)	8 (14.5)	NA	108 (7.1)
Neuropathic Pain DB	4 (3.3)	2 (2.8)	2 (2.9)	25 (10.6)	NA	29 (7.7)

Source: ISS Tables 20.7-10, 20.7-15, 20.7-16, 20.7-17, 44, 45

The following table summarizes the relative risk of SAEs by DB pooled groups. While none of the values reach statistical significance, there is a weak trend of higher incidences of SAEs in the perampanel group than placebo.

Table 28. Relative Risk of SAEs by DB Pooled Groups

Double-Blind Pool	Perampanel		Placebo		Relative Risk (95% C.I.)
	SAE	n	SAE	n	
Epilepsy DB Pool	60	1189	25	510	1.03 (0.65-1.62)
Phase 3 DB Pool	57	1038	22	442	1.10 (0.68-1.78)
Phase 2 DB Pool	3	151	3	68	0.45 (0.09-2.17)
Nonepilepsy DB Pool	138	2013	65	1079	1.14 (0.86-1.51)
Parkinson's DB Pool	108	1517	60	845	1.003 (0.74-1.36)
Neuropathic Pain DB Pool	29	377	4	121	2.33 (0.83-6.49)
All studies	198	3202	90	1589	1.09 (0.86-1.39)

The following table stratifies the SAEs by MedDRA system organ class (SOC). The incidence of SAEs in the total perampanel group was higher than placebo for the following SOCs in both the epilepsy and nonepilepsy DB pools: Psychiatric disorders and Injury/poisoning/procedural complications. A dose response relationship was present, with the highest dose groups with nearly 3 times the incidence of these SAEs than the placebo group. Smaller differences were seen in the SOCs Eye disorders, Neoplasms, and Vascular disorders.

Conversely, in the epilepsy pool, the SAE incidence in the total perampanel group was lower than placebo group for the following SOCs: Nervous system disorders, and Infections/infestations. Furthermore, there were no SAEs in the Epilepsy DB pool for the following 2 major organ systems: Cardiac and Respiratory disorders.

Table 29. SAEs by System Organ Class and Randomized Treatment Group, Epilepsy and Nonepilepsy Double-blind pools (with > 1 subject)

MedDRA SOC Pooled Group	Placebo n (%)	Perampanel n (%)*				Total
		<4 mg*	4 mg*	>4-8 mg*	>8-12 mg*	
Number of Subjects						
Epilepsy Phase 3 DB	442	180	172	431	255	1038
Epilepsy Phase 2 DB	68	12	101	0	38	151
Epilepsy DB Pool	510	192	273	431	293	1189
Nonepilepsy DB Pool	1079	908	814	291	0	2013
SAE Incidence in Perampanel group > Placebo group in BOTH pools for the following SOCs:						
Psychiatric disorders						
Epilepsy DB Pool	4 (0.8)	3 (1.6)	1 (0.4)	2 (0.5)	7 (2.4)	13 (1.1)
Nonepilepsy DB Pool	6 (0.6)	3 (0.3)	8 (1.0)	5 (1.7)	0	16 (0.8)
Injury/poisoning/procedure						
Epilepsy DB Pool	3 (0.6)	1 (0.5)	0	5 (1.2)	7 (2.4)	13 (1.1)
Nonepilepsy DB Pool	9 (0.8)	8 (0.9)	11 (1.4)	7 (2.4)	0	26 (1.3)
Eye disorders						
Epilepsy DB Pool	0	0	2 (0.7)	0	0	2 (0.2)
Nonepilepsy DB Pool	0	1 (0.1)	1 (0.1)	0	0	2 (0.1)
Neoplasms						
Epilepsy DB Pool	0	0	0	1 (0.2)	0	1 (0.1)
Nonepilepsy DB Pool	2 (0.2)	4 (0.4)	2 (0.2)	0	0	6 (0.3)
Vascular disorders						
Epilepsy DB Pool	0	0	0	1 (0.2)	0	1 (0.1)
Nonepilepsy DB Pool	2 (0.2)	4 (0.4)	1 (0.1)	1 (0.3)	0	6 (0.3)
SAE Incidence in Perampanel group > Placebo group in the EPILEPSY pool (but not in the nonepilepsy pool) for the following SOCs:						
Musculoskeletal & CT						
Epilepsy DB Pool	0	0	0	4 (0.9)	0	4 (0.3)
Nonepilepsy DB Pool	3 (0.3)	3 (0.3)	1 (0.1)	1 (0.3)	0	5 (0.2)
Renal & Urinary disorders						
Epilepsy DB Pool	0	1 (0.5)	0	0	2 (0.7)	3 (0.3)
Nonepilepsy DB Pool	4 (0.4)	0	2 (0.2)	2 (0.7)	0	4 (0.2)
Gastrointestinal disorders						
Epilepsy DB Pool	1 (0.2)	0	0	1 (0.2)	2 (0.7)	3 (0.3)
Nonepilepsy DB Pool	12 (1.1)	5 (0.6)	6 (0.7)	1 (0.3)	0	12 (0.6)
Hepatobiliary disorders						
Epilepsy DB Pool	0	0	1 (0.4)	1 (0.2)	0	2 (0.2)
Nonepilepsy DB Pool	2 (0.2)	1 (0.1)	0	1 (0.3)	0	2 (0.1)
Reproductive/Breast						
Epilepsy DB Pool	0	0	0	0	2 (0.7)	2 (0.2)
Nonepilepsy DB Pool	1 (0.1)	0	1 (0.1)	1 (0.3)	0	2 (0.1)

Source: ISS Tables 20.7-1 and 20.7-15

*Randomized treatment groups for Epilepsy Phase 3 DB Pool: 2 mg, 4 mg, 8 mg, and 12 mg

The following table lists the SAE preferred terms (PTs) that occurred in ≥ 2 subjects in the total perampanel group and more frequently than placebo in the epilepsy and

nonepilepsy DB pools. In the epilepsy DB pool, the most frequent SAEs were dizziness, somnolence, aggression, and head injury. In the nonepilepsy DB pool, the most frequent SAEs were fall and confusional state. Some of the SAEs that occurred in the nonepilepsy population did not occur in the epilepsy population because they were associated with the underlying disease (e.g., Parkinson’s disease). The SAE narratives were also reviewed for those that occurred in one perampanel subject. Those SAEs were grouped together and reviewed in detail in Sections 7.3.4 and 7.3.5.

Table 30. SAEs in ≥ 2 perampanel subjects and more frequent than placebo

MedDRA PT	Epilepsy DB Pool		Nonepilepsy DB Pool	
	Placebo	Perampanel	Placebo	Perampanel
All Subjects	510	1189	1079	2013
Subjects with any SAE	22 (4.3)	57 (4.8)	106 (9.8)	314 (15.6)
Dizziness	0	3 (0.3)		
Somnolence	0	3 (0.3)		
Aggression	0	3 (0.3)		
Head Injury	0	3 (0.3)		
Facial bones fracture	0	2 (0.2)		
Cholelithiasis	0	2 (0.2)		
Wound Infection Staphylococcal	0	2 (0.2)		
Fall			2 (0.2)	8 (0.4)
Confusional state			1 (0.1)	5 (0.2)
Parkinson’s disease			0	4 (0.2)
Atrial fibrillation			0	4 (0.2)
Non-cardiac chest pain			0	4 (0.2)
Urinary tract infection			1 (0.1)	4 (0.2)
Cellulitis			0	4 (0.2)
Dyspnoea			0	4 (0.2)
Cerebrovascular accident			0	3 (0.1)
Cystitis			0	3 (0.1)
Sepsis			0	3 (0.1)
Pulmonary embolism			0	2 (0.1)
Renal failure acute			0	2 (0.1)
Insomnia			0	2 (0.1)
Mental status changes			0	2 (0.1)
Suicide attempt			0	2 (0.1)
Akinesia			0	2 (0.1)
Dyskinesia			0	2 (0.1)
Lumbar vertebral fracture			0	2 (0.1)
Meniscus lesion			0	2 (0.1)
Cardiac failure			0	2 (0.1)
Cardiac failure congestive			0	2 (0.1)
Tachycardia			0	2 (0.1)
Cataract			0	2 (0.1)
Hospitalisation			0	2 (0.1)

Source: ISS Tables 20.7-1 and 20.7-15

Phase 1 Trials

There were 2 subjects who reported SAEs in the Phase 1 studies (both occurred in the multiple-dose studies). The SAEs and AEs (falls, head injury, concussion, loss of consciousness) in the first subject were likely a result of the rapid titration of perampanel. Falls will be further discussed in Section 7.3.4.2 Nervous System Disorders. The SAEs in the second subject (anxiety and paranoia) will be further discussed in Section 7.3.4.1 Psychiatric Disorders.

Subject 1001-0285, a 19 year-old white female treated with perampanel in Study 013 who developed the SAEs of loss of consciousness and concussion. The subject received 6 mg of perampanel on (b) (6) for 7 days. The dose was then increased to 8 mg for 1 day, 10 mg for 1 day, and then 12 mg for 7 days. After starting on the 12 mg dose, the subject experienced **multiple falls** (on (b) (6)). On Study Day 15 (b) (6) 2 hours postdose, the subject fell and **hit her head** while getting out of bed. The following AEs were reported: **concussion**, incisor loose, contusion (chin), headache, dizziness, somnolence, amnesia, neck pain, loss of consciousness, dyspnea, nausea, dysarthria, dyskinesia, asthenia, and abdominal pain. The subject was noted to be flaccid and responsive only to sternal rub and was hospitalized. The study drug was discontinued on Study Day 15. The subject recovered.

Subject 1001-1009, a 44 year-old white male treated with perampanel in Study 020 who developed the SAEs of anxiety, paranoia, and unsteadiness. The subject received 6 mg of perampanel for 10 days in the study. One day after the last dose of study drug, the subject experienced the SAE of **severe anxiety**. Two days later, the subject reported insomnia, vomiting, and diarrhea. The next day, the subject experienced the SAEs of **paranoia** (moderate) and unsteadiness. After treatment with diazepam 5 mg bid, by Study Day 36 (26 days after the last dose of perampanel), the subject recovered from the SAEs. Vitals were negative for orthostasis.

Ongoing Studies

In the 120-day Safety Update, the Sponsor reported additional SAEs in ongoing epilepsy OLE Studies 207, 233, and 307 (and recently initiated Studies 232, 235, and 332) up to the data cut-off date of January 15, 2012. No SAEs occurred in Studies 232 and 332. The SAEs that occurred in ongoing Studies 207, 233, 307, and 235 are listed in the following table. These SAEs are consistent with previously reported SAEs.

Table 31. List of SAEs in Ongoing Studies

Subject	Age (y)/Sex	Treatment	Adverse Event
Study 307^a			
18016007	59/M	Perampanel, 12 mg	Cerebral infarction
18066004	48/M	Perampanel, 12 mg	Craniocerebral injury
28025013	15/F	Perampanel, 8 mg	Mandible closed fracture
28065014	45/F	Perampanel, 12 mg	Gastroduodenitis
28065014	28/F	Perampanel, 12 mg	Sudden death
33014002	24/M	Perampanel, 12 mg	Fracture of ankle
36036006	22/F	Perampanel, (dose unknown)	Head injury, Partial seizures with secondary
39065007	18/M	Perampanel, 12 mg	Radius fracture, Contusion of forearm, Traumatic amputation
51144011	19/M	Perampanel, 12 mg	Obsessive thoughts
51394006	47/M	Perampanel, 12 mg	Syncope
51735001	46/M	Perampanel, 12 mg	Epilepsy
Study 207^a			
30021024	64/M	Perampanel, 6 mg	Partial epileptic seizure
30031039	38/M	Perampanel, 12 mg	Ileitis
Study 233^a			
10091001	37/F	Perampanel, 4 mg	Hemorrhoids
Study 235^a			
10011002	17/F	Perampanel or placebo (dose unknown)	Increased seizures
10111001	16/M	Perampanel, 12 mg	Increased aggressive behavior
10421001	16/F	Perampanel or placebo (dose unknown)	Foot fracture
10611003	14/M	Perampanel (dose unknown)	Gastroduodenitis
10621001	17/M	Perampanel, 10 mg	Status epilepticus
10621002	14/M	Perampanel, 12 mg	Fracture of right metacarpal

Source: 120-day Safety Update Table 29

a: Serious adverse events reported between the cutoff date for the Safety Update (01 Oct 2011) and 15 Jan 2012.

7.3.3 Dropouts and/or Discontinuations

Epilepsy population

In the epilepsy Phase 2/3 DB studies, a higher percentage of perampanel subjects (15.1%, 179/1189) discontinued compared to placebo subjects (11.4%, 58/510). After stratifying by the primary reason for discontinuation, discontinuations due to adverse events and subject choice occurred in perampanel subjects at a greater frequency than in placebo subjects. However, discontinuations due to inadequate therapeutic effect, lost to follow-up, and “other” occurred in perampanel subjects at a lower frequency than in placebo subjects.

Of the 179 subjects who discontinued in the epilepsy Phase 2/3 DB trials, the most common reason for discontinuation was adverse events (55.9%, 100/179) and the least common reasons were lost to follow-up (2.2%, 4/179) and inadequate therapeutic effect (3.9%, 7/179).

In the epilepsy all treated pool (Phase 2, Phase 3, and OLE studies), 46.7% (771/1651) of the perampanel subjects withdrew from the studies. As of the data cut-off date, 47.5% (784) were still participating and 5.9% (96) completed the study. Of the 771 subjects who discontinued, the most common reason for discontinuation was adverse events (35.8%, 276/771) and the least common reasons were lost to follow-up (2.2%, 17/771) and “other” (9.5%, 73/771).

The following table summarizes the discontinuations by perampanel dose for each of the epilepsy pooled groups.

Table 32. Disposition and Primary Reason for Discontinuation, Epilepsy Pools

Category	Placebo n (%)	Perampanel n (%)*				Total
		<4 mg	4 mg	>4-8 mg	>8-12 mg	
Treated						
Epilepsy Phase 3 DB	442	180	172	431	255	1038
Epilepsy Phase 2 DB	68	12	101	NA	38	151
Epilepsy DB Pool	510	192	273	431	293	1189
Epilepsy All: Modal		153	192	354	952	1651
Discontinued						
Epilepsy Phase 3 DB	50 (11.3)	26 (14.4)	14 (8.1)	64 (14.8)	62 (24.3)	166 (16.0)
Epilepsy Phase 2 DB	8 (11.8)	0	9 (8.9)	NA	4 (10.5)	13 (8.6)
Epilepsy DB Pool	58 (11.4)	26 (13.5)	23 (8.4)	64 (14.8)	66 (22.5)	179 (15.1)
Epilepsy All: Modal		106 (69.3)	124 (64.6)	221 (62.4)	320 (33.6)	771 (46.7)
Primary reason for discontinuation from therapy:						
Adverse event						
Epilepsy Phase 3 DB	17 (3.8)	10 (5.6)	5 (2.9)	31 (7.2)	47 (18.4)	93 (9.0)
Epilepsy Phase 2 DB	5 (7.4)	0	5 (5.0)	NA	2 (5.3)	7 (4.6)
Epilepsy DB Pool	22 (4.3)	10 (5.2)	10 (3.7)	31 (7.2)	49 (16.7)	100 (8.4)
Epilepsy All: Modal		43 (28.1)	47 (24.5)	91 (25.7)	95 (10.0)	276 (16.7)
Subject choice						
Epilepsy Phase 3 DB	17 (3.8)	9 (5.0)	8 (4.7)	22 (5.1)	8 (3.1)	47 (4.5)
Epilepsy Phase 2 DB	0	0	1 (1.0)	NA	0	1 (0.7)
Epilepsy DB Pool	17 (3.3)	9 (4.7)	9 (3.3)	22 (5.1)	8 (2.7)	48 (4.0)
Epilepsy All: Modal		34 (22.2)	39 (20.3)	75 (21.2)	106 (11.1)	254 (15.4)
Inadequate therapeutic effect (includes one case of progressive disease in placebo group)						
Epilepsy Phase 3 DB	4 (0.9)	3 (1.7)	0	1 (0.2)	3 (1.2)	7 (0.7)
Epilepsy Phase 2 DB	0	0	0	0	0	0
Epilepsy DB Pool	4 (0.8)	3 (1.6)	0	1 (0.2)	3 (1.0)	7 (0.6)
Epilepsy All: Modal		10 (6.5)	10 (5.2)	40 (11.3)	91 (9.6)	151 (9.1)
Lost to follow-up						
Epilepsy Phase 3 DB	4 (0.9)	1 (0.6)	0	3 (0.7)	0	4 (0.4)
Epilepsy Phase 2 DB	0	0	0	0	0	0
Epilepsy DB Pool	4 (0.8)	1 (0.5)	0	3 (0.7)	0	4 (0.3)
Epilepsy All: Modal		2 (1.3)	1 (0.5)	3 (0.8)	11 (1.2)	17 (1.0)
Other						
Epilepsy Phase 3 DB	8 (1.8)	3 (1.7)	1 (0.6)	7 (1.6)	4 (1.6)	15 (1.4)
Epilepsy Phase 2 DB	3 (4.4)	0	3 (3.0)	NA	2 (5.3)	5 (3.3)
Epilepsy DB Pool	11 (2.2)	3 (1.6)	4 (1.5)	7 (1.6)	6 (2.0)	20 (1.7)
Epilepsy All: Modal		17 (11.1)	27 (14.1)	12 (3.4)	17 (1.8)	73 (4.4)

Source: ISS Tables 12, 13, 20.1-3 and 120-day Safety Update Table 20.1-23.1

*Randomized treatment groups used for Epilepsy Phase 3 DB Pool (2 mg, 4 mg, 8 mg, and 12 mg) and Epilepsy Phase 2 DB Pool.

Comment: A dose-response relationship was only observed for discontinuations due to adverse events. Discontinuations due to adverse events occurred more frequently at the higher dose groups in the epilepsy controlled trials (randomized treatment groups). However, in the epilepsy all treated pool using modal dose groups, discontinuations due to adverse events occurred more frequently at the lower dose groups.

The listings of subjects with “other” reason for discontinuation were reviewed for the 73 perampanel subjects and 11 placebo subjects (ISS Tables 20.1-1.6, 20.1-8, and Table 20.1-6). Most of the reasons were due to noncompliance or other reasons for ineligibility (e.g., prohibited concomitant medication use, pregnancy, incarceration). However, the list included at least 25 cases of lack of efficacy (all in perampanel treated subjects in the OLE Study 207). The Sponsor reported that for Study 207, inadequate therapeutic effect did not appear on the case report form as a reason for discontinuation (ISS, page 56). Therefore, these 25 cases should have been listed under the category of inadequate therapeutic effect.

Of note, there is a remarkable increase (15x) in the frequency of discontinuations due to inadequate therapeutic effect between the epilepsy DB pool (0.6%, 7/1189) and the epilepsy all treated pool (9.1%, 151/1651) which includes the OLE studies. After including the 25 cases noted above, the frequency would increase to 10.7% (176/1651) or 18 times that of the epilepsy DB pool. Even after adjusting for exposure time, the incidence rate of discontinuations due to inadequate therapeutic effect is still 4 times higher after including the OLE trials (1.5 per 1000 subject weeks or 176/118920.0) than in the DB pool (0.4 per 1000 subject weeks or 7/19863.6). This information was forwarded to the medical officer, Dr. Martin Rusinowitz, who is reviewing the efficacy of perampanel.

Nonepilepsy population

In the nonepilepsy DB pool, a higher percentage of perampanel subjects (28.0%, 563/2013) discontinued compared to placebo subjects (22.8%, 246/1078). After stratifying by the primary reason for discontinuation, discontinuations due to adverse events and inadequate therapeutic effect occurred in perampanel subjects at a greater frequency than in placebo subjects. However, discontinuations due to subject choice and “other” occurred in perampanel subjects at approximately the same or lower frequency than in placebo subjects.

Of the 563 subjects who discontinued in the nonepilepsy controlled trials, the most common reason for discontinuation was adverse events (54.7%, 308/563) and the least common reason was inadequate therapeutic effect (11.4%, 64/563).

In the nonepilepsy all treated pool, 74.3% (2018/2717) of the perampanel subjects withdrew from the studies. Of the 2018 subjects who discontinued, the most common reason for discontinuation was “other” (56.4%, 1139/2018) followed by adverse events (24.9%, 503/2018). The Sponsor reported that the high rate of discontinuation due to “other” reflected the Sponsor’s decision to terminate some Parkinson’s disease studies early (e.g., Studies 204, 309).

The following table summarizes the discontinuations by perampanel dose for each of the nonepilepsy pooled groups.

Table 33. Disposition and Primary Reason for Discontinuation, Nonepilepsy Pools

Category	Placebo n (%)	Perampanel n (%)*				Total
		<4 mg	4 mg	>4-8 mg	>8-12mg	
Treated						
Parkinson's DB	844	717	745	55	NA	1517
Neuropathic Pain DB	121	72	69	236	NA	377
Nonepilepsy DB	1078	908	814	291	NA	2013
Nonepilepsy All		1048	1441	188	40	2717
Discontinued						
Parkinson's DB	209 (24.8)	150 (20.9)	234 (31.4)	18 (32.7)	NA	420 (26.5)
Neuropathic Pain DB	25 (20.7)	16 (22.2)	12 (17.4)	112 (47.5)	NA	140 (37.1)
Nonepilepsy DB	246 (22.8)	187 (20.6)	246 (30.2)	130 (44.7)	NA	563 (28.0)
Nonepilepsy All		742 (70.8)	1175 (81.5)	90 (47.9)	11 (27.5)	2018 (74.3)
Primary reason for discontinuation from therapy:						
Adverse event						
Parkinson's DB	91 (10.8)	80 (11.2)	112 (15.0)	15 (27.3)	NA	207 (13.6)
Neuropathic Pain DB	10 (8.3)	7 (9.7)	9 (13.0)	77 (32.6)	NA	93 (24.7)
Nonepilepsy DB	105 (9.7)	95 (10.5)	121 (14.9)	92 (31.6)	NA	308 (15.3)
Nonepilepsy All		269 (25.7)	172 (11.9)	59 (31.4)	3 (7.5)	503 (18.5)
Subject choice						
Parkinson's DB	32 (3.8)	19 (2.6)	28 (3.8)	3 (5.5)	NA	50 (3.3)
Neuropathic Pain DB	5 (4.1)	6 (8.3)	1 (1.4)	13 (5.5)	NA	20 (5.3)
Nonepilepsy DB	41 (3.8)	34 (3.7)	29 (3.6)	16 (5.5)	NA	79 (3.9)
Nonepilepsy All		107 (10.2)	77 (5.3)	8 (4.3)	4 (10.0)	196 (7.2)
Inadequate therapeutic effect						
Parkinson's DB	22 (2.6)	28 (3.9)	27 (3.6)	0	NA	55 (3.6)
Neuropathic Pain DB	3 (2.5)	1 (1.4)	1 (1.4)	7 (3.0)	NA	9 (2.4)
Nonepilepsy DB	25 (2.3)	29 (3.2)	28 (3.4)	7 (2.4)	NA	64 (3.2)
Nonepilepsy All		77 (7.3)	92 (6.4)	8 (4.3)	3 (7.5)	180 (6.6)
Other						
Parkinson's DB	64 (7.6)	23 (3.2)	67 (9.0)	0	NA	90 (5.9)
Neuropathic Pain DB	7 (5.8)	2 (2.8)	1 (1.4)	15 (6.4)	NA	18 (4.8)
Nonepilepsy DB	75 (7.0)	29 (3.2)	68 (8.4)	15 (5.2)	NA	112 (5.6)
Nonepilepsy All		289 (27.6)	834 (57.9)	15 (8.0)	1 (2.5)	1139 (41.9)

Source: ISS Tables 15, 16, 17, 20.1-9

*Randomized treatment groups used for Parkinson's Disease DB Pool, Neuropathic Pain DB Pool, and Nonepilepsy DB Pool. Modal dose groups used for Nonepilepsy All Treated Pool.

Comment: A dose-response relationship was only observed for discontinuations due to adverse events. Discontinuations due to adverse events occurred more frequently at the higher dose groups in the nonepilepsy controlled trials (randomized treatment groups). However, in the nonepilepsy all treated pool using modal dose groups, a dose-response relationship does not exist.

The listings of subjects with "other" reason for discontinuation were reviewed for the 112 perampanel subjects and 75 placebo subjects (ISS Table 20.1-15). Most of the reasons were due to sponsor decision (early study terminations), lost to follow-up, noncompliance, or other reasons for ineligibility (e.g., prohibited concomitant medication

use or change, failed to meet inclusion criteria). However, this “other” category did also include a few discontinuations due to adverse events: disorientation, elevated liver enzymes, prolonged QTc on ECG, and abnormal ECG.

Phase 1 trials

During the Phase 1 trials, 8.7% (94/1083) of subjects discontinued prematurely. A higher percentage of perampanel subjects (9.7%, 89/922) discontinued compared to placebo subjects (3.1%, 5/161). The most common reason for discontinuation for perampanel treated subjects was due to AEs (5.0%, n=46). The other reasons for discontinuation were withdrawal of consent (2.0%, n=18), other (2.2%, n=20), and protocol violation (0.5%, n=5) (ISS Tables 22.1-2 and 22.1-8).

Additional Analyses

The Sponsor performed a comprehensive search for additional safety-related discontinuations in subjects who were originally categorized as discontinuing due to subject choice, withdrawal of consent, or other (284 epilepsy, 1640 nonepilepsy, 67 Phase 1) (Figure 20.1, ISS Appendix B). The Sponsor identified a total of 121 (6.1%) subjects (19 epilepsy *described below*, 100 nonepilepsy, 2 Phase 1) where a safety-related comment was included on the disposition page of the CRF or had ongoing AEs or markedly abnormal laboratory values within 2 weeks of discontinuation/last visit. In the 120-day Safety Update, the Sponsor identified an additional 49 subjects in this category out of a total of 76 epilepsy subjects who discontinued for reasons other than AEs (Figure 20.2, 120-day Safety Update).

Comment: According to the Sponsor, the incidence of discontinuation due to subject choice, withdrawal of consent, or other that may have been safety-related was low (6.1%). However, interestingly, the majority of these subjects with safety-related discontinuations were perampanel treated subjects (81%, 18 epilepsy and 78 nonepilepsy) rather than placebo subjects (16%, 1 epilepsy and 18 nonepilepsy). Therefore, discontinuations due to adverse events were even higher in the perampanel group (compared to placebo) than suggested by Table 32 and Table 33.

The Sponsor identified an additional 1309 (65.7%) subjects (198 epilepsy, 1069 nonepilepsy, 42 Phase 2) where the AEs or markedly abnormal laboratory values resolved within 2 weeks of discontinuation/last visit (and had no safety-related comment included on the disposition page of the CRF). The remaining 561 (28.2%) subjects had neither a safety-related comment nor any AEs/markedly abnormal laboratory values.

The following table summarizes the 19 subjects in the epilepsy trials where a safety-related comment was included on the disposition page of the CRF or had ongoing AEs or markedly abnormal laboratory values within 2 weeks after the discontinuation/last visit. Of note, 2 weeks is within approximately 3 elimination half-lives of perampanel (within the time that the drug effect could still be present).

Table 34. Listing of Adverse Event and Lab Details for Subjects with Possible Safety-related Discontinuations, Epilepsy All Treated Pool

Study	Subject ID	Severe/Moderate AEs or Related AEs (verbatim terms)*	Mild or Unrelated AEs (verbatim)	Markedly Abnormal Labs
Placebo only				
304	304-5111-4007	back pain , nausea, flu symptoms	diarrhea	bicarbonate
Perampanel Exposed				
207	206-0032-0155	dizziness, irritability, drowsiness, pneumonia , decreased memory	photophobia, cough	potassium
207	206-0076-0086		stomach pain	sodium
207	206-0009-0127	intractable epilepsy , gait ataxia, head laceration due to seizure fall, slurred speech, blurred vision		
207	206-0064-0116	vertigo , vomitus, insomnia, otitis media, nausea , fatigue, common cold, diplopia		
208	208-3004-1038	dizzy feeling, red flushing to the face, metastatic polyp , palmar erythema	hyperventilation	
208	208-3010-1008			creatinine kinase
304	304-1005-4008		dysmenorrhea	
304	304-1007-4019	dizziness, drowsiness, irritability, anguish, nervousness head trauma due to seizure		sodium
304	304-5129-4003	dizziness, irritability	anxiety, seasonal allergies, tired	lymphocytes
306	306-4305-6007	none reported		
307	306-2951-6002	increase in seizures, loss of memory slow down in cognitive/motor, tiredness, ataxia, confusion, visual worsening	ankle sprain	
307	306-4306-6002	irritability	fatigue, dizziness	phosphate
307	306-2102-6007	dizziness		glucose
307	306-3001-6004	discoordination, insomnia, irritability nervousness , worsening of mood change in appetite, common cold arthropathy right ankle, mood swings	nausea, diarrhea, nose bleeding	
307	306-3002-6002	asthenia, vomiting, headache	common cold, herpes on lips	hemoglobin
307	306-3502-6003	imbalance, drowsiness		urate
307	306-3603-6007	status epilepticus increased level of CPK, depression anemia, neutropenia, proteinuria viral infection, increased eosinophils		neutrophils
233	231-1005-1002	altered mental state anemia, gastritis	pharyngitis	hemoglobin

Source: ISS Tables 20.1-22.2, 20.1-22.3

*AEs categorized as severe are bolded.

Discontinuations, Drug Interruption, or Dose Reduction Due to TEAEs

The following section analyses the TEAEs leading to treatment discontinuation, drug interruption, or dose reduction. These TEAEs include any laboratory abnormalities that were reported as TEAEs.

In the epilepsy DB pool, the overall incidence of perampanel interruption, dose reduction, or discontinuation due to TEAEs was 25.9% (308/1189). There were more subjects who experienced TEAEs that resulted in perampanel interruption or dose reduction (17.0%, 202/1189) than discontinuation (8.9%, 106/1189). However, in the nonepilepsy DB pool, there were more subjects who experienced TEAEs that resulted in perampanel discontinuation (15.6%, 314/2013) than drug interruption or reduction (3.1%, 63/2013). The overall incidence of perampanel interruption/reduction/discontinuation due to TEAEs was 18.7% (377/2013) in the nonepilepsy DB pool.

The following table summarizes the number of subjects with TEAEs by randomized treatment group leading to treatment discontinuation, drug interruption, or dose reduction in the epilepsy and nonepilepsy DB pools. A dose-response relationship is suggested for both the epilepsy DB pool and nonepilepsy DB pool. The highest dose groups have the highest percentage of subjects with TEAEs leading to discontinuation, drug interruption, or dose reduction. In the epilepsy Phase 3 DB pool, the risk of developing TEAEs that resulted in drug interruption, dose reduction, or drug discontinuation was almost 3 times higher in the perampanel treated subjects than in the placebo subjects.

Table 35. TEAEs Leading to Discontinuation, Interruption, or Dose Reduction by Randomized Treatment, Epilepsy and Nonepilepsy DB Pools

Category	Placebo n (%)	Perampanel n (%)*				Total
		<4 mg	4 mg	>4-8 mg	>8-12mg	
Epilepsy Phase 2 DB Pool	68	12	101		38	151
Subjects with any TEAE leading to discontinuation	4 (5.9)	0	5 (5.0)		2 (5.3)	7 (4.6)
Drug interruption or reduction	5 (7.4)	0	9 (8.9)		18 (47.4)	27 (17.9)
Total	9 (13.2)	0	14 (13.9)		20 (52.6)	34 (22.5)
Epilepsy Phase 3 DB Pool*	442	180	172	431	255	1038
Subjects with any TEAE Leading to discontinuation	21 (4.8)	12 (6.7)	5 (2.9)	33 (7.7)	49 (19.2)	99 (9.5)
Drug interruption or reduction	17 (3.8)	3 (1.7)	12 (7.0)	84 (19.5)	76 (29.8)	175 (16.9)
Total	36 (8.1)	14 (7.8)	16 (9.3)	107 (25)	107 (42)	244 (23.5)
Nonepilepsy DB Pool	1079	908	814	291		2013
Subjects with any TEAE leading to discontinuation	106 (9.8)	97 (10.7)	124(15.2)	93 (32.0)		314 (15.6)
Drug interruption or reduction	16 (1.5)	8 (0.9)	20 (2.5)	35 (12.0)		63 (3.1)
Total	121 (11.2)	102(11.2)	142(17.4)	119 (41)		363 (18.0)

Source: ISS Tables 46, 47, 51

*Randomized treatment groups used for Epilepsy Phase 3 DB Pool: 2 mg, 4 mg, 8 mg, and 12 mg

The following table summarizes the relative risk between perampanel and placebo subjects of developing TEAEs that resulted in drug discontinuation by indication.

Table 36. Relative Risk of TEAEs Leading to Discontinuation, DB Pooled Groups

Double-Blind Pool	Perampanel		Placebo		Relative Risk (95% C.I.)
	AE*	n*	AE*	n*	
Epilepsy DB Pool	106	1189	25	510	1.82 (1.19-2.78)
Phase 3 DB Pool	99	1038	21	442	2.01 (1.27-3.17)
Phase 2 DB Pool	7	151	4	68	0.79 (0.24-2.60)
Nonepilepsy DB Pool	314	2013	106	1079	1.59 (1.29-1.95)
Parkinson's DB Pool	211	1517	92	845	1.28 (1.02-1.61)
Neuropathic Pain DB Pool	96	377	10	121	3.08 (1.66-5.72)
All studies	420	3202	131	1589	1.59 (1.32-1.92)

Source: ISS Tables 46, 47, 51

*AE = number of subjects with any TEAE leading to discontinuation; n= number of treated subjects

Comment: The Sponsor submitted a Safety Information Amendment on March 30, 2012 in response to our request to explain the discrepancy between the number of subjects who discontinued due to AE (in the Disposition Section 2 of the ISS) and the number of subjects who had TEAEs leading to treatment discontinuation (in Section 7.4 of the ISS). The Sponsor stated that the discrepancies were a result of whether the subject discontinued due to an adverse event based on what was reported in the Disposition section of the CRF versus the Adverse Event CRF. After reviewing each of the specific reasons the subjects who were counted in ISS Section 2 but were not counted in ISS Section 7.4, the explanations provided by the Sponsor were reasonable.

The following table lists the TEAEs leading to discontinuations by MedDRA SOC (in descending order of frequency in the epilepsy all treated pool) for both the epilepsy and nonepilepsy all treated pools. In the epilepsy pool, TEAEs leading to treatment discontinuation occurred in 19.5% of the perampanel subjects and occurred most frequently in the Nervous system disorders SOC (9.4%), followed by Psychiatric disorders (6.0%) and General disorders (3.9%). The TEAE most often leading to treatment discontinuation was dizziness (4.5%, 75/1651). In the nonepilepsy pool, the incidence rate for TEAEs leading to discontinuation (6.34 per 100 subject-weeks) was more than twice that of the epilepsy pool (2.71 per 100 subject-weeks). Differences in the SOC distribution between the epilepsy and nonepilepsy pools were likely due to differences in the underlying diseases and comorbidities.

In the epilepsy pool, 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. However, there were cases of transaminase elevations, thrombocytopenia, acute pancreatitis, CK elevation, QT prolonged, and toxic skin eruption (reviewed in detail in Sections 7.3.5, 7.4.2, and 7.4.4).

In the nonepilepsy pool, there were no subjects who discontinued for the TEAEs of Stevens Johnson syndrome, toxic epidermal necrolysis, acute liver failure, aplastic anemia, agranulocytosis, pancytopenia, or anaphylaxis. However, there were cases of transaminase elevations, acute pancreatitis, rhabdomyolysis, acute renal failure, CK elevation, and QT prolonged (reviewed in detail in Sections 7.3.5, 7.4.2, and 7.4.4).

Table 37. TEAEs Leading to Discontinuations by System Organ Class

	Epilepsy All Treated		Nonepilepsy All Treated	
Total number of subjects	1651		2717	
Subjects with any TEAE leading to discontinuation	322		546	
Incidence per number of subjects	19.5%		20.1%	
Total exposure (subject-weeks)	118920		86176.1	
Incidence per 1000 subject-weeks	2.71		6.34	
MedDRA SOC	n (%)	per 1000 subj-wks	n (%)	per 1000 subj-wks
Nervous System Disorders	156 (9.4)	1.31	290 (10.7)	3.37
Psychiatric Disorders	99 (6.0)	0.83	118 (4.3)	1.37
General Disorders and Administration Site	64 (3.9)	0.54	71 (2.6)	0.82
Gastrointestinal Disorders	23 (1.4)	0.19	40 (1.5)	0.46
Ear and Labyrinth Disorders	17 (1.0)	0.14	11 (0.4)	0.13
Eye Disorders	17 (1.0)	0.14	4 (0.1)	0.05
Skin and Subcutaneous Tissue Disorders	16 (1.0)	0.13	12 (0.4)	0.14
Investigations	15 (0.9)	0.13	21 (0.8)	0.24
Injury, Poisoning and Procedural Complications	12 (0.7)	0.10	25 (0.9)	0.29
Metabolism and Nutrition Disorders	11 (0.7)	0.09	4 (0.1)	0.05
Musculoskeletal and Connective Tissue Disorders	9 (0.5)	0.08	36 (1.3)	0.42
Cardiac disorders	7 (0.4)	0.06	33 (1.2)	0.38
Infections and Infestations	5 (0.3)	0.04	16 (0.6)	0.19
Blood and Lymphatic System Disorders	4 (0.2)	0.03	0	0
Vascular Disorders	2 (0.1)	0.02	17 (0.6)	0.20
Reproductive System and Breast Disorders	2 (0.1)	0.02	1 (0.0)	0.01
Pregnancy, Puerperium and Perinatal Conditions	1 (0.1)	0.01	0	0
Respiratory, Thoracic and Mediastinal Disorders	1 (0.1)	0.01	16 (0.6)	0.19
Neoplasms Benign, Malignant and Unspecified	1 (0.1)	0.01	14 (0.5)	0.16
Renal and Urinary Disorders	1 (0.1)	0.01	9 (0.3)	0.10
Hepatobiliary Disorders	1 (0.1)	0.01	2 (0.1)	0.02
Blood and lymphatic system disorders	0	0	3 (0.1)	0.03
Endocrine disorders	0	0	2 (0.1)	0.02
Social circumstances	0	0	1 (0.0)	0.01
Surgical and Medical Procedures	0	0	1 (0.0)	0.01

Source: ISS Tables 20.8-7, 20.8-21 and 120-day Safety Update Table 20.8-44.1

In the epilepsy Phase 3 DB pool, the number of subjects with TEAEs leading to discontinuation was highest in the higher dose groups (8 mg and 12 mg). After stratifying by study, the strongest dose response relationship was seen in Study 305. After including the OLE studies, the incidence rate for the total perampanel group for the all treated pool was lower at 2.71 (322/118920 subject weeks) than the Phase 3 DB pool at 5.54 (99/17862.6 subject-weeks).

Table 38. TEAEs Leading to Discontinuation by Randomized Dose, Epilepsy DB Pools

Subjects with TEAE leading to Discontinuation	Placebo n (%)	Perampanel n (%)				
		2 mg	4 mg	8 mg	12 mg	Total
Epilepsy Phase 2 DB	4 (5.9)	0	5 (5.0)	0	2 (5.3)	7 (4.6)
Epilepsy Phase 3 DB	21 (4.8)	12 (6.7)	5 (2.9)	33 (7.7)	49 (19.2)	99 (9.5)
Study 304	8 (6.6)			9 (6.8)	26 (19.4)	35 (13.1)
Study 305	6 (4.4)			12 (9.3)	23 (19.0)	35 (14.0)
Study 306	7 (3.8)	12 (6.7)	5 (2.9)	12 (7.1)		29 (5.6)

Source: ISS Tables 20.8-1, 20.8-15 and CSR 304 Table 12.7, CSR 305 Table 12.7, CSR 306 Table 12.7

The following table stratifies the TEAEs leading to discontinuation by SOC and double-blind pools. The incidence of TEAEs leading to discontinuation in the total perampanel group was much greater than placebo for the following SOCs in both the epilepsy and nonepilepsy pools: Nervous system, Psychiatric, and General disorders. The highest dose groups had 2-3 times the incidence of these TEAEs than the placebo group.

Conversely, in the epilepsy pool, the incidence of TEAEs (leading to discontinuation) in the total perampanel group was lower than placebo for the following SOCs: Cardiac disorders and Injury/poisoning. Furthermore, there were no TEAEs (leading to discontinuation) in the epilepsy DB pool for the following 2 SOCs: Respiratory disorders and Neoplasms.

Table 39. TEAEs Leading to Discontinuation by SOC and Randomized Treatment Group for the Epilepsy and Nonepilepsy Double-blind Pools in at Least 2 subjects

MedDRA SOC Pooled Group	Placebo n (%)	Perampanel n (%)*				Total
		<4 mg*	4 mg*	>4-8 mg*	>8-12 mg*	
Number of Subjects						
Epilepsy Phase 3 DB	442	180	172	431	255	1038
Epilepsy Phase 2 DB	68	12	101	0	38	151
Epilepsy DB Pool	510	192	273	431	293	1189
Nonepilepsy DB Pool	1079	908	814	291	0	2013
DC TEAE Incidence in Perampanel group > Placebo group in BOTH pools for the following SOCs:						
Nervous system disorders						
Epilepsy DB Pool	16 (3.1)	4 (2.1)	4 (1.5)	18 (4.2)	31 (10.6)	57 (4.8)
Nonepilepsy DB Pool	41 (3.8)	52 (5.7)	71 (8.7)	59 (20.3)	0	182 (9.0)
Psychiatric disorders						
Epilepsy DB Pool	7 (1.4)	5 (2.6)	1 (0.4)	4 (0.9)	17 (5.8)	27 (2.3)
Nonepilepsy DB Pool	12 (1.1)	19 (2.1)	24 (2.9)	16 (5.5)	0	59 (2.9)
General disorders						
Epilepsy DB Pool	2 (0.4)	3 (1.6)	3 (1.1)	4 (0.9)	10 (3.4)	20 (1.7)
Nonepilepsy DB Pool	11 (1.0)	10 (1.1)	16 (2.0)	20 (6.9)	0	46 (2.3)
Ear and Labyrinth disorders						
Epilepsy DB Pool	0	0	0	1 (0.2)	3 (1.0)	4 (0.3)
Nonepilepsy DB Pool	0	2 (0.2)	2 (0.2)	3 (1.0)	0	7 (0.3)
Eye disorders						
Epilepsy DB Pool	0	0	0	1 (0.2)	3 (1.0)	4 (0.3)
Nonepilepsy DB Pool	0	0	1 (0.1)	2 (0.7)	0	3 (0.1)
Metabolism & Nutrition						
Epilepsy DB Pool	1 (0.2)	1 (0.5)	0	1 (0.2)	2 (0.7)	4 (0.3)
Nonepilepsy DB Pool	0	1 (0.1)	0	1 (0.3)	0	2 (0.1)
DC TEAE Incidence in Perampanel group > Placebo group in the EPILEPSY pool (but not in the nonepilepsy pool) for the following SOCs:						
Gastrointestinal disorders						
Epilepsy DB Pool	2 (0.4)	1 (0.5)	1 (0.4)	4 (0.9)	4 (1.4)	10 (0.8)
Nonepilepsy DB Pool	15 (1.4)	6 (0.7)	10 (1.2)	9 (3.1)	0	25 (1.2)
Skin and subcutaneous						
Epilepsy DB Pool	0	0	3 (1.1)	4 (0.9)	3 (1.0)	10 (0.8)
Nonepilepsy DB Pool	5 (0.5)	5 (0.6)	6 (0.7)	0	0	11 (0.5)
Infections and infestations						
Epilepsy DB Pool	0	1 (0.5)	0	1 (0.2)	0	2 (0.2)
Nonepilepsy DB Pool	5 (0.5)	4 (0.4)	1 (0.1)	4 (1.4)	0	9 (0.4)
Vascular disorders						
Epilepsy DB Pool	0	0	0	1 (0.2)	0	1 (0.1)
Nonepilepsy DB Pool	5 (0.5)	3 (0.3)	2 (0.2)	4 (1.4)	0	9 (0.4)
Renal & Urinary disorders						
Epilepsy DB Pool	0	0	0	0	1 (0.3)	1 (0.1)
Nonepilepsy DB Pool	3 (0.3)	0	3 (0.4)	2 (0.7)	0	5 (0.2)

Source: ISS Tables 20.8-15, 20.8-1, and 20.8-27

*Randomized treatment group for Epilepsy Phase 3 DB Pool: 2 mg, 4 mg, 8 mg, and 12 mg

The following table summarizes the TEAEs leading to discontinuation by Preferred Term that occurred in at least 2 perampanel subjects and that occurred more frequently compared to placebo in the epilepsy DB pool. In the epilepsy DB pool, the most frequent TEAEs leading to discontinuation were dizziness, somnolence, vertigo, fatigue, ataxia, and rash. A dose response was suggested for most of these TEAEs. These events also occurred more frequently in perampanel subjects than placebo subjects in the nonepilepsy DB pool. Some of the TEAEs that occurred in the nonepilepsy population did not occur in the epilepsy population because of their association with the underlying disease (e.g., on and off phenomenon, dyskinesia).

Table 40. TEAEs Leading to Discontinuation by Preferred Term (Events in ≥ 2 perampanel-treated subjects and $>$ placebo in the Epilepsy DB pool)

MedDRA PT	Epilepsy DB Pool		Nonepilepsy DB Pool*	
	Placebo	Perampanel	Placebo	Perampanel
All Subjects	510	1189	1079	2013
Subjects with any TEAE leading to discontinuation	25 (4.9)	106 (8.9)	106 (9.8)	314 (15.6)
Dizziness	4 (0.8)	24 (2.0)	7 (0.6)	44 (2.2)
Somnolence	1 (0.2)	10 (0.8)	1 (0.1)	35 (1.7)
Vertigo	0	8 (0.7)	0	6 (0.3)
Fatigue	0	8 (0.7)	1 (0.1)	8 (0.4)
Ataxia	0	7 (0.6)	0	5 (0.2)
Rash	0	7 (0.6)	0	4 (0.2)
Aggression	0	5 (0.4)		
Anger	0	4 (0.3)		
Gait disturbance	1 (0.2)	4 (0.3)	1 (0.1)	18 (0.9)
Dysarthria	0	4 (0.3)	0	10 (0.5)
Irritability	1 (0.2)	4 (0.3)	0	2 (0.1)
Vision blurred	0	4 (0.3)		
Vomiting	1 (0.2)	4 (0.3)	2 (0.2)	6 (0.3)
Nausea	0	4 (0.3)	3 (0.3)	11 (0.5)
Balance disorder	0	3 (0.3)	2 (0.2)	13 (0.6)
Coordination abnormal	0	2 (0.2)		
Fall	0	2 (0.2)	0	9 (0.4)
Asthenia	0	2 (0.2)	3 (0.3)	10 (0.5)
Confusional state	0	2 (0.2)	1 (0.1)	15 (0.7)
Suicidal ideation	0	2 (0.2)		
Constipation	0	2 (0.2)		
Gastroenteritis	0	2 (0.2)		
On and off phenomenon			18 (1.7)	36 (1.8)
Dyskinesia			2 (0.2)	17 (0.8)
Tremor			3 (0.3)	13 (0.6)
Dyspnoea			2 (0.2)	10 (0.5)
Hallucination			1 (0.1)	10 (0.5)
Parkinson's disease			2 (0.2)	10 (0.5)
Depression			0	7 (0.3)
Bradykinesia			0	7 (0.3)
Diarrhoea			2 (0.2)	6 (0.3)
Weight increased			0	5 (0.2)
Paranoia			0	5 (0.2)

Source: ISS Tables 20.8-15, 20.8-1, 20.8-27

*TEAEs leading to discontinuation in ≥ 5 perampanel-treated subjects and $>$ placebo in nonepilepsy pool

Phase 1 Trials

During the Phase 1 trials, 35 perampanel subjects discontinued prematurely due to TEAEs (4 in single-dose studies, 31 in multiple-dose studies). TEAEs leading to treatment discontinuation occurred in 3.8% (35/916) of the perampanel-treated subjects in the entire Phase 1 program. There was a much higher incidence of discontinuations

due to AEs during the multiple-dose studies (9.0%, 31/343) than during the single-dose studies (0.7%, 4/573).

In the single-dose studies, the subjects who discontinued were treated with high doses of perampanel (from 8 mg to 36 mg). The adverse events leading to discontinuation were coded to the following preferred terms in the MedDRA SOC, Investigations: electrocardiogram QT prolonged (8 mg), haemoglobin decreased (24 mg), blood creatine phosphokinase increased (perampanel 28 mg), and WBC count increased (36 mg) (ISS Table 22.4-23).

Comment: After reviewing the Clinical Study Report for the single-dose Study 024, one additional subject was found by the reviewer. Subject #1001-9069 discontinued due to the AEs agitation and aggression. In a Safety Information Amendment on March 23, 2012, the Sponsor responded to the Division's request and confirmed (after reviewing the CRFs) that this was the only subject in the Phase 1 studies that was inadvertently not included in the number of subjects who had TEAEs leading to treatment discontinuation.

In the Phase 1 multiple-dose studies, the adverse events leading to discontinuation were coded most frequently to the Nervous system disorders SOC (somnolence and dizziness PTs) and Investigations SOC (positive rombergism PT). The following table summarizes the most common adverse events leading to discontinuation in the multiple-dose studies for ≥ 2 perampanel subjects. The narratives were also reviewed for the TEAEs that led to discontinuations in one perampanel subject. Those discontinuation TEAEs were grouped together and reviewed in detail in Sections 7.3.4 and 7.3.5.

Table 41. TEAEs Leading to Discontinuation in ≥ 2 Perampanel Subjects, Phase 1 Multiple Dose Pool

MedDRA Preferred Term	Perampanel (n=343)
Subjects with any TEAE leading to discontinuation	31 (9.0%)
Somnolence	8 (2.3)
Dizziness	7 (2.0)
Positive Rombergism	5 (1.5)
Feeling drunk	3 (0.9)
Ataxia	3 (0.9)
Balance disorder	3 (0.9)
Dysarthria	3 (0.9)
Nausea	3 (0.9)
Abdominal pain	3 (0.9)
Vomiting	2 (0.6)
Sedation	2 (0.6)
Vertigo	2 (0.6)
Elevated mood	2 (0.6)
Mental status changes	2 (0.6)

Source: ISS Table 167

7.3.4 Significant Adverse Events

In the next four subsections (7.3.4.1 to 7.3.4.4), I will discuss my analyses along with the Sponsor's analyses of the following major safety issues: psychiatric disorders, nervous system disorders, metabolic changes, and tendon/ligament rupture. These are the most important safety concerns with perampanel and should be incorporated into labeling or further evaluated in the postmarketing period.

7.3.4.1 Psychiatric Disorders

A higher number of subjects in the perampanel group experienced TEAEs related to psychiatric disorders than in the placebo group in both the epilepsy Phase 3 DB pool (15.3% vs 12.4%) and the nonepilepsy DB pool (11.4% vs 10.5%). Discontinuations due to TEAEs in the Psychiatric disorders SOC occurred almost 3 times as often in perampanel subjects than placebo in the nonepilepsy DB pool (2.9% vs 1.1%). Psychiatric disorder SAEs occurred more often in the perampanel subjects than placebo in both the epilepsy Phase 3 DB pool (1.2% vs 0.9%) and the nonepilepsy DB pool (0.8% vs 0.6%). The following table summarizes the adverse events in the Psychiatric Disorders SOC in the epilepsy Phase 3 DB, nonepilepsy DB, and all treated pools. In both of the all treated pools, the most common TEAE was insomnia. Aggression was the most common SAE and discontinuation TEAE in the epilepsy all treated pool.

Table 42. Summary of TEAEs, SAEs, DCs in the Psychiatric Disorders SOC

	Epilepsy Phase 3 DB Pool		Nonepilepsy DB Pool	
	Placebo	Perampanel	Placebo	Perampanel
SOC Psychiatric Disorders	n=442	n=1038	n=1079	n=2013
TEAEs	12.4%	15.3%	10.5%	11.4%
Deaths	0	0	0	0
SAEs	0.9%	1.2%	0.6%	0.8%
Discontinuations (DCs)	1.6%	2.5%	1.1%	2.9%
	Epilepsy All Treated Pool		Nonepilepsy All Treated	
	n=1651		n=2717	
TEAEs n (%), most common PT	475 (28.8%), insomnia (4.9%)		501 (18.4%), insomnia (5.3%)	
Deaths	0		0	
SAEs n (%), most common PT	59 (3.6%), aggression		43 (1.6%), hallucination	
DCs n (%), most common PT	99 (6.0%), aggression		118 (4.3%), confusional state	

Source: ISS Tables 20.7-1, 160, 165, 55, 20.5-2, 63, 20.5-8, 75, 79, 20.5-36, 22.4-2, 22.4-27 and 120-day Safety Update Tables 20.5-75.1, 20.7-18.1, 20.8-44.1

There were other MedDRA SOCs that included psychiatric-related TEAEs such as the SOCs General disorders and Social circumstances. The following table summarizes the psychiatric-related TEAEs that occurred in at least 2 perampanel subjects (and greater than placebo) in the epilepsy Phase 3 DB pool.

Table 43. Psychiatric-Related TEAEs in ≥ 2 Perampanel Subjects > Placebo, Epilepsy Phase 3 DB Pool

Psychiatric-related PT	Placebo n = 442	Perampanel n = 1038
SOC General disorders		
Irritability	13 (2.9)	73 (7.0)
Feeling drunk	0	7 (0.7)
SOC Psychiatric disorders		
Anxiety	5 (1.1)	29 (2.8)
Aggression	2 (0.5)	17 (1.6)
Anger	1 (0.2)	12 (1.2)
Sleep disorder	1 (0.2)	11 (1.1)
Nervousness	3 (0.7)	9 (0.9)
Confusional state	2 (0.5)	9 (0.9)
Mood swings	3 (0.7)	8 (0.8)
Mood altered	2 (0.5)	7 (0.7)
Euphoric mood	0	5 (0.5)
Panic attack	1 (0.2)	4 (0.4)
Abnormal behaviour	0	4 (0.4)
Disorientation	1 (0.2)	3 (0.3)
Affect lability	0	2 (0.2)
Affective disorder	0	2 (0.2)
Psychomotor retardation	0	2 (0.2)
SOC Social circumstances		
Physical assault	0	*1 (0.1)

Source: ISS Table 20.5-2

*This notable TEAE was included in this table although only 1 perampanel subject reported this TEAE.

Of the TEAEs that occurred in perampanel subjects more frequently than placebo, the most commonly reported TEAEs by perampanel subjects were irritability, anxiety, aggression, and anger. Similar TEAEs that perampanel subjects experienced more frequently than placebo included nervousness and panic attack. Perampanel subjects also experienced changes in mood (mood swings, mood altered, euphoric mood), affect (affect lability, affective disorder), and behavior (abnormal behavior) more often than placebo. The TEAEs, confusional state and disorientation, will be discussed in more detail in Section 7.3.4.2 on cognitive dysfunction. For the TEAEs feeling drunk and euphoric mood, the reader is also referred to the Controlled Substance Staff review by Dr. Alicja Lerner for further details on drug abuse potential, withdrawal, and rebound effects of perampanel.

Comment: In the context of the TEAEs such as anger and aggression experienced by perampanel subjects more than placebo, it was concerning that there was 1 physical assault TEAE reported for a perampanel subject (described in more detail later in this section). Therefore, I performed additional more detailed analyses regarding the effects of perampanel on hostility and aggression (presented later in this section).

Notably, the following TEAEs were less common in perampanel subjects than placebo in the epilepsy Phase 3 DB pool: insomnia (2.9% vs 3.6%) and hallucination (0.3% vs 0.5%). Furthermore, in the nonepilepsy DB pool, fewer perampanel subjects than placebo experienced insomnia (3.4% vs 3.6%) and hallucination (1.0% vs 1.2%).

In the Phase 1 single- and multiple-dose studies, euphoric mood and insomnia were the most common TEAEs, respectively. Additional TEAEs that occurred in the Phase 1 studies but not in the epilepsy pools were daydreaming, dissociation, flat affect, thinking abnormal, delusional perception, disturbance in sexual arousal, dysphoria, illusion, inappropriate affect, and staring, each of which occurred in $\leq 0.6\%$ of the perampanel-treated subjects (most often in the higher dose groups) (ISS Tables 22.4-7 and 22.4-32).

To further analyze the psychiatric-related SAEs, the following table summarizes those that occurred in the perampanel group greater than in the placebo group in the epilepsy Phase 3 DB and nonepilepsy DB pools.

Table 44. SAEs in Psychiatric SOC Occurring in Perampanel Subjects > Placebo*

Psychiatric disorders SOC Preferred Term	Placebo	Perampanel
Epilepsy Phase 3 DB Pool	n = 442	n = 1038
Psychiatric disorders SOC	4 (0.9)	12 (1.2)
Aggression	0	3 (0.3)
Adjustment disorder	0	1 (0.1)
Belligerence	0	1 (0.1)
Confusional state	0	1 (0.1)
Disorientation	0	1 (0.1)
Impulse-control disorder	0	1 (0.1)
Suicidal ideation	0	1 (0.1)
Nonepilepsy Double-blind Pool	n = 1079	n = 2013
Psychiatric disorders SOC	6 (0.6)	16 (0.8)
Confusional state	1 (0.1)	5 (0.2)
Insomnia	0	2 (0.1)
Mental status changes	0	2 (0.1)
Suicide attempt	0	2 (0.1)
Disorientation	0	1 (0.0)
Homicidal ideation	0	1 (0.0)
Paranoia	0	1 (0.0)

Source: ISS Tables 20.7-1 and 20.7-15

*There were no psychiatric-related SAEs in the SOC's General disorders and Social circumstances.

Additional psychiatric-related SAEs included 1 mental status changes (Phase 2 pool) and 1 anxiety/paranoia (Phase 1 pool, described below).

Subject 020-1001-1009, 44 yo white male developed the SAEs of anxiety, paranoia, and unsteadiness. The subject received 6 mg of perampanel for 10 days in the study. One day after the last dose of study drug, the subject experienced the SAE of severe anxiety. Two days later, the subject reported insomnia, vomiting, and diarrhea. The next day, the subject experienced the SAEs

of paranoia (moderate) and unsteadiness. After treatment with diazepam 5 mg bid, by Study Day 36 (26 days after the last dose of perampanel), the subject recovered from the SAEs. Vitals were negative for orthostasis.

The time course for these events suggest that the events are likely due to perampanel. These events started after 10 days of perampanel exposure and resolved after 5 elimination half-lives of perampanel (along with diazepam treatment).

The TEAEs that led to discontinuations in at least 2 perampanel subjects in the epilepsy Phase 3 DB pool included aggression (5), anger (4), anxiety (3), confusional state (2), and suicidal ideation (2). No placebo subjects discontinued due to these TEAEs.

Comment: It is concerning that only perampanel subjects (and no placebo subjects) in the epilepsy Phase 3 and nonepilepsy DB pools experienced the SAEs of aggression, belligerence, impulse-control disorder, suicidal ideation, suicide attempt, and homicidal ideation. These narratives are described in more detail below. There was one additional perampanel subject in the epilepsy OLE Study 307 with the TEAE homicidal ideation. In the next few pages in this section, I will first present the analyses of suicidal behavior and ideation. Then, I will separately present the analyses of this issue of hostility and aggression. Of note, these adverse events of hostility and aggression (with physical assault and homicidal ideations) were not adequately addressed in the Sponsor's ISS.

(b) (4)

Suicidal Behavior and Ideation

Only subjects in the perampanel group (and no placebo subjects) experienced suicide attempts (and overdoses) in both the epilepsy Phase 3 DB pool (n=1) and the nonepilepsy DB pool (n=2). A higher number of perampanel subjects than placebo experienced TEAEs in the MedDRA SMQ Depression and Suicide/Self-Injury (broad).

Table 45. Summary of Suicidal Behavior and Ideation TEAEs and Suicide/Self-Injury SMQ

	Epilepsy Phase 3 DB Pool		Nonepilepsy DB Pool	
	Placebo	Perampanel	Placebo	Perampanel
	n=442	n=1038	n=1079	n=2013
Suicidality group (Sponsor)	2 (0.5%)	3 (0.3%)	0	2 (0.1%)
Suicidal ideation	2 (0.5%)	2 (0.2%)	0	1 (0.05%)
Suicide attempt	0	0	0	2 (0.1%)
Intentional overdose	0	0	0	0
Multiple drug overdose intentional	0	1 (0.1%)	0	0
SMQ Depression & Suicide/self-injury				
Broad	26 (5.9%)	78 (7.5%)	30 (2.8%)	70 (3.5%)
Narrow	12 (2.7%)	20 (1.9%)	21 (2.0%)	45 (2.2%)
	Epilepsy All Treated Pool		Nonepilepsy All Treated	
	n=1651		n=2717	
Suicidal ideation	12 (0.7%)		3 (0.1%)	
Suicide attempt	4 (0.2%)		3 (0.1%)	
Intentional overdose	1 (0.1%)		0	
Multiple drug overdose intentional	1 (0.1%)		0	
TOTAL SUBJECTS in suicidality group	18 (1.1%)		5 (0.2%)	

Source: ISS Tables 20.5-2, 20.9-84 and 120-day Safety Update Table 22

SMQ analysis performed by reviewer using MAED (MedDRA-based Adverse Event Diagnostic) service

There were a total of 25 subjects with AEs coded to suicidal ideation or behavior in the entire safety database: 23 (0.4%) perampanel subjects and 2 placebo subjects. The events were SAEs in 17 subjects (74%) and led to discontinuation of treatment in 12 subjects (52%). SAEs and discontinuations only occurred in the perampanel subjects. In the epilepsy all treated pool, the 6 subjects with suicide attempts (including overdoses) were taking 12 mg of perampanel. No subject had TEAEs related to suicidality in the Phase 1 study pool, epilepsy Phase 2 double-blind pool, migraine study (Study 210), or the MS study (Study 201). There were no deaths (no completed suicides). Please see Section 7.6.4 of this review for further details regarding the adverse events resulting from perampanel overdoses.

The following table summarizes the narratives of suicide attempts, overdoses, and suicidal ideations with physical assaults in the epilepsy and nonepilepsy studies.

Comment: Most of these subjects did not have a prior psychiatric history (with one narrative clearly stating that there was “no prior history of this type of behavior”). The narratives also contained events of aggressive behavior leading to physical assaults, threats of violence with a weapon (knife), and arrests. Therefore, not only are there cases of self-harm, perampanel subjects were harming others (with the potential of more serious injuries with a weapon). Of note, these events were not coded to the MedDRA preferred terms, physical assault or homicidal ideations. When the Sponsor was queried regarding these possible coding omissions, the Sponsor stated that

additional information regarding an SAE was entered into CIOMS forms and it was “not standard practice to use that CIOMS description to then add new events to the AE database” that were not originally reported by an investigator (Safety Information Amendment, June 21, 2012). However, events such as physical assaults and threats of violence with a knife would be significant enough adverse events to warrant inclusion into the AE database. Additionally, there were coding omissions for suicidal ideations within the narratives for hostility and aggression (described in the next section). Therefore, the numbers of perampanel subjects with suicidal ideations in the above table are an underestimation.

Table 46. Narratives of Suicide Attempts, Overdoses, and Suicidal Ideations with Physical Assaults, Epilepsy and Nonepilepsy Studies

Subject #	Age, Sex, Race	Dose	Adverse event	Study day	Psychiatric Prior history
Epilepsy Studies:					
305-3905-5004	22, M, W	12 mg	Suicide attempt	OLE 19	None
<p>Subject without any psychiatric history attempted suicide on OLE Day 19 (was on 12 mg perampanel in DB Study 305) with a “non-penetrating stab wound to the abdomen.” Treatment was not reported. Perampanel was continued and the event resolved 4 days later. One week later, the subject “dropped out of the study and refused to go to the scheduled visit.”</p> <p>Concomitant medications included valproic acid (~5 years).</p> <p><i>These events could be related to perampanel use (with the time course and positive dechallenge). The narrative did not report any prior psychiatric history for this subject. The time course of events suggest that it was unlikely due to valproic acid (taken chronically for more than five years).</i></p>					
305-4201-5006	35, F, O	10 mg	Suicide attempt	OLE 145	None
<p>Subject without any psychiatric history attempted suicide on OLE Day 145 while on 10 mg perampanel (subject received placebo in DB 305). The subject ingested an overdose of carbamazepine tablets after a “domestic dispute.” Treatment was not reported. Perampanel was discontinued and the event resolved within 2 days. Concomitant medications included clonazepam (2 years), valproic acid (2 years), carbamazepine (>1 year), lorazepam as needed.</p> <p><i>These events could be related to perampanel use (with the time course and positive dechallenge). The narrative did not report any prior psychiatric history for this subject. The time course of events suggest that it was unlikely due to the other concomitant medications (taken chronically for more than one year).</i></p>					
304-5136-4002	35, F, W	12 mg	Multiple drug OD intentional, Impulse control disorder	DB 112	None
<p>Subject with a history of craniotomy strip implant s/p removal who experienced an impulse control disorder with an intentional drug overdose (10 oxycodone and 10 cyclobenzaprine pills) on Day 112. Treatment was not reported. Perampanel was discontinued. The events resolved 5 days later. Concomitant medications included levetiracetam (>3 yrs) and pregabalin (>1 yr).</p> <p><i>These events could be related to perampanel use (with the time course and positive dechallenge). The narrative did not report any prior psychiatric history for this subject. The time course of events suggest that it was unlikely due to the other concomitant medications (both taken chronically for more than one year). It is concerning that the subject experienced a lack of impulse control suggesting an inability to control her behavior.</i></p>					
305-5005-5001	33, M, W	8 mg	Irritability, Aggression, Agitation Suicidal ideation	OLE 14,30 OLE 32	None
<p>Subject without any psychiatric history who experienced irritability on OLE Day 14 (subject received placebo in DB 305). Then on OLE Day 30, the subject experienced paranoia, aggression, and agitation. The subject “twice removed all of his clothing for no reason and had no recollection of these events.” No</p>					

<p>prior history of this type of behavior. Treatment included clobazam. On Day 32, the subject experienced suicidal ideation and was involved in a “physical altercation with a pub bouncer.” Perampanel was discontinued and the events resolved on Day 63. Concomitant medications included levetiracetam (>5 years) and zonisamide (>3 years). <i>These events could be related to perampanel use (with the time course and positive dechallenge). The narrative specifically reported that the subject had no prior history of this type of behavior. The time course of events suggest that it was unlikely due to the other concomitant medications (both taken chronically for more than three years). It is concerning that the subject experienced a lack of knowledge of some of these events suggesting an inability to control his behavior.</i></p>					
306-3607-6006	24, F, W	12 mg	Aggression Suicidal ideation	OLE 63 OLE 64	None
<p>Subject without any psychiatric history who experienced aggression on OLE Day 63 (subject received placebo in DB 306). The next day, the subject had suicidal ideations and was hospitalized. Treatment included “benzodiazepines.” Perampanel was discontinued and the events resolved on Day 68. Concomitant medications included levetiracetam (<1 year), lamotrigine (5 years), valproic acid (1 year). <i>These events could be related to perampanel use (with the time course and positive dechallenge). The narrative did not report any prior psychiatric history for this subject. The time course of events suggest that it was unlikely due to the other concomitant medications (although levetiracetam was started about 11 months prior to the onset of aggression).</i></p>					
306-2453-6007	33, F, W	12 mg	Suicide attempt -overdose of perampanel (~264mg)	OLE 162	Aggression
<p>Subject with a 2 year history of “increasingly abnormal” mental state (with aggressive outbursts) attempted suicide on OLE Day 162 by taking an overdose of perampanel. The subject had “no history of suicide attempts or major depression but was experiencing psychosocial stressors at the time of this event.” The subject was awake and oriented after the overdose and taken to the emergency room where a gastric lavage was performed. The subject was agitated with “targeted defensive reactions of biting and scratching.” Subject was treated with lorazepam, and perampanel was discontinued. The event of “suicide attempt resolved on Day 185.” Concomitant medications included levetiracetam (started 3 years prior), topiramate (started 2.5 years prior), pregabalin (started 1 year prior), fexofenadine, certirizine. <i>This case is confounded by levetiracetam use (known to cause aggression) which was started before the subject began to have aggressive outbursts. However, it is concerning that the subject’s condition worsened with a suicide attempt after perampanel was started (the subject had no previous history of suicide attempts). Therefore, perampanel use may have exacerbated an underlying disorder caused by another medication.</i></p>					
306-2454-6005	21, F, W	12 mg	Aggression x 2, Depression Suicidal ideation	OLE 5 OLE~212	Suicidal ideations
<p>Subject with a history of “toxic encephalopathy and learning disability” and a 1 year history of “suicidal thoughts and self-directed aggression” who experienced depression and aggression on OLE Day 5 (subject received placebo in DB 306). Citalopram was initiated and perampanel was continued. The subject became increasingly aggressive as the perampanel dose was increased. She exhibited increasing episodes of “aggressive outbursts, bouts of temper, and self-harming behavior.” On Day 212, while on 12 mg, the subject “threatened to cut another student’s face with a knife, slapped a co-worker in the face, and then ran into the street and laid down in front of a car.” The subject was hospitalized. Treatment included lorazepam, quetiapine. Perampanel was continued with the event of aggression ongoing. Concomitant medications included valproic acid (~2 years) and levetiracetam (>1 year). <i>This case is confounded by levetiracetam use (known to cause aggression) which was started before the subject began to have aggressive and suicidal thoughts. However, it is concerning that the subject’s condition worsened with threats and actual harm to others after perampanel was started (it was only reported that the subject had “self-directed aggression” previously). Therefore, perampanel use may have exacerbated an underlying disorder caused by another medication.</i></p>					

304-5110-4012	25, M, W	12 mg	*Aggression *Suicidal ideation	OLE 42 OLE 46	"anger management problems"
<p>Subject with a history of traumatic brain injury, anger management problems, panic attacks, anxiety disorder, mood swings, depression who developed aggression on OLE Day 42 while on 12 mg perampanel. The subject experienced violent outbursts and assaulted family members. The subject was arrested and later hospitalized. On Day 46, the subject experienced suicidal ideations, more "anger outbursts", and admitted to the psychiatric ward. The subject's mother reported that the subject's anger and violent outbursts have escalated since up-titration in the open-label phase. Perampanel was discontinued and the events resolved on Day 50.</p> <p>Concomitant medications included topiramate (>1 year), lamotrigine (1 year), fluoxetine (>6 months), hydroxyzine (>6 months).</p> <p><i>This case is confounded by the subject's previous psychiatric history of anxiety, depression, and anger problems. However, it is concerning that the subject's "anger and violent outbursts escalated" after the perampanel dose was increased. Therefore, perampanel use may have exacerbated the subject's underlying disorder.</i></p>					
306-1806-6003	21, F, A	12 mg	Intentional overdose -overdose of perampanel (48 mg)	OLE 198	None
<p>Subject without any psychiatric history experienced irritability while taking 8 mg perampanel on DB Day 35. About 300 days later (OLE Day 198), while on 12 mg perampanel, the subject experienced an intentional overdose of perampanel as a "manipulative anger gesture toward her mother." Perampanel was interrupted for 3 days and was restarted. The subject received her most recent dose of perampanel on OLE Day 330. Concomitant medications included carbamazepine (>2 years), levetiracetam (>1 year), topiramate (~7 months).</p> <p><i>This case is unlikely related to perampanel use given the negative rechallenge.</i></p>					
304-5135-4008	47, M, W	12 mg	Suicide attempt	OLE 471	Depression
<p>Subject with a 3 year history of depression experienced the AE of depression on OLE Day 33 on 10 mg perampanel (subject received placebo in DB 304). Treatment included aripiprazole (atypical antipsychotic) for 5 days and perampanel was continued. On OLE Day 471, on 12 mg of perampanel, the subject experienced major depression and attempted suicide. Two weeks prior to this event, the subject reported "high anxiety and depression since his wife left." The subject was hospitalized and the major depression resolved one month later. Perampanel was continued. On OLE Day 505, the subject was diagnosed with borderline personality disorder which remained ongoing. No treatment was reported and perampanel was continued (most recent dose on OLE Day 722).</p> <p>Concomitant medications included phenytoin (3 years), levetiracetam (1 year), fenofibrate, lisinopril.</p> <p><i>This case is unlikely related to perampanel use given the subject's prior history of depression along with the preceding psychosocial stressor.</i></p>					
<p>Nonepilepsy Studies: <i>The role of perampanel cannot be ruled out in these cases listed below (with the time course shown below and positive dechallenge that was noted for two of the subjects). The narratives did not report any prior psychiatric history for any of these subjects.</i></p>					
302-0576-0007	39, M, O	4 mg	Suicide attempt -tried to "cut his veins" after subject was attacked -resolved 21 days after perampanel d/c'ed on Day 24		DB 24
301-0181-0006	60, F, W	2 mg	Suicide attempt -overdose of 8 bromzolam tablets one week after perampanel was discontinued due to delusions and hallucinations		DB 42
227-1318-1019	60, F, W	8 mg	Suicide attempt -overdose of 20 lisinopril tablets -resolved and continued on perampanel for 1 month (until AEs panic attack, paranoia, and somnolence).		DB 30

Source: Created by the reviewer using narratives provided by the Sponsor

*The original narrative included in the resubmission did not include the narrative for the SAEs aggression and suicidal ideation. The updated narrative was provided by the Sponsor in response to an information request dated June 15, 2012. The Sponsor explained that the narrative that had been updated for the resubmission was “inadvertently not included in the Study 307 CSR Addendum provided in the NDA resubmission.”

Hostility and Aggression

The following table summarizes the percentages of subjects reporting TEAEs in the Psychiatric SMQs Hostility/Aggression and Psychosis/Psychotic disorders in the epilepsy Phase 3 DB pool. Perampanel subjects compared to placebo had a higher risk of experiencing TEAEs in the SMQ Hostility and Aggression but not in the SMQ Psychosis/Psychotic disorders. This finding is supported in the PK/PD analysis, where the probability of anger, aggression, and irritability increased with perampanel concentration. The reader is referred to the Pharmacometric Review for further details.

Table 47. Relative Risk of Psychiatric disorders SOC and SMQs, Epilepsy Phase 3 DB Pool

Category	Placebo		Perampanel		Relative Risk (95% C.I.)
	n (%)	total	n (%)	total	
SOC Psychiatric disorders	55 (12.4)	442	159 (15.3)	1038	1.23 (0.93-1.64)
SMQ Hostility and Aggression					
Narrow SMQ	3 (0.7)	442	31 (3.0)	1038	4.40 (1.35-14.3)
Broad SMQ	25 (5.7)	442	123 (11.9)	1038	2.10 (1.38-3.17)
Modified Hostility SMQ*	40 (9.0)	442	151 (14.5)	1038	1.61 (1.16-2.24)
SMQ Psychosis and Psychotic disorders					
Narrow SMQ	6 (1.4)	442	6 (0.6)	1038	0.43 (0.14-1.31)
Broad SMQ	11 (2.5)	442	25 (2.4)	1038	0.97 (0.48-1.95)

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

*See comment below for the list of PTs included in this Modified SMQ

Comment: The Hostility and Aggression SMQ contains PTs such as injury, laceration, and skin laceration that may be due to fall- or seizure-related events in this epilepsy population, instead of due to aggressive behavior. Conversely, this SMQ excludes some PTs that may describe factors that are precursors to homicidality. There are symptoms that may represent precursors to emerging suicidality (Prozac® labeling, Warnings section 5.1 Clinical Worsening and Suicide Risk).

“The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for Major Depressive Disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.”

There are cases where homicidality and suicidality are closely related. Therefore, I developed the Modified Aggression SMQ to increase the likelihood of capturing relevant

cases. This modified SMQ includes additional PTs (akathisia, anxiety, insomnia, sleep disorder, panic attack, and restlessness) and excludes the injury-related PTs (injury, laceration, and skin laceration). Interestingly, the relative risk for this modified SMQ (1.61) is lower than either the broad (2.10) or narrow (4.40) SMQ.

Similar Hostility/Aggression SMQ results were noted for the other DB pooled groups. In the epilepsy Phase 2 DB pool, a higher percentage of perampanel subjects than placebo experienced TEAEs in the broad SMQ (6.6% vs 1.5%) although the results were driven by the PTs irritability and skin laceration. None of these TEAEs were SAEs or led to discontinuation. (Of note, a smaller percentage, 25%, of perampanel subjects were treated at doses > 4 mg in the Phase 2 trials than in Phase 3 trials where 66% were treated at doses > 4 mg).

In the nonepilepsy DB pool, a higher percentage of perampanel subjects than placebo subjects experienced TEAEs in the SMQ (broad 2.5% vs 1.8%, narrow 0.1% vs 0). (Of note, only 14% of the perampanel subjects were treated at doses > 4 mg). More perampanel subjects than placebo subjects experienced SAEs (0.2% vs 0.1%) and discontinuations (0.7% vs 0.2%) due to TEAEs in this SMQ in this pool.

In the Phase 1 single- and multiple-dose studies, perampanel subjects experienced TEAEs in this SMQ (broad) more frequently than placebo subjects (1.5% vs 0.7% and 7.3% vs 0.9%, respectively) (Safety Information Amendment July 5, 2012 Tables 24.9-2 and 24.9-6). The highest frequency was noted for the highest dose groups (8.3% in >12 mg group and 8.4% in >8-12 mg group, respectively). One perampanel subject experienced the SAE of acute paranoia (narrative summarized earlier in this section).

The following table summarizes the outcome of the TEAEs in the broad hostility and aggression SMQ and modified hostility SMQ for the epilepsy Phase 3 DB pool. Of the TEAEs in both of these SMQs, perampanel subjects experienced more AEs that were serious, severe, and led to dose reduction, interruption, and discontinuation.

Table 48. Outcome of Hostility-related TEAEs, Epilepsy Phase 3 DB Pool

	Placebo	Perampanel
SMQ Hostility and Aggression	25 (100)	123 (100)
SAEs	1 (4.0)	7 (5.7)
Discontinuations (DCs)	3 (12.0)	17 (13.8)
Dose reduction/interruption	0	19 (15.4)
Severe	0	13 (10.6)
Modified Hostility SMQ	40 (100)	151 (100)
SAEs	1 (2.5)	6 (4.0)
Discontinuations (DCs)	3 (7.5)	18 (11.9)
Dose reduction/interruption	2 (5.0)	19 (12.6)
Severe	1 (2.5)	13 (8.6)

Source: Created by the reviewer using JReview and Epilepsy ADAE, ADSL datasets

The following table summarizes the narratives for some of the subjects with TEAEs coded to the Hostility and Aggression SMQ (homicidal ideation, aggression, belligerence, personality change, anger, agitation, impulse-control disorder, abnormal behaviour, psychotic disorder, and personality disorder) and to additional PTs such as mental disorder due to a general medical condition and delirium.

Comment: After reviewing the narratives for psychiatric-related SAEs, there were additional coding omissions for physical assaults, suicidal ideations, and homicidal ideations. There were 6 additional subjects in the epilepsy all treated pool with homicidal or suicidal ideations. This prompted an information request to the Sponsor to search their safety database for any homicides. In the Safety Information Amendment dated July 17, 2012, the Sponsor stated that no homicides were committed by a subject while taking perampanel or within 30 days after drug discontinuation.

In response to the Division's information request, the Sponsor provided narratives for the TEAEs coded to human bite (2) and physical assault (1). For each of these events, the subject was the recipient of the bite or assault. One human bite occurred during the prerandomization phase. The subject who experienced the TEAE of physical assault reported the AE of anxiety 5 days prior to the event. No additional information on the events surrounding these incidents was provided in the narratives.

In response to the Division's information request, the Sponsor provided additional information for the three subjects who discontinued the trials with a reason listed as "other" who had incarceration listed as the reason. At least one incarceration (failure to pay child support) is likely unrelated to perampanel use. However, there were no details provided for the other incarceration. Therefore, no conclusions can be made regarding perampanel's role in these cases. It is important to note that there was one case of an arrest of a perampanel subject that was noted in the CIOMS but not in the narrative provided by the Sponsor in the NDA. Therefore, there may be cases of incarcerations that were not reported by the Sponsor.

Subject 305-5185-5002 (placebo) - incarcerated for a "domestic problem with her daughter"

Subject 306-1801-6010 -reason for incarceration not disclosed by the family

Subject 227-1314-1019 - incarcerated as a result of "failure to pay child support"

Table 49. Narratives of Physical Assaults, Suicidal Ideations, Homicidal Ideations, and Damage to Property, Epilepsy and Nonepilepsy Studies

Subject #	Age, Sex, Race	Study: Treatment, Dose	Adverse event (Preferred Term)	Study day	Phase of Study
1314-1018	57, M, W	DB 227: Pera 8 mg	Homicidal ideation	DB 45	
<p>Subject had a history of abnormal ECG, HTN, DM, migraines, “situational anxiety”, with “no previous history of psychiatric disorders.” On Day 45, the subject experienced homicidal ideations along with confusion and dizziness. Subject felt increased anger and rage. He had no specific plan or target but did report looking for his old shotgun. These thoughts “frightened the subject” who told his wife, who then hid the shotgun. The subject was unable to think clearly, finding it hard to spell common words and was writing sentences backwards. He was “literally bouncing off the walls.” Perampanel was discontinued due to these events (last dose taken on Day 49). The confusional state and homicidal ideations resolved within 24 hours on Day 50.</p> <p>Concomitant medications included nortriptyline (>2 years), rizatriptan (8 years), metformin, glibenclamide (sulfonylurea), and prinzide (lisinopril and hydrochlorothiazide).</p> <p><i>The events in this case are very concerning and could be related to perampanel use. The narrative specifically reported that the subject did not have any previous history of psychiatric disorders. The onset of these events correspond to the initiation (after 6 weeks) of perampanel (along with a positive dechallenge). The other concomitant medications (nortriptyline and rizatriptan) were taken chronically for more than 2 years. Furthermore, these symptoms of confusion and inability to control his behavior are particularly worrisome with the subject’s access to a potentially lethal weapon. This lack of impulse control was also seen in other perampanel subjects (narratives described in the Suicidal Behavior and Ideation section above). Additionally, this subject exhibited akathisia (psychomotor restlessness) which may represent a precursor to events that can cause harm to themselves or to others.</i></p>					
5118-4013	42, F, W	DB 304: Pera 8 mg OLE 307: Pera 12 mg	Homicidal ideation	OLE 259	Maintenance
<p>Subject with a history of anxiety, chronic depression (treated with duloxetine and alprazolam) who was hospitalized for homicidal ideation and suicidal ideation on OLE Day 259. Treatment included aripiprazole and continuation of duloxetine. Perampanel was reduced in response to these events. The events resolved 5 days later on Day 264. On Day 305, perampanel was discontinued because of subject choice.</p> <p><i>This case is confounded by the subject’s previous psychiatric history of chronic depression. Furthermore, there was a negative rechallenge as perampanel was continued without any further events (for 41 days). Therefore, it is difficult to make any conclusions regarding perampanel’s role in this case especially with the lack of details regarding past homicidal or suicidal ideations.</i></p>					
5167-5010	57, F, W	DB 305: Pera 12 mg	Belligerence x 2	DB 33, 40	Titration
<p>Subject with a complicated medical history including cerebral palsy, CVA, falls, asthma, hypertension who experienced belligerence. During a second episode of belligerence, the subject was hitting the office staff and biting her sister’s finger during the office visit. Treatment included olanzapine. Perampanel was discontinued and the events resolved 5 days later. Concomitant medications included lorazepam as needed (3 years), baclofen (5 years), lacosamide (6 months), pregabalin (3 months).</p> <p><i>These events could be related to perampanel use (with the time course and positive dechallenge). The narrative did not report any prior psychiatric history (or aggression) for this subject. The time course of events suggests that it was unlikely due to the other concomitant medications (lorazepam and baclofen were taken chronically and lacosamide and pregabalin are not associated with aggressive behavior according to their labeling).</i></p>					
5118-4014	47, M, O	DB 304: Pera 8 mg OLE 307: Pera 12 mg	Aggression	OLE 59	Conversion
<p>Subject with a history of anxiety and musculoskeletal pain who experienced aggression and</p>					

<p>perseveration on OLE Day 59 (after previously experiencing anxiety, paranoia, and perseverative behavior on OLE Day 14). The subject became irritable, paranoid, resulting in aggressive behavior, striking his wife. His perseverative thoughts included “harm done to him by the primary care physician” and accused his family of mistreating him. Perampanel was discontinued and these events resolved 3 days later. Concomitant medications included pregabalin, topiramate, captopril, rufinamide, and simvastatin. The subject reportedly did not have a history of alcohol or drug abuse.</p> <p><i>These events could be related to perampanel use (with the time course and positive dechallenge). The narrative did not report any prior history of aggression for this subject. The other concomitant medications, pregabalin and rufinamide, are not associated with aggression (according to labeling).</i></p>					
5134-4005	56, F, W	DB 304: Pera 8 mg OLE 307: Pera 12 mg	Affective disorder Psychotic disorder	OLE 79	Conversion
<p>Subject with a history of mental retardation, fall, vertigo, and urge incontinence who was hospitalized in a psychiatric inpatient unit for delirium, affective disorder, and psychotic disorder on OLE Day 79. The subject was observed physically attacking her caregiver. She was also physically aggressive toward her mother. It was noted that the subject did not have the correct doses of her other medications in the pill boxes and had not taken perampanel for 4 days prior to these events. Treatment included escitalopram, olanzapine, aripiprazole. Perampanel was discontinued. The events resolved 8 days later. Concomitant medications included carbamazepine (>10 years), lamotrigine (>10 years), citalopam (>10 years).</p> <p><i>These events could be related to perampanel use (with the time course and positive dechallenge). The narrative did not report any prior history of aggression for this subject. The time course of events suggest that it was unlikely due to the other concomitant medications (taken chronically for more than 10 years).</i></p>					
3950-6001	17, M, W	DB 306: Pera 4 mg OLE 307: Pera 12 mg	Aggression	OLE 85	Conversion
<p>Subject without any prior psychiatric history who experienced aggression on OLE Day 85. The subject experienced an episode of “psychoemotional excitement,” during which he had a physical altercation with a friend and relative and destroyed some personal property.” Subject was hospitalized. Treatment was not reported. Perampanel was discontinued. The events resolved on Day 92. Concomitant medications included topiramate and valproic acid.</p> <p><i>The onset of these events corresponds to the titration from the 4 mg to the 12 mg dose of perampanel (with a positive dechallenge). The narrative did not report any prior psychiatric history (or aggression) for this subject. Therefore, the role of perampanel cannot be ruled out.</i></p>					
2504-6003	21, F, A	DB 306: Pera 8 mg	Personality change	DB 30	Maintenance
<p>Subject without any previous psychiatric history who experienced personality change (severe) on Day 30. The subject became hostile and defiant towards her mother, with the subject moving away from home and quitting her job. These events continued until Day 106 and perampanel was discontinued. The events resolved on Day 127. Concomitant medications included valproic acid (6 months) and topiramate (6 months).</p> <p><i>The onset of these events corresponds to the initiation (after 4 weeks) of perampanel (along with a positive dechallenge). The other concomitant medications were taken for more than 6 months and are not associated with aggressive behavior (according to their labeling). The narrative did not report any prior psychiatric history (or aggression) for this subject. Therefore, the role of perampanel cannot be ruled out.</i></p>					
5181-5001	16, M, W	DB 305: Pera 8 mg OLE 307: Pera 12 mg	Aggression x 2 Aggression x 4	DB~15,44 OLE 1-125	Titration Maintenance
<p>Subject with a history of cognitive delay who experienced aggression soon after starting perampanel in DB Study 305. Perampanel was reduced. Aggression developed again and subject was taken to the emergency room by his mother who feared he might harm her due to aggression.” Treatment included risperidone and benztropine. Perampanel was continued and the subject entered the OLE</p>					

<p>Study 307. The subject experienced multiple recurrences of aggression which led to a hospitalization in a psychiatric hospital on OLE Day 125 due to increasing verbal and physical aggressive behavior. Treatment was not reported. Aggression resolved and perampanel was continued (most recent dose OLE Day 486).</p> <p>Concomitant medications included phenobarbital (>3 years) and clonazepam as needed (>2 years). <i>The time course of these events suggests that they could be related to perampanel use (and unlikely due to the other medications which were taken chronically). The narrative did not report any prior psychiatric history (or aggression) for this subject. Furthermore, there was evidence of positive rechallenge with the events progressively worsening in severity (led to psychiatric hospitalization due to increasing aggressive behavior). It was not reported why perampanel was continued after this hospitalization. However, there were reportedly no further recurrences of aggression despite continuation of perampanel (this could be suggestive of possible tolerance).</i></p>					
3501-6006	24, F, A	DB 306: Pera 2 mg OLE 307: Pera 6 mg	Irritability Aggression/ Impulse-control disorder	DB 72 OLE 27/462	Maintenance Conversion
<p>Subject without any prior psychiatric history who experienced irritability on Day 72 of DB Study 306. Perampanel was continued and the subject entered the OLE Study 307. On OLE Day 27, while taking 6 mg of perampanel, the subject became violent. She fought with a friend “kicking and slapping her” and hit a wall with her left hand. Perampanel was reduced and the event of aggression resolved on Day 282. On Day 462, the subject experienced impulse-control disorder, becoming “wild” and shouting at relatives. The subject obtained a knife and threatened a relative because of anger. Perampanel was continued and the event of impulse-control disorder remained ongoing (the subject received her most recent dose of perampanel on Day 653). Concomitant medications included phenobarbital (1 year) and valproic acid (5 months).</p> <p><i>The onset of these events corresponds to the initiation (after 2 months) of perampanel. The other concomitant medications were either taken for more than 1 year or were not associated with aggressive behavior (according to valproic acid labeling). The narrative did not report any prior psychiatric history (or aggression) for this subject. It is concerning that the subject’s behavior became increasingly violent (physical assault and property damage) as the dose of perampanel was increased. When perampanel was continued, the events took a prolonged time to resolve or did not resolve (impulse-control disorder remains ongoing). Furthermore, it is concerning that the subject experienced a lack of impulse control (also seen in other perampanel subjects) with access to a potentially lethal weapon.</i></p>					
5118-4002	32, M, W	DB 304: Pera 12 mg	Aggression [^]	DB 41	Titration
<p>Subject with a history of intermittent aggressive behavioral disorder and depression who experienced irritability and worsening of aggressive behavior on Day 19. Perampanel was continued and the subject experienced aggression on Day 41. The subject had a “fight with his father and threatened him and the police with a knife [included in the CIOMS report and not in the narrative].” The subject was admitted to a psychiatric inpatient unit for homicidal and suicidal threats. Perampanel was discontinued and the events of aggression resolved 30 days later.</p> <p>Concomitant medications included felbamate (2 yrs), pregabalin (3 months), venlafaxine (3 months), and lisinopril. It is noted in the CIOMS report that the subject may have been taking the wrong doses of pregabalin and venlafaxine.</p> <p><i>This case is confounded by the subject’s previous history of aggressive behavioral disorder and the concomitant use of venlafaxine (possibly taken at incorrect doses). However, it is concerning that the subject’s aggressive behavior worsened (with the use of a weapon) after perampanel was initiated. Therefore, perampanel use may have exacerbated the subject’s underlying disorder.</i></p>					
5140-4004	33, F, W	DB 304: placebo OLE 307: Pera 12 mg	Anger	OLE 49	Conversion
<p>Subject with a history of depression, migraines, irritability, anxiety, and chronic fatigue who was hospitalized for anger on OLE Day 49 (received placebo in the DB Study 304). Quetiapine was recently</p>					

<p>stopped and the subject's mood improved with the reinitiation of quetiapine. On Day 88, the subject had verbal and physical altercations with family members and was admitted to a psychiatric hospital. Mood slowly improved and perampanel was continued. On Day 214, the subject experienced a third episode of anger with a verbal confrontation with her parents. Treatment included escitalopram with resolution of the event. On Day 377, the subject physically attacked one of the staff members in the group home (the Medical Monitor was not notified of this event). On Day 399, the subject again physically attacked the staff members. This outburst was thought secondary to being told by her mother that she had to stay in the group home. Perampanel was continued. Concomitant medications included propranolol, clonazepam, quetiapine, nortriptyline, and carbamazepine.</p> <p><i>This case is confounded by the subject's previous psychiatric history of anxiety, depression, and irritability. However, it is concerning that the subject began to assault family and staff members after perampanel was initiated in the OLE Study (prior history of this behavior was not reported in the narrative). Therefore, perampanel use may have exacerbated the subject's underlying disorder. However, there were reportedly no further recurrences of aggression despite continuation of perampanel</i></p>					
5128-4001	25, M, W	DB 304: Pera 12 mg OLE 307: Pera 10 mg	Adjustment disorder Aggression	DB 11, OLE 13	Conversion
<p>Subject with a history of oppositional defiant disorder, behavior disorder, learning disorder who was hospitalized for adjustment disorder on DB Day 11. Perampanel was temporarily discontinued and then later restarted. On OLE Day 13, the subject experienced aggressive outbursts and was hospitalized. Treatment included lorazepam, olanzapine. Perampanel was discontinued. The next day, the subject experienced worsened aggressive outbursts. Five days later, the event of aggression resolved. Concomitant medications included valproic acid and zonisamide.</p> <p><i>This case is confounded by the subject's previous psychiatric history. However, there is possible evidence of a positive dechallenge and positive rechallenge with perampanel for these events. Therefore, perampanel use may be associated with exacerbating underlying psychiatric disorders.</i></p>					
4703-6008	39, F, A	DB 306: placebo OLE 307: Pera 10 mg	Mental disorder due to a general medical condition*	OLE 93	Maintenance
<p>Subject with a history of mental retardation who received placebo in the DB Study 306, had no ongoing adverse events, and entered the OLE Study 307. On OLE Day 81, the subject experienced depression ("mixed anxiety depressive disorder"). Treatment for this event included paroxetine, trazodone, trihexyphenidyl, clorazepam, and haloperidol. Perampanel was reduced. On Day 93, the subject experienced "mental disorder due to a general medical condition" and was hospitalized. The subject was "self-talking, had suicide ideation, was self-mutilating, was hostile to her family, and experienced aggravated delusion of persecution." Treatment included quetiapine and lorazepam. The subject developed severe psychosis and perampanel was discontinued on Day 112. The events resolved on Day 150.</p> <p>Concomitant medications included lamotrigine, valproic acid, phenobarbital.</p> <p><i>Although the onset of the "mixed anxiety depressive disorder" corresponds to the initiation (after 2 months) of perampanel, the events of aggression and suicidal ideations and behavior are confounded by the subject's recent treatment with multiple psychiatric medications.</i></p>					
4001-6012	26, F, W	DB 306: Pera 2 mg OLE 307: Pera 12 mg	Agitation	OLE 254	Maintenance
<p>Subject with a history of "personality change due to a general medical condition" who became agitated and had a "quarrel and altercation with her father." Subject was hospitalized. Treatment included haloperidol, diazepam. Perampanel was discontinued and the events resolved 17 days later. Concomitant medications included valproic acid, lamotrigine, topiramate.</p> <p><i>Although there was a positive dechallenge with perampanel for these events, these events developed after prolonged exposure to perampanel. Therefore, given the details of this narrative, it is difficult to ascertain the etiology of these events. However, given the lack of prior psychiatric history, the role of</i></p>					

<i>perampanel for these events cannot be ruled out. Furthermore, the concomitant medications are not typically associated with aggressive behavior (according to labeling).</i>					
4302-6011	27, F, A	DB 306: Pera 4 mg OLE 307: Pera 8 mg	Abnormal behavior	OLE 3	Conversion
<p>Subject without any psychiatric history who experienced abnormal behavior with aggression. She "shouted, attacked her parents, and ran away from home." Perampanel was discontinued and the events resolved 2 days later. Concomitant medications included valproic acid (2 years), levetiracetam (7 months), phenobarbital (7 months).</p> <p><i>This case is confounded by levetiracetam use (known to cause aggression). However, the onset of the aggressive behavior corresponds more to the timing of perampanel initiation (along with a positive dechallenge with perampanel). Therefore, the role of perampanel for these events cannot be ruled out.</i></p>					
3601-6007	31, M, W	DB 306: Pera 2 mg OLE 307: Pera 12 mg	Personality disorder Irritability, anxiety	OLE 92	Conversion
<p>Subject with a history of head injury who experienced personality disorder on Day 92 and was hospitalized. The subject's "behavior was changing for several months" and was more irritable with suicidal intentions. The subject was "talkative with chaotic, multidirectional statements" with limited control of impulses. The events resolved on Day 104 and perampanel was continued until Day 300 (discontinued due to bradycardia). In the follow up phase, 9 days later, the subject experienced irritability, anxiety, mood swings, panic disorder, and tearfulness. The events resolved 18 days later. Concomitant medications included valproic acid (>1 year) and levetiracetam (~9 months).</p> <p><i>This case is confounded by levetiracetam use. Although, it is difficult to know when the events started ("behavior was changing for several months"), the worsening of the events corresponded to the titration from the 2 mg to the 12 mg dose of perampanel. Therefore, perampanel use may have exacerbated an underlying disorder caused by another medication. Furthermore, it is concerning that the subject experienced a lack of impulse control (also seen in other perampanel subjects).</i></p>					
1104-5001	29, M, W	DB 305: placebo OLE 307: Pera 12 mg	Aggression	OLE 228	Maintenance
<p>Subject with a history of febrile convulsion, bursitis who was hospitalized in a psychiatric facility due to aggression on OLE Day 228. Treatment included clonazepam for "behavioral disorder with aggressive tendencies and impulse control dysregulation." The event remained ongoing and perampanel was discontinued due to the event of aggression. Concomitant medications included levetiracetam (>1 year), zonisamide (~4 months), lacosamide (~2 months).</p> <p><i>This case is confounded by zonisamide (associated with psychosis) and levetiracetam use (associated with aggression). However, the role of perampanel cannot be ruled out especially with the changes in impulse control (also seen in other perampanel subjects).</i></p>					
5104-4007	12, M, W	DB 304: Pera 8 mg OLE 307: Pera 12 mg	Aggression x 5	OLE 122-483	Maintenance
<p>Subject with a history aggression who experienced multiple episodes of aggression and abnormal behavior starting on OLE Day 122. Treatment included guanfacine and risperidone (not taken due to economic factors). Perampanel was continued. On Day 483, the subject experienced a fifth episode of aggression and was hospitalized. Subject had a history of aggression but "of late" the outbursts were becoming more difficult to manage. The subject beat his mother and "pulled a knife on her and threatened to kill [the family]". The subject reported that he only had outbursts when provoked by his stepfather who would verbally and physically abuse him. The mother noted an increased in "non-convulsive events." Perampanel was continued (received his most recent dose on Day 697). Aggression resolved on Day 505. Concomitant medications included valproic acid.</p> <p><i>This case is confounded by the subject's previous history of aggression. However, it is concerning that the subject's aggressive behavior worsened (with the use of a weapon) during treatment with perampanel. Therefore, perampanel use may have exacerbated the subject's underlying disorder. However, there were reportedly no further recurrences of aggression despite continuation of</i></p>					

<i>perampanel.</i>					
1011-1001	16, M, O	DB 235: Pera 12 mg	Aggressive behavior	DB 59	Maintenance
<p>Subject with a history of attention deficit hyperactivity disorder, mood disorder (not otherwise specified) who experienced increasing aggressive behavior starting on Day 36. The subject struck his adoptive mother. On Day 59, the subject was admitted to a psychiatric hospital for aggression. Treatment included increased doses of aripiprazole. The events resolved on Day 66. Perampanel was continued (received most recent dose of study drug on Day 206).</p> <p>Concomitant medications included dexamethylphenidate, lamotrigine, sertraline, and aripiprazole.</p> <p><i>This case is confounded by the subject's previous psychiatric history. Even though the narrative did not report any prior history of aggression and the onset of these events correspond to the initiation (after 5 weeks) of perampanel, there were reportedly no further recurrences of aggression despite continuation of perampanel.</i></p>					
1105-5006	39, M, W	DB 305: Pera 8 mg	Psychotic disorder	DB 39	Titration
<p>Subject with a history of gastric ulcer, viral meningoencephalitis, depressive episodes who experienced a psychotic disorder with mood swings, irritability, dysphoria, intermittent euphoria, dysarthrophonia, and engagement in risky behavior on Day 39. Perampanel was discontinued on Day 41 and the events resolved on Day 49. Concomitant medications included lacosamide.</p> <p><i>These events could be related to perampanel use (with the time course and positive dechallenge). The narrative did not report any prior history of psychosis and irritability for this subject.</i></p>					
2757-6001	21, F, A	DB 306: Pera 2 mg	Delirium	DB 61	Maintenance
<p>Subject without any psychiatric history who experienced acute psychiatric manifestations on Day 61. No prior history of abnormal behavior or psychiatric manifestations. The subject began to have hallucinations, delusions of grandeur, frequent hand washing, and labile speech. Subject was hospitalized and last dose of perampanel was taken on Day 62. On Day 79, the subject's symptoms worsened and she became "violent, aggressive, irritable with irrelevant excessive talk, and had bizarre wandering." The subject was rehospitalized. Treatment included serenace (haloperidol), lorazepam, olanzapine, and valproic acid. The events resolved in Day 104.</p> <p>Concomitant medications included clobazam (3 years) and oxcarbazepine (~6 months).</p> <p><i>The onset of these events corresponds to the initiation (after 2 months) of perampanel. The other concomitant medications were either taken chronically or were not associated with aggressive behavior (according to oxcarbazepine labeling). However, the episode that occurred 17 days after perampanel discontinuation was unlikely due to perampanel (after 4 elimination half-lives).</i></p>					
2503-6005	19, M, A	DB 306: placebo OLE 307: Pera 10 mg	Aggression, Psychotic disorder	OLE 29, 69	Follow-up
<p>Subject with a history of tuberculosis meningitis who experienced aggression on Day 29. Perampanel was discontinued on Day 32. On Day 69, the subject experienced psychotic disorder. The father reported that the subject had been having anxiety, insomnia, chaotic thoughts with suicidal ideations, and hallucinations. The subject was hospitalized. Treatment included clonazepam, quetiapine, and diazepam. The events resolved on Day 121.</p> <p>Concomitant medications included levetiracetam (~6 months) and valproic acid (~6 months).</p> <p><i>This case is confounded by the levetiracetam use. Although the onset of aggression corresponds to perampanel initiation, the psychotic events are unlikely due to perampanel (after 5 elimination half-lives).</i></p>					
1301-1009	71, M, W	DB 227: Pera 6 mg	Encephalopathy	DB 16	
<p>Subject without any psychiatric history who experienced severe encephalopathy on Day 16. The subject became confused and urinated on the carpet. He also "tried to light a match as he thought he was burning leaves and tried to crush bugs on the kitchen counter that were not there." The subject's wife notified EMS and the subject was admitted to the hospital. An EEG revealed an "encephalopathic process." Perampanel was discontinued and the encephalopathy resolved 10 days later.</p> <p>Concomitant medications included enalapril, simvastatin, glimepiride, gabapentin (>15 years), and</p>					

amitriptyline (7 years).

These events could be related to perampanel use (with the time course and positive dechallenge). The narrative did not report any prior psychiatric history for this subject. The time course of events suggest that it was unlikely due to the other concomitant medications (taken chronically for more than 7 years). Furthermore, it is concerning that the subject experienced a lack of impulse control (also seen in other perampanel subjects) with access to a potentially destructive item.

Source: Created by the reviewer using narratives provided by the Sponsor

A=Asian, O=Other, Unknown, American Indian or Alaska Native

*The original narrative included in the resubmission did not include the narrative for the SAE of Mental Disorder Due to a General Medical Condition. The updated narrative was provided by the Sponsor in response to an information request dated June 13, 2012. The Sponsor explained that the narrative that had been updated for the resubmission was "inadvertently not included in the Study 307 CSR Addendum provided in the NDA resubmission."

^Additional details were provided in the CIOMS provided by the Sponsor in a safety information amendment on June 21, 2012.

In the placebo group, there were 2 subjects with SAEs in the Hostility/Aggression SMQ: 1 subject in epilepsy phase 3 DB pool and 1 in nonepilepsy DB pool. The AEs were both coded to the PT psychotic disorder. Neither of the narratives contained any events of physical assaults, abuse, homicidal ideations/threats, or suicidal ideations/attempts.

The following table summarizes the dose response that was observed for the hostility SMQs (broad, narrow, and modified) in the epilepsy Phase 3 DB pool. After stratifying by study, a dose response relationship is more clearly seen with subjects randomized to the higher dose groups (8 mg and 12 mg) with approximately 2 times higher incidence than placebo of experiencing hostility and aggression TEAEs. When only preferred terms in the narrow SMQ are used, there is a stronger dose-response with up to 11 times the incidence in the higher dose groups.

Table 50. Dose Response for Hostility/Aggression SMQ (Broad), Epilepsy Phase 3 DB Pool

Broad Hostility SMQ	Placebo n (%)	Perampanel n (%), Randomized Dose Group				
		2 mg	4 mg	8 mg	12mg	Total
	442	180	172	431	255	1038
Irritability	13 (2.9)	7 (3.9)	7 (4.1)	29 (6.7)	30 (11.8)	73 (7.0)
Aggression	2 (0.5)	1 (0.6)	1 (0.6)	7 (1.6)	8 (3.1)	17 (1.6)
Skin Laceration	7 (1.6)	1 (0.6)	0	7 (1.6)	6 (2.4)	14 (1.4)
Anger	1 (0.2)	0	0	5 (1.2)	7 (2.8)	12 (1.2)
Abnormal Behaviour	0	0	0	2 (0.5)	2 (0.8)	4 (0.4)
Agitation	2 (0.5)	0	0	3 (0.7)	1 (0.4)	4 (0.4)
Laceration	0	0	0	2 (0.5)	1 (0.4)	3 (0.3)
Affect Lability	0	0	0	0	2 (0.8)	2 (0.2)
Belligerence	0	0	0	0	1 (0.4)	1 (0.1)
Disinhibition	0	0	0	1 (0.2)	0	1 (0.1)
Hypomania	0	0	0	1 (0.2)	0	1 (0.1)
Impulse-Control Disorder	0	0	0	0	1 (0.4)	1 (0.1)
Injury	0	0	0	0	1 (0.4)	1 (0.1)
Personality Change	1 (0.2)	0	0	1 (0.2)	0	1 (0.1)
Personality Disorder	0	0	0	1 (0.2)	0	1 (0.1)
Physical Assault	0	0	1 (0.6)	0	0	1 (0.1)
Psychomotor Hyperactivity	0	0	0	1 (0.2)	0	1 (0.1)
Psychotic Disorder	1 (0.2)	0	0	1 (0.2)	0	1 (0.1)
Total subjects	25 (5.7)	9 (5.0)	9 (5.2)	53 (12.3)	52 (20.4)	123 (11.8)
Study 304	11 (9.1)			21 (15.8)	33 (24.6)	54 (20.2)
Study 305	10 (7.4)			17 (13.2)	19 (15.7)	36 (14.4)
Study 306	4 (2.2)	9 (5.0)	9 (5.2)	15 (8.9)		33 (6.3)

Source: Created by the reviewer using JReview and Epilepsy ADAE, ADSL datasets

Table 51. Dose Response for Modified Hostility SMQ, Epilepsy Phase 3 DB Pool

Modified Hostility SMQ	Placebo n (%)	Perampanel n (%), Randomized Dose Group				
		2 mg	4 mg	8 mg	12mg	Total
	442	180	172	431	255	1038
Irritability	13 (2.9)	7 (3.9)	7 (4.1)	29 (6.7)	30 (11.8)	73 (7.0)
Insomnia	16 (3.6)	2 (1.1)	2 (1.2)	15 (3.5)	11 (4.3)	30 (2.9)
Anxiety	5 (1.1)	4 (2.2)	3 (1.7)	13 (3.0)	9 (3.5)	29 (2.8)
Aggression	2 (0.5)	1 (0.6)	1 (0.6)	7 (1.6)	8 (3.1)	17 (1.6)
Anger	1 (0.2)	0	0	5 (1.2)	7 (2.8)	12 (1.2)
Sleep Disorder	1 (0.2)	2 (1.1)	1 (0.6)	6 (1.4)	2 (0.8)	11 (1.1)
Abnormal Behaviour	0	0	0	2 (0.5)	2 (0.8)	4 (0.4)
Agitation	2 (0.5)	0	0	3 (0.7)	1 (0.4)	4 (0.4)
Panic Attack	1 (0.2)	1 (0.6)	0	1 (0.2)	2 (0.8)	4 (0.4)
Affect Lability	0	0	0	0	2 (0.8)	2 (0.2)
Belligerence	0	0	0	0	1 (0.4)	1 (0.1)
Disinhibition	0	0	0	1 (0.2)	0	1 (0.1)
Hypomania	0	0	0	1 (0.2)	0	1 (0.1)
Impulse-Control Disorder	0	0	0	0	1 (0.4)	1 (0.1)
Personality Change	1 (0.2)	0	0	1 (0.2)	0	1 (0.1)
Personality Disorder	0	0	0	1 (0.2)	0	1 (0.1)
Physical Assault	0	0	1 (0.6)	0	0	1 (0.1)
Psychomotor Hyperactivity	0	0	0	1 (0.2)	0	1 (0.1)
Psychotic Disorder	1 (0.2)	0	0	1 (0.2)	0	1 (0.1)
Restlessness	1 (0.2)	0	0	0	1 (0.4)	1 (0.1)
Akathisia	1 (0.2)	0	0	0	0	0
Total subjects	40 (9.1)	13 (7.2)	14 (8.1)	65 (15.1)	59 (23.1)	151 (14.6)
Study 304	16 (13.2)			29 (21.8)	38 (28.4)	67 (25.1)
Study 305	15 (11.0)			19 (14.7)	21 (17.4)	40 (16.0)
Study 306	9 (4.9)	13 (7.2)	14 (8.1)	17 (10.1)		44 (8.4)

Source: Created by the reviewer using JReview and Epilepsy ADAE, ADSL datasets

Table 52. Dose Response for Hostility/Aggression SMQ (Narrow), Epilepsy Phase 3 DB Pool

Narrow Hostility SMQ	Placebo n (%)	Perampanel n (%), Randomized Dose Group				
		2 mg	4 mg	8 mg	12mg	Total
	442	180	172	431	255	1038
Aggression	2 (0.5)	1 (0.6)	1 (0.6)	7 (1.6)	8 (3.1)	17 (1.6)
Anger	1 (0.2)	0	0	5 (1.2)	7 (2.8)	12 (1.2)
Belligerence	0	0	0	0	1 (0.4)	1 (0.1)
Physical assault	0	0	1 (0.6)	0	0	1 (0.1)
Total subjects	3 (0.7)	1 (0.6)	2 (1.2)	12 (2.8)	16 (6.3)	31 (3.0)
Study 304	1 (0.8)			7 (5.3)	12 (9.0)	19 (7.1)
Study 305	1 (0.7)			2 (1.6)	4 (3.3)	6 (2.4)
Study 306	1 (0.5)	1 (0.6)	2 (1.2)	3 (1.8)		6 (1.2)

Source: Created by the reviewer using JReview and Epilepsy ADAE, ADSL datasets

Notably, the highest incidences of hostility and aggression TEAEs occurred in Study 304 which has the highest percentage of subjects from the United States (52.3% vs

23.6% in Study 305 and 0% in Study 306). Therefore, I performed additional analyses for the 294 subjects from the US (in Studies 304 and 305) using both randomized and actual dose groups (see tables below). For the highest dose group (>8-12 mg actual dose and 12 mg randomized dose groups), there was approximately a 2- to 3-fold increase in the incidence of hostility TEAEs (in the broad and modified SMQ) compared to placebo in US subjects. For the 8 mg dose group (and >4-8 mg actual dose group), there was approximately a 1.5- to 2.5-fold increased incidence of hostility TEAEs (in the broad and modified SMQ) compared to placebo in US subjects. For the narrow SMQ, there were even larger differences between the dose groups and placebo in US subjects (an increase of 5-fold for the >4-8 mg actual dose group and 8 mg randomized dose group, 8-fold for the >8-12 mg actual dose group, and 15-fold for the 12 mg randomized dose group).

Table 53. Hostility TEAEs in Subjects from the United States by Randomized Dose Groups, Epilepsy Phase 3 DB Pool

SMQ	Placebo n (%)	Perampanel n (%)				
		2 mg	4 mg	8 mg	12mg	Total
	99			95	100	195
Broad Hostility SMQ	10 (10.1)			20 (21.1)	32 (32.0)	52 (26.7)
Modified Hostility SMQ	11 (11.1)			26 (27.4)	36 (36.0)	62 (31.8)
Narrow Hostility SMQ	1 (1.0)			5 (5.3)	15 (15.0)	20 (10.3)

Source: Created by the reviewer using JReview and Epilepsy ADAE, ADSL datasets

Table 54. Hostility TEAEs in Subjects from the United States by Actual Dose at or Prior to AE Onset, Epilepsy Phase 3 DB Pool

SMQ	Placebo n (%)	Perampanel n (%)				Total
		<4 mg	4 mg	>4-8 mg	>8-12mg	
	97	197*	193*	191*	82*	197
Broad Hostility SMQ	10 (10.3)	9 (4.6)	5 (2.6)	31 (16.2)	14 (17.1)	52
Modified Hostility SMQ	11 (11.3)	10 (5.1)	6 (3.1)	36 (18.8)	18 (22.0)	62
Narrow Hostility SMQ	1 (1.0)	2 (1.0)	3 (1.6)	9 (4.7)	7 (8.5)	20

Source: Created by the reviewer using JReview and Epilepsy ADAE, ADSL datasets

*Total number of subjects who were exposed to the dose during the study.

A subject may be counted more than once if the subject had another AE under a different dose group.

Another anticonvulsant, Keppra®, contains information regarding Psychiatric Reactions as the first heading within the Warnings and Precautions section of labeling. Keppra®-treated patients experienced more non-psychotic behavioral symptoms than placebo patients. Incidences for Keppra® are listed in the following table, along with other demographic variables.

Table 55. Relative Risk of Hostility/Aggression Broad SMQ by Demographics, Epilepsy Phase 3 DB Pool

Category	Placebo		Perampanel		Relative Risk (95% C.I.)
	n (%)	total	n (%)	total	
Sex:					
Male	12 (5.5)	220	66 (13.2)	499	2.42 (1.34-4.39)
Female	13 (5.9)	222	57 (10.6)	539	1.81 (1.01-3.23)
Age:					
Adults (>16 yrs)	22 (5.5)	404	111 (10.7)	966	2.11 (1.36-3.28)
Adolescents (12-16 yrs)	3 (7.9)	38	12 (16.7)	72	2.11 (0.63-7.03)
(Adults, Modified SMQ)	38 (9.4)	404	135 (14.0)	966	1.49 (1.06-2.09)
(Adolescents, Modified SMQ)	2 (5.3)	38	16 (22.2)	72	4.22 (1.02-17.4)
Other Antiepileptic Drugs:					
Keppra [^]			Keppra		
Adults (>16 yrs)	6.2%		13.3%		2.15
Pediatrics (4-16 yrs)	18.6%		37.6%		2.02

Source: Created by the reviewer using JReview and Epilepsy ADAE, ADSL datasets

[^]“non-psychotic behavioral symptoms” included following PTs: aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, hyperkinesias, irritability, nervousness, neurosis, and personality disorder

Comment: The Keppra labeling describes “non-psychotic behavioral symptoms” using similar AE terms such aggression, anger, agitation, anxiety, hostility, and irritability. Although, the other AE terms reported in Keppra labeling (apathy, depersonalization, depression, emotional lability, hyperkinesias, nervousness, neurosis) describe events that are similar to the adverse events seen in perampanel, they are not contained in the Hostility and Aggression SMQ (or Modified Hostility SMQ) that is being used for the perampanel analyses. The converse is also true; there are terms contained in the SMQ that were not used in the Keppra analyses (notably, the PTs homicidal ideation, homicide, physical abuse/assault). Although it is not possible to directly compare across studies, particularly from different development programs, it is interesting that the relative risk values are quite similar between Keppra and perampanel (broad SMQ).

I reviewed the original clinical review of the Keppra NDA 21035 submission written by Dr. Joel Freiman dated 11/18/99. Narratives were described for levetiracetam-treated subjects who discontinued due to adverse behavioral events (hostility, psychosis, personality disorder, and emotional lability) on pages 46-48 of the review. One subject who had a completed suicide was described along with other subjects with aggressive behavior, mood swings, and suicidal ideations. One subject with a history of a major aggressive episode developed increasingly aggressive behavior after receiving levetiracetam for 42 days and “threatened to kill his wife and was committed to a psychiatric hospital.” The subject’s symptoms “abated over 9 days” after levetiracetam was discontinued and treatment was initiated with loxapine, trihexyphenidyl, tinaptine and zolpidem.

Notably in the Keppra review, there were no other narratives that described AEs of homicidal ideations (in subjects without prior psychiatric history), physical assaults, property damage, or homicides.

There is a trend towards a higher risk in males than females for experiencing hostility-related TEAEs. Although the data for adolescents is limited by a small sample size, adolescents may have a slightly higher risk than adults for the Modified SMQ.

In response to the Division's information request, an analysis of possible risk factors was performed by the Sponsor for prior psychiatric history, history of hostility and aggression, relationship to seizure episodes for possible post-ictal psychosis, and concomitant medications (summarized in the following table). Among the subjects with TEAEs in the Hostility/Aggression Broad SMQ in epilepsy Phase 3 DB pool, a lower percentage of perampanel subjects than placebo had the risk factors of prior psychiatric history (40.7 vs 60%) possible post-ictal psychosis (47.2% vs 56.0%), and Keppra® use (33.3% vs 36.0%). The concomitant use of antipsychotics, antidepressants, and benzodiazepines was lower in perampanel subjects than placebo (8.9% vs 12.0%, 17.9% vs 20.0%, 34.1% vs 40.0%, respectively) which may support the data that there was less prior psychiatric history. The concomitant use of AED inducers (carbamazepine, phenytoin, and oxcarbazepine) was similar between the two groups. Furthermore, the percentage of subjects with a history of hostility and aggression was similar between the two groups.

A risk factor for developing hostility and aggression was identified in the Phase 1 Study 030. The effects of alcohol and perampanel in combination were assessed in healthy volunteers using the Profile of Mood State (POMS) questionnaire as part of the general psychomotor and cognitive test battery. The study reported alcohol in combination with 12 mg of perampanel significantly worsened mood with increased anger, tension, confusion, depression, and reduced vigour. Of note, the narratives provided by the Sponsor for SAEs and discontinuations lacked consistent information regarding alcohol use by the subject.

Table 56. Risk Factors, Hostility/Aggression Broad SMQ, Epilepsy Phase 3 DB

Risk Factor	Placebo n=25	Perampanel n=123
Prior psychiatric history*	15 (60.0)	50 (40.7)
Axis I	12 (48.0)	39 (31.7)
Axis II	1 (4.0)	1 (0.8)
Axis III	1 (4.0)	3 (2.4)
Unknown	7 (28.0)	25 (20.3)
History of hostility/aggression (broad SMQ)	3 (12.0)	15 (12.2)
Possible post-ictal psychosis (when AE occurred within 1 day of seizure in diary)		
Any seizures	14 (56.0)	58 (47.2)
Complex partial + secondarily generalized sz	11 (44.0)	42 (34.1)
Unknown	4 (16.0)	15 (12.2)
Concomitant medications^		
Antipsychotics	3 (12.0)	11 (8.9)
Antidepressants	5 (20.0)	22 (17.9)
Benzodiazepines	10 (40.0)	42 (34.1)
Psychostimulants	0	1 (0.8)
Levetiracetam	9 (36.0)	41 (33.3)
Valproic acid	10 (40.0)	32 (26.0)
Carbamazepine	5 (20.0)	27 (22.0)
Phenytoin	2 (8.0)	9 (7.3)
Oxcarbazepine	5 (20.0)	25 (20.3)
Lamotrigine	8 (32.0)	33 (26.8)
Topiramate	3 (12.0)	30 (24.4)
Phenobarbital	3 (12.0)	9 (7.3)
Clobazam	0	16 (13.0)
Clonazepam	6 (24.0)	13 (10.6)

Source: Safety Information Amendment 7/17/12 Table 23.9-29.2.5

*According to the DSM-IV-TR:

Axis I: Clinical disorders, including major mental disorders, learning disorders, substance use disorders

Axis II: Personality disorders and intellectual disabilities

Axis III: Acute medical conditions and physical disorders (such as brain injuries and other disorders which may aggravate existing diseases or present similar symptoms).

^Antipsychotics include any medication under the pharmacologic subclass of 'antipsychotics'.

Antidepressants include any medication under the pharmacologic subclass of 'antidepressants'.

Benzodiazepines include any medication under the pharmacologic subclass of 'anxiolytics' and 'hypnotics and sedatives'. Psychostimulants include any medication under the pharmacologic class of 'appetite stimulants' or 'immunostimulants', or under the pharmacologic subclass of 'cardiac stimulants excl. cardiac glycosides'.

An analysis was performed for the subset of subjects who continued in the study after experiencing TEAEs in the Hostility and Aggression SMQ (the subjects who did not have the study drug discontinued). Of the subjects who continued in the study, a higher number of perampanel subjects (14.2%) developed recurrences of TEAEs in this SMQ compared to placebo subjects (9.1%). Of the subjects who continued in the study but had a reduction or interruption of perampanel due to TEAEs in this SMQ, nearly one-fourth (22.2%, 4/18) of the perampanel subjects had recurrences of TEAEs in the SMQ.

The subjects in the higher dose groups (8 mg and 12 mg) had up to twice the incidence of recurrence compared to placebo subjects (18.4% and 15.4%, respectively) and with a shorter time to recurrence (4 to 17 days vs 113 days).

Perampanel subjects had similar incidences of subsequent TEAEs in the Suicidality SMQ. However, after taking into account the many coding omissions for these terms for the perampanel group, the incidences may be higher in the perampanel group than placebo.

Table 57. Subjects who Continued in the Study after TEAEs in Hostility and Aggression Broad SMQ, Epilepsy Phase 3 DB Pool

Category	Placebo n (%)	Perampanel n (%)				
		2 mg	4 mg	8 mg	12mg	Total
# of Subjects*	22	9	9	49	39	106
No further TEAEs in SMQ	20 (90.9)	9 (100)	9 (100)	40 (81.6)	33 (84.6)	91 (85.8)
Recurrence of TEAEs in SMQ [^]	2 (9.1)	0	0	9 (18.4)	6 (15.4)	15 (14.2)
recurrence of same TEAE	1 (4.5)	0	0	2 (4.1)	4 (10.3)	6 (5.7)
recurrence of different TEAE	1 (4.5)	0	0	7 (14.3)	2 (5.1)	9 (8.5)
Subsequent TEAE in the suicidality SMQ	5 (22.7)	1 (11.1)	2 (22.2)	9 (18.4)	6 (15.4)	18 (17.0)

Source: Safety Information Amendment 7/17/12 Table 23.9-29.2.6

*Subjects who did not have the study drug discontinued.

[^]Recurrence of same TEAE means that the subsequent TEAE needs to start after the first TEAE has resolved. A resolved TEAE is one with (1) an outcome of "Recovered", "Recovered with sequelae" or "Fatal", or (2) a complete/partial AE end date.

Table 58. Subjects who Continued in the Study after TEAEs in Hostility and Aggression Broad SMQ, Epilepsy Phase 3 DB Pool

Category	Placebo	Perampanel				
		2 mg	4 mg	8 mg	12mg	Total
# of Subjects*	22	9	9	49	39	106
Avg # of recurrences (including those without any further recurrences) [^]	0.05	0	0	0.06	0.10	0.07
Mean time to recurrence of TEAE in SMQ (days)	113.0			17.0	4.0	10.5
Mean time to resolution of TEAE in SMQ (days)	22.5	14.0	39.3	22.6	30.5	26.8
Mean time to TEAE in suicidality SMQ	48.3	0	92.0	3.9	49.0	26.0
Mean time to last dose of study drug for subjects without any recurrences of TEAEs in SMQ	50.9	105.0	48.0	71.2	65.8	69.1
Mean time to last dose of study drug for subjects with recurrences of TEAEs in SMQ	115.0			19.7	91.5	67.6

Source: Safety Information Amendment 7/17/12 Table 23.9-29.2.8

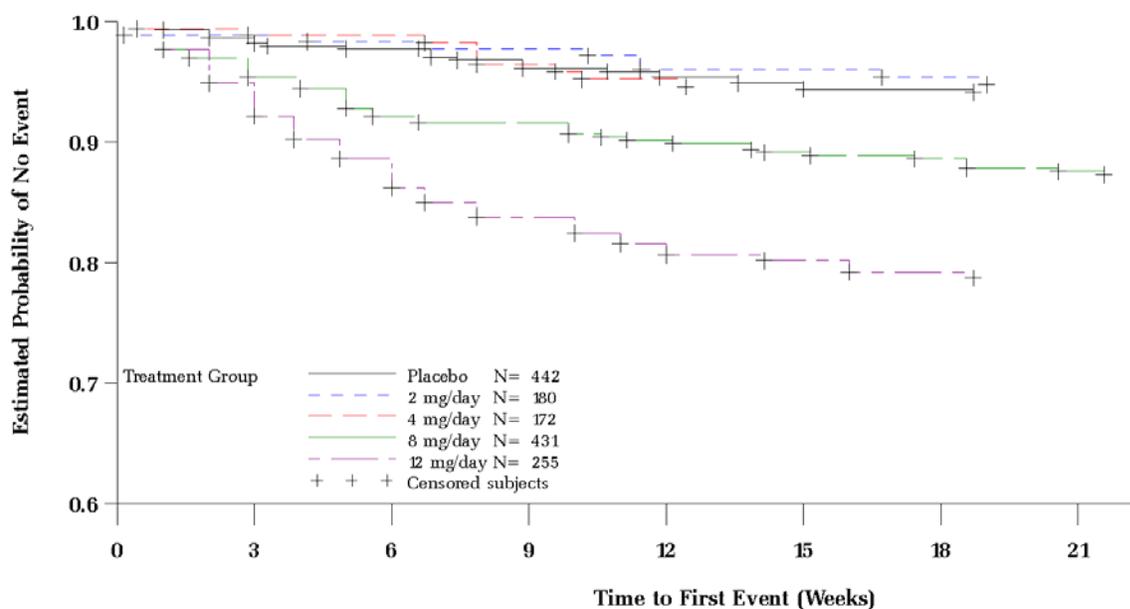
*Subjects who did not have the study drug discontinued.

[^]A recurrence means that the subsequent TEAE needs to start after the first TEAE has resolved and both TEAEs have the same preferred term (PT). A resolved TEAE is one with (1) an outcome of "Recovered", "Recovered with sequelae" or "Fatal", or (2) a complete AE end date. For each subject, the category value is calculated as a mean across all relevant events the subject had.

Summary statistics are across all subjects with non-missing value in the treatment group. For the time calculations, no imputation of dates was used. Only cases with relevant complete dates are summarized.

An analysis was performed to ascertain the timing of these hostility and aggression episodes. In the epilepsy Phase 3 studies, most of the perampanel subjects in the 8 and 12 mg dose groups developed the first episode within the first 6 weeks (titration period of the studies). A plateau is noted during the maintenance period. Of note, most of the discontinuations due to the TEAEs in this SMQ (76.5%, 13/17) occurred during the first 6 weeks of the trials.

Figure 3. Time to First Occurrence of TEAEs in Hostility/Aggression Broad SMQ, Epilepsy Phase 3 DB Pool



Source: Safety Information Amendment, 7/5/12 Figure 23.9-1.2

The Sponsor reported that for the all treated epilepsy pool, most of the perampanel subjects who experienced these events had the first occurrence within the first 14 weeks of treatment. Subjects continued to have first occurrences of aggressiveness during perampanel treatment for up to 2 years.

Discussion

Perampanel use was associated with aggression, hostility, and changes in mood, behavior, and personality. Only perampanel subjects (and no placebo subjects) experienced SAEs of suicidal ideations, suicide attempts, homicidal ideations, aggression, belligerence, disorientation, and impulse-control disorder. Perampanel use was associated with a statistically significant increased risk of developing TEAEs in the Hostility and Aggression MedDRA SMQ (narrow RR 4.40, 95% CI 1.35-14.3 and broad RR 2.10, 95% CI 1.38-3.17) compared to placebo. Of the TEAEs in the SMQs, perampanel subjects experienced more AEs that were serious, severe, and led to dose reduction, interruption, and discontinuation than placebo subjects.

In the epilepsy Phase 3 DB pool, there was a higher incidence of hostility and aggression AEs in perampanel subjects than placebo despite having a lower percentage of perampanel subjects with risk factors such as prior psychiatric history, possible post-ictal psychosis, and concomitant use of levetiracetam. In the epilepsy Phase 3 DB pool, there was a higher incidence of hostility and aggression AEs during the titration period (first 6 weeks) than the maintenance period, in male subjects than females, and in the higher randomized dose groups (8 mg and 12 mg) compared to the lower dose groups (2 mg and 4 mg).

A dose response was observed for both the MedDRA SMQs and the Modified SMQ. After restricting the population to US subjects and using actual dose groups, while a dose response was still seen in the highest dose groups (>4-8 mg and >8-12 mg dose groups), the differences were attenuated (when compared to the randomized dose group results).

Of the subjects who developed hostility TEAEs but were continued in the study (at the same dose), perampanel subjects in the higher dose groups had up to twice the incidence of recurrence compared to placebo subjects with a shorter time to recurrence. Of the subjects who continued in the study with a reduction or interruption of perampanel due to TEAEs in this SMQ, nearly one-fourth had recurrences of TEAEs in the SMQ. After experiencing these hostility TEAEs, some perampanel subjects developed suicidal and homicidal ideations and committed harmful acts (suicide attempts, property damage, physical assaults, and threats with a weapon). There were no placebo subjects with hostility TEAEs who committed similar acts of violence (no events of physical assaults, abuse, homicidal ideations/threats, or suicidal ideations/attempts).

The acts of violence reported in the narratives were concerning. Although the causal role of perampanel cannot be concluded for all of these cases, there were many cases where there was close temporal association between perampanel initiation and hostility TEAEs with positive dechallenge or rechallenge experience. Furthermore, many subjects did not have any prior psychiatric history or take any concomitant medications associated with aggression. Even in cases that were confounded by prior psychiatric history or levetiracetam use, there was suggestion that perampanel use may exacerbate these conditions. Many subjects exhibited a lack of impulse control during a period of confusion. The subjects' inability to control their behavior is particularly worrisome with the subjects' access to potentially lethal weapons. Finally, these cases appear to be more severe than the narratives that were described in the Keppra NDA 21035 in which there were no reports of physical assaults, damage to property, threats with weapons, or homicidal ideations in patients without prior history.

Notably, there may have been an underreporting of these cases of violence for the following reasons: information regarding homicides and arrests are not routinely

collected in studies, domestic violence cases are generally not always reported to authorities, and all of the information in the CIOMS was not included in the narratives (e.g., a threat with the use of a knife was noted in the CIOMS for one subject but was not included in the narrative provided in the NDA by the Sponsor).

Furthermore, in all of the epilepsy studies, an exclusion criterion was suffering from active psychotic disorder(s) and/or unstable recurrent affective disorder(s) with use of antipsychotics or had a suicide attempt(s) within the past 2 years. Therefore, the results from the epilepsy studies may not represent the effects of perampanel in the general population. The psychiatric adverse events in patients with active psychotic disorders and/or unstable recurrent affective disorders have not been studied. The above analyses for psychiatric disorders may represent less severe cases than in the general population.

In conclusion, there are serious, life-threatening neuropsychiatric events associated with perampanel use. As required by the Division for all antiepileptic medications, suicidal behavior and ideation is already in the Warnings section of the Sponsor's proposed labeling. If perampanel is approved, I recommend that a boxed warning should be used 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.⁷ Furthermore, this is a serious adverse reaction that might be reduced in frequency or severity by the following appropriate use of the drug:

- careful monitoring by physicians and family members of anger, irritability, hostility, or changes in mood, behavior, or personality.
- careful monitoring during the titration period and at higher doses.
- avoiding the use in patients with a history of aggression or any unstable psychiatric disorder.
- close monitoring in patients who have less severe (or stable) psychiatric disorders or are taking levetiracetam or other medications associated with these behaviors.
- reducing the dose as soon as these symptoms develop.
- discontinuing the drug immediately if symptoms worsen (or if there is a lack of impulse-control or threats/acts of violence).

7.3.4.2 Nervous System Disorders

A higher number of subjects in the perampanel group experienced TEAEs related to neurological disorders than in the placebo group in both the epilepsy Phase 3 DB pool (50.9% vs 31.0%) and the nonepilepsy DB pool (37.4% vs 28.6%). Discontinuations

⁷ 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.

due to TEAEs in the Nervous system disorders SOC occurred more often in perampanel subjects than placebo in both the epilepsy Phase 3 DB pool (5.1% vs 2.9%) and the nonepilepsy DB pool (9.0% vs 3.8%). Nervous system disorder SAEs occurred twice as often in perampanel subjects than placebo in the nonepilepsy DB pool (1.6% vs 0.8%). The following table summarizes the adverse events in the Nervous System Disorders SOC in the epilepsy Phase 3 DB, nonepilepsy DB, and all treated pools. In both of the all treated pools, the most common TEAE was dizziness (and most frequently led to discontinuations).

Table 59. Summary of TEAEs, SAEs, DCs in the Nervous System Disorders SOC

SOC Nervous System Disorders	Epilepsy Phase 3 DB Pool		Nonepilepsy DB Pool	
	Placebo	Perampanel	Placebo	Perampanel
	n=442	n=1038	n=1079	n=2013
TEAEs	31.0%	50.9%	28.6%	37.4%
SAEs	2.5%	1.8%	0.8%	1.6%
Discontinuations (DCs)	2.9%	5.1%	3.8%	9.0%
	Epilepsy All Treated Pool		Nonepilepsy All Treated	
	n=1651		n=2717	
TEAEs n (%), most common PT	1177 (71.3%), dizziness		1298 (47.8%), dizziness	
SAEs n (%), most common PT	110 (6.7%), convulsion		82(3.0%), on/off phenomenon	
DCs n (%), most common PT	156 (9.4%), dizziness		290 (10.7%), dizziness	

Source: ISS Tables 20.7-1, 160, 165, 55, 20.5-2, 63, 20.5-8, 75, 79, 20.5-36, 22.4-2, 22.4-27

To further analyze these SAEs, the following table summarizes those that occurred in at least 2 subjects in either the placebo or the total perampanel group in the epilepsy and nonepilepsy DB pools. In the epilepsy DB pool, dizziness and somnolence SAEs occurred in perampanel subjects more frequently than placebo, while seizure-related SAEs (convulsion, status epilepticus, grand mal convulsion) occurred more frequently in placebo subjects. Some of the SAEs that occurred in the nonepilepsy population did not occur in the epilepsy population because they were associated with the underlying disease (Parkinson's disease, akinesia, dyskinesia, on and off phenomenon).

Comment: In the MedDRA High Level Group Term (HGLT) Seizures, less perampanel subjects reported TEAEs than placebo (3.9% vs 5.2%). The reader is referred to Dr. Martin Rusinowitz's review of efficacy for a detailed analysis of rebound epilepsy, worsening of seizures, and the TEAEs of status epilepticus and generalized seizures with perampanel use.

Table 60. SAEs in Nervous System Disorders SOC Occurring in ≥ 2 Subjects

Nervous system disorders SOC Preferred Term	Placebo	Perampanel
Epilepsy DB (Phase 3 + Phase 2)	n = 510	n = 1189
Nervous system disorders SOC	14 (2.7)	21 (1.8)
Convulsion	5 (1.0)	6 (0.5)
Dizziness	0	3 (0.3)
Somnolence	0	3 (0.3)
Status Epilepticus	2 (0.4)	3 (0.3)
Grand Mal Convulsion	2 (0.4)	2 (0.2)
Nonepilepsy Double-blind Pool	n = 1079	n = 2013
Nervous system disorders SOC	9 (0.8)	32 (1.6)
Parkinson's Disease	0	4 (0.2)
Syncope	1 (0.1)	3 (0.1)
Cerebrovascular accident	0	3 (0.1)
On and Off phenomenon	1 (0.1)	2 (0.1)
Akinesia	0	2 (0.1)
Dyskinesia	0	2 (0.1)

Source: ISS Tables 20.7-1 and 20.7-15

In the Phase 1 studies, one healthy volunteer experienced the SAEs of loss of consciousness and concussion after multiple falls leading to head trauma. Perampanel was rapidly titrated from 6 mg to 12 mg in 10 days.

Subject 1001-0285, a 19 year-old white female treated with perampanel in Study 013 who developed the SAEs of loss of consciousness and concussion. The subject received 6 mg of perampanel on (b) (6) for 7 days. The dose was then increased to 8 mg for 1 day, 10 mg for 1 day, and then 12 mg for 7 days. After starting on the 12 mg dose, the subject experienced multiple falls (on (b) (6)). On Study Day 15 (b) (6) 2 hours postdose, the subject fell and hit her head while getting out of bed. The following AEs were reported: concussion, incisor loose, contusion (chin), headache, dizziness, somnolence, amnesia, neck pain, loss of consciousness, dyspnea, nausea, dysarthria, dyskinesia, asthenia, and abdominal pain. The subject was noted to be flaccid and responsive only to sternal rub and was hospitalized. The study drug was discontinued on Study Day 15. The subject recovered.

To further analyze the TEAEs leading to drug discontinuation in the Nervous system disorders SOC, the following table summarizes those that occurred in the epilepsy Phase 3 DB pool in at least 2 subjects. Perampanel subjects discontinued more frequently than placebo due to the TEAEs dizziness, somnolence, ataxia, dysarthria, balance disorder, and coordination abnormal (but not the TEAEs convulsion or headache). Similar results were noted in the epilepsy Phase 2 DB and nonepilepsy DB pools (ISS Tables 20.8-15 and 20.8-27). Additionally, in other SOC, there were related TEAEs that were experienced by perampanel subjects more frequently than placebo: vertigo (0.8% n=8), vision blurred (0.4% n=4), fatigue (0.7% n=7), asthenia (0.2% n=2), fall (0.2% n=2). No placebo subjects discontinued due to these TEAEs.

Table 61. Discontinuations in Nervous System Disorders SOC in ≥ 2 Subjects, Epilepsy Phase 3 DB Pool

Nervous system disorders SOC Preferred Term	Placebo	Perampanel
Epilepsy Phase 3 DB Pool	n = 442	n = 1038
Nervous system disorders SOC	13 (2.9)	53 (5.1)
Dizziness	4 (0.9)	22 (2.1)
Convulsion	5 (1.1)	10 (1.0)
Somnolence	1 (0.2)	10 (1.0)
Ataxia	0	7 (0.7)
Dysarthria	0	4 (0.4)
Headache	3 (0.7)	3 (0.3)
Balance disorder	0	3 (0.3)
Coordination abnormal	0	2 (0.2)

Source: ISS Table 20.8-1

The narratives of some of the healthy subjects who discontinued perampanel treatment during the Phase 1 studies are summarized below.

Subject 002-0666-0025, a 20 year-old white male randomized to perampanel 4 mg. On Study Day 2, the subject experienced somnolence (severe). On Study Day 3, the subject experienced vertigo (severe). Perampanel was discontinued and the events resolved.

Subject 002-0666-0032, a 26 year-old Asian male randomized to perampanel 4 mg. On Study Day 7, the subject experienced somnolence (moderate) and vertigo (severe). Physical examination revealed marked drowsiness, past pointing, diplopia on lateral gaze, muscle weakness (4/5 strength globally), and inability to perform Romberg. Perampanel was discontinued and the events resolved.

Subject 013-1001-0004, a 28 year-old white male who experienced dizziness and nausea. He received perampanel 6 mg for 7 days, then 8 mg and 10 mg for 1 day each, and then 12 mg for 4 days. On Study Day 11 (after taking 12 mg for 2 days), the subject developed nausea and dizziness. During the next couple of days, the subject experienced unsteady Romberg, photosensitivity, drowsiness, and ataxic gait. On Study Day 14, perampanel was discontinued.

Subject 013-1001-0021, a 40 year-old white female who experienced balance disorder and ataxia. She received perampanel 6 mg for 7 days, then 8 mg and 10 mg and 12 mg for 1 day each. While on 6 mg, the subject experienced balance disorder and dizziness. While on 8 mg, the subject experienced headache, paresthesia, and nasal congestion. While taking 10 mg, the subject experienced cold sweat, emotional disorder, dysarthria, and feeling drunk. While on 12 mg, the subject experienced chest pain, dyspnea, feeling hot, pharyngolaryngeal pain, tongue hemorrhage, increased respiratory rate, and rhinorrhea. On Study Day 11, perampanel was discontinued.

Subject 013-1001-0103, a 55 year-old white female who experienced ataxia and dysarthria. She received perampanel 6 mg for 7 days, then 8 mg and 10 mg for 1 day each, and then 12 mg for 4 days. While on the 12 mg dose, the subject experienced feeling drunk, dizziness, somnolence, headache, dyspnea, upper abdominal pain, and finger fracture. On Study Day 14, the subject experienced severe ataxia, mild dysarthria, and a positive romberg. Perampanel was discontinued and the events resolved 12 days later.

Subject 013-1001-0280, a 27 year-old white male who experienced tunnel vision. He received perampanel 6 mg for 7 days, then 8 mg and 10 mg for 1 day each, and then 12 mg for 2 days. While on 8 mg, the subject experienced tunnel vision and hypoesthesia. Perampanel was discontinued on Study Day 11 and the events resolved.

Subject 013-1001-0428, a 31 year-old American Indian/Alaskan Native male who received perampanel 6 mg for 7 days, and then 8 mg and 10 mg for 1 day each. While on 6 mg, the subject experienced dysarthria. While on 8 mg, the subject experienced sedation and a fall with complications. While on 10 mg, the subject experienced ataxia, mental status changes, positive romberg, headache, abdominal pain, and nephrolithiasis. Perampanel was discontinued and the events resolved within 22 days (except for the mental status changes).

Subject 013-1001-0463, a 52 year-old white female who received perampanel 6 mg for 7 days, then 8 mg and 10 mg for 1 day each, and then 12 mg for 5 days. While on 12 mg, on Study Day 11, the subject experienced positive romberg and mental status changes. Two days later, the subject experienced dizziness, vision blurred, and balance disorder. Two days later, the subject experienced poisoning (intoxication) and impaired judgment, and perampanel was discontinued (Day 15). All of events resolved 11 days later.

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, Cognitive dysfunction, and Paresthesia. 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) and neurologic events in the eye disorders SOC.

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. Subjects treated with perampanel experienced all of these TEAEs at a higher frequency than placebo subjects, resulting in a 3 times higher incidence of this AE group for perampanel subjects. A dose response is observed with the higher dose groups (8 mg and 12 mg) with 4 and 5 times higher incidence than placebo, respectively.

Table 62. Dizziness and Coordination Group, Epilepsy Phase 3 DB Pool

MedDRA PT	Placebo n (%)	Perampanel n (%)				Total
		2 mg	4 mg	8 mg	12 mg	
	442	180	172	431	255	1038
Dizziness	40 (9.05%)	18 (10.0%)	28 (16.28%)	137 (31.8%)	109 (42.8%)	292 (28%)
Vertigo	4 (0.90%)	6 (3.33%)	7 (4.07%)	14 (3.25%)	12 (4.71%)	39 (3.76%)
Ataxia	0	0	1 (0.58%)	14 (3.25%)	21 (8.24%)	36 (3.47%)
Gait disturbance	6 (1.36%)	1 (0.56%)	2 (1.16%)	18 (4.18%)	10 (3.92%)	31 (2.99%)
Balance disorder	2 (0.45%)	0	0	22 (5.10%)	8 (3.14%)	30 (2.89%)
Coordination abnl	0	0	1 (0.58%)	1 (0.23%)	4 (1.57%)	6 (0.58%)
Total subjects	48 (10.9%)	25 (13.9%)	36 (20.9%)	181 (42.0%)	138 (54.1%)	380 (37%)

Source: Created by the reviewer using JReview and Epilepsy ADAE, ADSL datasets

Comment: Of note, in the Phase 1 Study 013 during the neurologic physical examination, the Romberg test was performed and reported as normal or abnormal. A higher percentage of perampanel subjects experienced shifts in Romberg results from normal to abnormal relative to baseline than placebo (or moxifloxacin) subjects from Study Day 10 to 18. This suggests that the loss of coordination experienced by perampanel subjects is sensory in nature (due to the loss of proprioception) rather than cerebellar in nature.

Table 63. Shifts in Romberg Results from Normal to Abnormal, Study 013

Visit/Study Day	Placebo N=75 (%)	Perampanel N=107 (%)	Moxifloxacin N=75 (%)
Day 3	0	1 (1.0)	0
Day 6	0	1 (1.0)	1 (1.4)
Day 9	2 (2.7)	4 (4.0)	4 (5.4)
Day 10	4 (5.3)	7 (7.2)	1 (1.4)
Day 11	2 (2.7)	11 (11.3)	2 (2.7)
Day 13	5 (6.7)	19 (20.4)	0
Day 15	3 (4.1)	19 (21.3)	2 (2.8)
Day 17	1 (1.3)	12 (13.8)	1 (1.4)
Day 18	0	4 (5.6)	0
Follow up	0	1 (1.0)	0

Source: CSR Study 013 Table 34

Somnolence and Fatigue

The following table summarizes the percentages of subjects who reported the following TEAEs: somnolence, fatigue, asthenia, lethargy, and sedation. Subjects treated with perampanel experienced these TEAEs (except for sedation) at a higher frequency than placebo subjects, resulting in a 2 times higher incidence of this AE group for perampanel subjects. A dose response is observed.

Table 64. Somnolence and Fatigue Group, Epilepsy Phase 3 DB Pool

MedDRA PT	Placebo n (%)	Perampanel n (%)				Total
		2 mg	4 mg	8 mg	12 mg	
	442	180	172	431	255	1038
Somnolence	32 (7.24%)	22 (12.2%)	16 (9.30%)	67 (15.5%)	45 (17.65%)	150 (14.5%)
Fatigue	21 (4.75%)	8 (4.44%)	13 (7.56%)	36 (8.35%)	31 (12.16%)	88 (8.48%)
Asthenia	2 (0.45%)	1 (0.56%)	1 (0.58%)	10 (2.32%)	6 (2.35%)	18 (1.73%)
Lethargy	1 (0.23%)	0	0	5 (1.16%)	3 (1.18%)	8 (0.77%)
Sedation	2 (0.45%)	0	0	1 (0.23%)	1 (0.39%)	2 (0.19%)
Total subjects	54 (12.22%)	30 (16.7%)	27 (15.7%)	111 (25.8%)	79 (30.98%)	247 (23.8%)

Source: Created by the reviewer using JReview and Epilepsy ADAE, ADSL datasets

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. The following table summarizes the percentages of subjects who reported the following TEAEs: dysarthria, memory impairment, confusional state, disturbance in attention, aphasia, speech disorder,

disorientation, amnesia, cognitive disorder, apraxia, delirium mental impairment, and incoherent. Except for dysarthria and confusional state, perampanel subjects experienced these TEAEs less frequently than (or similarly as) placebo subjects. For the entire cognitive dysfunction group, perampanel subjects have a higher incidence than placebo subjects. However, this result is driven mainly by the PT dysarthria (2.3% perampanel vs 0 placebo). A review of the verbatim terms for dysarthria revealed that the reported terms included slurred speech and dysarthria.

Of note, in the Phase 1 Study 030, 3 subjects reported amnesia (12 mg perampanel). For two of the subjects the duration of the event exceeded three weeks.

Table 65. Cognitive Dysfunction Group, Epilepsy Phase 3 DB Pool

MedDRA PT	Placebo n (%)	Perampanel n (%)				Total
		2 mg	4 mg	8 mg	12 mg	
	442	180	172	431	255	1038
Dysarthria	0	0	2 (1.16%)	13 (3.02%)	9 (3.53%)	24 (2.31%)
Memory Impairment	5 (1.13%)	2 (1.11%)	0	5 (1.16%)	5 (1.96%)	12 (1.16%)
Confusional State	2 (0.45%)	1 (0.56%)	1 (0.58%)	3 (0.70%)	4 (1.57%)	9 (0.87%)
Disturbance in Attention	6 (1.36%)	2 (1.11%)	1 (0.58%)	5 (1.16%)	1 (0.39%)	9 (0.87%)
Aphasia	3 (0.68%)	0	0	3 (0.70%)	3 (1.18%)	6 (0.58%)
Speech Disorder	2 (0.45%)	0	0	3 (0.70%)	2 (0.78%)	5 (0.48%)
Disorientation	1 (0.23%)	0	0	1 (0.23%)	2 (0.78%)	3 (0.29%)
Amnesia	1 (0.23%)	1 (0.56%)	0	1 (0.23%)	1 (0.39%)	3 (0.29%)
Cognitive Disorder	2 (0.45%)	0	0	2 (0.46%)	0	2 (0.19%)
Apraxia	1 (0.23%)	0	0	0	1 (0.39%)	1 (0.10%)
Delirium	1 (0.23%)	1 (0.56%)	0	0	0	1 (0.10%)
Mental Impairment	1 (0.23%)	0	1 (0.58%)	0	0	1 (0.10%)
Incoherent	0	0	0	0	0	0
Total subjects	20 (4.52%)	5 (2.78%)	5 (2.91%)	30 (6.96%)	27 (10.59%)	67 (6.45%)

Source: Created by the reviewer using JReview and Epilepsy ADAE, ADSL datasets

Paresthesia

The following table summarizes the percentages of subjects who reported the following TEAEs: paraesthesia, hypoaesthesia, hypoaesthesia facial, paraesthesia oral, oral dysaesthesia, hypoaesthesia oral, sensory disturbance, and hyperaesthesia.

Perampanel subjects reported terms in this group slightly more often than placebo (2.2% vs 1.6%). The percentages of subjects reporting terms in this group were small.

Table 66. Paresthesia Group, Epilepsy Phase 3 DB Pool

MedDRA PT	Placebo n (%)	Perampanel n (%)				Total
		2 mg	4 mg	8 mg	12 mg	
	442	180	172	431	255	1038
Paraesthesia	3 (0.68%)	2 (1.11%)	0	2 (0.46%)	6 (2.35%)	10 (0.96%)
Hypoaesthesia	3 (0.68%)	1 (0.56%)	0	0	7 (2.75%)	8 (0.77%)
Hypoaesthesia Facial	0	0	1 (0.58%)	2 (0.46%)	0	3 (0.29%)
Paraesthesia Oral	1 (0.23%)	0	0	0	2 (0.78%)	2 (0.19%)
Oral Dysaesthesia	0	0	0	1 (0.23%)	0	1 (0.10%)
Hypoaesthesia Oral	1 (0.23%)	0	0	0	0	0
Sensory disturbance	0	0	0	0	0	0
Hyperaesthesia	0	0	0	0	0	0
Total subjects	7 (1.58%)	3 (1.67%)	1 (0.58%)	5 (1.16%)	14 (5.49%)	23 (2.22%)

Source: Created by the reviewer using JReview and Epilepsy ADAE, ADSL datasets

The following table summarizes the SAEs and TEAEs that led to discontinuations in these groups of neurologic events by treatment group. Perampanel is associated with an increased incidence of SAEs and discontinuations related to coordination/dizziness, somnolence/fatigue, cognitive dysfunction, and paresthesias.

Table 67. SAEs, DCs in Neurologic Groups, Epilepsy Phase 3 DB Pool

Groups of Neurologic Events	Placebo n = 442	Perampanel n = 1038
Dizziness/coordination group TEAEs	48 (10.9)	380 (36.6)
SAEs	0	3 (0.3)
Discontinuations	5 (1.1)	36 (3.5)
Somnolence/fatigue group TEAEs	54 (12.2)	247 (23.8)
SAEs	0	3 (0.3)
Discontinuations	2 (0.5)	20 (1.9)
Cognitive dysfunction group TEAEs	20 (4.5)	67 (6.5)
SAEs	1 (0.2)	3 (0.3)
Discontinuations	0	7 (0.7)
Paresthesia group TEAEs	7 (1.6)	23 (2.2)
SAEs	0	0
Discontinuations	0	1 (0.1)

Source: Created by the reviewer using JReview and Epilepsy ADAE, ADSL datasets

In the nonepilepsy DB pool, perampanel subjects developed 3 SAEs in the dizziness/coordination group (vs 0 placebo), 1 SAE in the somnolence/fatigue group (vs 1 placebo), 8 SAEs in the cognitive dysfunction group (vs 2 placebo), and 1 SAE in the paresthesia group (vs 0 placebo).

The following table summarizes the frequencies of these groups of neurological events in different age groups (elderly ≥ 65 years, adults >16 and <65 , and adolescents ≤ 16). Of note, these analyses were not performed for the Paresthesia group due to the small percentages of subjects reporting terms in this group. In the total perampanel group, a higher percentage of elderly subjects experienced TEAEs in these groups of

neurological events than adults or adolescents. However, in the placebo group, elderly subjects did not experience any TEAEs in the dizziness/coordination and somnolence/fatigue groups. Therefore, after stratifying by age group, it appears that the elderly population is at the highest risk for experiencing dizziness/coordination and somnolence/fatigue-related TEAEs with perampanel use.

Table 68. Neurologic Events by Age Group, Epilepsy Phase 3 DB Pool

Age Group	Placebo n = 442	Perampanel n = 1038
Dizziness/coordination group	48 (10.9)	380 (36.6)
Elderly (≥65)	0	11 (55.0)
Adults (>16 yrs and <65)	44 (11.1)	354 (37.4)
Adolescents (12-16 yrs)	4 (10.5)	15 (20.8)
Somnolence/fatigue group	54 (12.2)	247 (23.8)
Elderly (≥65)	0	7 (35.0)
Adults (>16 yrs and <65)	49 (12.4)	225 (23.8)
Adolescents (12-16 yrs)	5 (13.2)	15 (20.8)
Cognitive dysfunction group	20 (4.52)	67 (6.45)
Elderly (≥65)	1 (12.5)	3 (15.0)
Adults (>16 yrs and <65)	18 (4.6)	61 (6.5)
Adolescents (12-16 yrs)	1 (2.6)	3 (4.2)*

Source: Created by the reviewer using JReview and Epilepsy ADAE, ADSL datasets

*PTs: 1 disorientation, 1 dysarthria, 1 speech disorder in perampanel group (1 cognitive disorder in placebo)

The following table summarizes the frequencies of these groups of neurological events in the different periods of the epilepsy Phase 3 studies (titration period weeks 1-6 and maintenance period weeks 7-19). After stratifying by study period, it appears that there is a higher risk for perampanel subjects to develop TEAEs in these 3 groups during the titration period than the maintenance period.

Table 69. Neurologic Events by Study Period, Epilepsy Phase 3 DB Pool

Phase of Study	Placebo		Perampanel	
	n (%)	total	n (%)	total
Dizziness/coordination group	48 (10.9)	442	380 (36.6)	1038
Titration (weeks 1-6)	32 (7.2)	442	323 (31.1)	1038
Maintenance (weeks 7-19)	21 (5.0)	416	115 (12.0)	958
Somnolence/fatigue group	54 (12.2)	442	247 (23.8)	1038
Titration (weeks 1-6)	43 (9.7)	442	204 (19.7)	1038
Maintenance (weeks 7-19)	14 (3.4)	416	56 (5.8)	958
Cognitive dysfunction group	20 (4.52)	442	67 (6.45)	1038
Titration (weeks 1-6)	11 (2.5)	442	44 (4.2)	1038
Maintenance (weeks 7-19)	11 (2.6)	416	27 (2.8)	958

Source: Created by the reviewer using JReview and Epilepsy ADAE, ADSL datasets

Total = number of subjects who were in the study at the start of that period

n=number of subjects with AE onset during that period (a subject may be counted several times if a new onset event happens under different time slot).

Eye Disorders

A higher number of perampanel subjects than placebo experienced vision blurred, diplopia, and visual impairment. Although these TEAEs were not SAEs, they led to discontinuation of perampanel more frequently than placebo. The following table summarizes the TEAEs in the Eye Disorders SOC that occurred in at least 2 perampanel subjects and more than Placebo.

Table 70. Eye disorders SOC, TEAEs in ≥ 2 Perampanel Subjects and $>$ Placebo

MedDRA Preferred Term in SOC Eye disorders	Placebo n = 442	Perampanel n = 1038
Epilepsy Phase 3 DB Pool	16 (3.6)	64 (6.2)
Vision blurred	6 (1.4)	25 (2.4)
Diplopia	4 (0.9)	18 (1.7)
Conjunctival hyperaemia	0	2 (0.2)
Eye irritation	0	2 (0.2)
Eye pruritus	0	2 (0.2)
Lacrimation increased	0	2 (0.2)
Nonepilepsy DB Pool	22 (2.0)	60 (3.0)
Visual impairment	0	4 (0.2)
Eye inflammation	0	2 (0.1)
Eyelid ptosis	0	2 (0.1)
Glaucoma	0	2 (0.1)
Macular degeneration	0	2 (0.1)

Source: ISS Tables 20.7-1 and 20.8-1

In the epilepsy Phase 3 DB pool, there were 2 eye-related SAEs (iritis after an assault and conjunctivitis allergic). Four perampanel subjects discontinued due to vision blurred. No placebo subjects withdrew due to eye-related TEAEs.

In the epilepsy Phase 2 DB pool, the following TEAEs occurred in ≥ 2 perampanel subjects and greater than placebo: diplopia (2.0% vs 1.5%) eye pain (1.3% vs 0), and visual impairment (1.3% vs 0). None of the TEAEs were SAEs or led to discontinuations.

In the nonepilepsy DB pool, 2 perampanel subjects experienced the SAE of cataract (vs 0 placebo subjects). Perampanel subjects withdrew from the studies due to diplopia (1), photophobia (1), and vision blurred (1). No placebo subjects withdrew due to eye-related TEAEs. Of note, in the SOC Nervous system disorders (HLGT neurological disorders of the eye), tunnel vision and visual field defect occurred less frequently in perampanel subjects than placebo subjects.

In the Phase 1 studies, there were no eye-related SAEs. Perampanel subjects withdrew from the studies due to vision blurred (1), conjunctivitis (1) and ocular discomfort (1).

Falls and Injuries

A higher percentage of perampanel subjects experienced a fall than placebo subjects in every DB pooled group. A dose response was observed with a 3 times higher incidence of fall in the highest dose groups than placebo. The following table summarizes the incidence of fall by treatment group in each DB pool. Furthermore, the Sponsor reported that the PK/PD analysis showed that the probability of occurrence of fall, grouped with gait disturbance and balance disorder, increased with increasing average plasma concentration of perampanel. The reader is referred to the Pharmacometric Review for further details.

Table 71. Incidence of the PT Fall, DB pools

Pooled Group	Placebo n (%)	Perampanel n (%)				Total
		<4 mg	4 mg	>4-8 mg	>8-12mg	
Epilepsy Phase 3 DB Pool	15 (3.4)	2 (1.1)	3 (1.7)	22 (5.1)	26 (10.2)	53 (5.1)
Epilepsy Phase 2 DB Pool	0	0	5 (5.0)		1 (2.6)	6 (4.0)
Nonepilepsy DB Pool	37 (3.4)	49 (4.6)	42 (5.4)	19 (10.7)		110 (5.5)
Parkinson's DB Pool	33 (3.9)	42 (5.1)	35 (5.2)	3 (12.5)		80 (5.3)
Neuropathic pain DB Pool	2 (1.7)	4 (3.2)	7 (7.2)	16 (10.4)		27 (7.2)

Source: ISS Tables 20.5-2, 20.5-28, 20.5-54

The following table summarizes the incidence of falls by study period of the epilepsy Phase 3 DB studies (titration period weeks 1-6 and maintenance period weeks 7-19). It appears that falls occurred slightly more often during the maintenance period than the titration period.

Table 72. Incidence of Falls by Study Period, Epilepsy Phase 3 DB Pool

Phase of Study	Placebo		Perampanel	
	n (%)	total	n (%)	total
Fall PT	15 (3.4)	442	53 (5.1)	1038
Titration (weeks 1-6)	7 (1.6)	442	24 (2.3)	1038
Maintenance (weeks 7-19)	8 (1.9)	415	33 (3.5)	948

Source: 120-day Safety Update Table 14-1

The following table summarizes the incidence of falls in different age groups (elderly ≥65 years, adults >16 and <65, and adolescents ≤16). After stratifying by age group, it appears that the elderly population is at the highest risk for experiencing falls with perampanel use in both the epilepsy Phase 3 and nonepilepsy DB pools.

Table 73. Falls by Age Group, Epilepsy Phase 3 and Nonepilepsy DB Pools

Age Group	Placebo		Perampanel	
	n (%)	total	n (%)	total
Epilepsy Phase 3 DB Pool	15 (3.4)	442	53 (5.1)	1038
Elderly (≥65)	0	8	5 (25.0)	20
Adults (>16 yrs and <65)	14 (3.5)	396	46 (4.9)	946
Adolescents (12-16 yrs)	1 (2.6)	38	2 (2.8)	72
Nonepilepsy DB Pool	37 (3.4)	1079	110 (5.5)	2013
Elderly (≥65)	15 (3.3)	450	54 (6.0)	905
Adults (<65)	22 (3.5)	629	56 (5.1)	1108

Source: 120-day Safety Update Table 20-2

To assess whether these falls were occurring with seizures, the Sponsor submitted further analyses on June 7, 2012 in response to the Division's information request. Not only were there more falls per subject in perampanel subjects than placebo (1.38 vs 1.07), there were more falls that occurred without seizure events (39.7% vs 25.0%).

Table 74. Incidence of Falls by Absence of Seizures, Epilepsy Phase 3 DB Pool

	Placebo		Perampanel	
	n (%)	total	n (%)	total
# Subjects with TEAE of Fall	15 (3.4)	442	53 (5.1)	1038
Number of falls per subject	1.07		1.38	
Falls without seizure event	4 (25.0)	16	29 (39.7)	73

Source: Safety information amendment June 7, 2012, Tables 23.9-28.1, 23.9-28.2

To assess for the sequelae of the falls, an analysis was performed for fall-related adverse events in the SOC Injury, Poisoning, and Procedural Complications and the SMQ Accidents and Injury. The following table summarizes the incidence of TEAEs in this MedDRA SOC and SMQ by treatment group and DB pooled group. The results of the SMQ analyses were similar to the SOC. In all of the DB pooled groups, perampanel subjects experienced higher frequencies of these injury-related TEAEs than placebo. A dose response relationship was observed in the epilepsy Phase 3 DB and nonepilepsy DB pools (ISS Table 20.5-2, 20.5-54).

Table 75. TEAEs in the Injury SOC and Accidents/Injury SMQ

	Placebo	Perampanel
Epilepsy Phase 3 DB Pool	442	1038
SOC Injury, Poisoning/Procedural Complications	51 (11.5)	147 (14.2)
SMQ Accidents and Injury (broad)	49 (11.1)	135 (13.0)
Epilepsy Phase 2 DB Pool	68	151
SOC Injury, Poisoning/Procedural Complications	5 (7.4)	24 (15.9)
SMQ Accidents and Injury (broad)	4 (5.9)	23 (15.2)
Nonepilepsy DB Pool	1079	2013
SOC Injury, Poisoning/Procedural Complications	86 (8.0)	244 (12.1)
SMQ Accidents and Injury (broad)	83 (7.7)	223 (11.1)

Source: ISS Tables 20.5-2, 20.5-28, 20.5-54 and SMQ analyses performed by reviewer using MAED

The following table summarizes the SAEs that occurred in the SOC Injury, Poisoning and Procedural Complications. A higher percentage of perampanel subjects than placebo experienced injury-related SAEs in both the epilepsy DB (1.1% vs 0.6%) and nonepilepsy DB pools. It is concerning that the SAEs head injury and facial bone fracture occurred more frequently in the perampanel group than placebo in the epilepsy DB pool (and lumbar vertebral fractures in the nonepilepsy DB pool).

Table 76. SAEs in Injury SOC Occurring in at Least 2 Subjects

MedDRA System Organ Class Preferred Term	Placebo	Perampanel
Epilepsy DB (Phase 3 + Phase 2)	n = 510	n = 1189
SOC Injury/Poisoning/Procedural	3 (0.6)	13 (1.1)
Head injury	0	3 (0.3)
Facial bones fracture	0	2 (0.2)
Nonepilepsy Double-blind Pool	n = 1079	n = 2013
SOC Injury/Poisoning/Procedural	9 (0.8)	26 (1.3)
Fall	2 (0.2)	8 (0.4)
Hip fracture	3 (0.3)	3 (0.1)
Femur fracture	1 (0.1)	3 (0.1)
Humerus fracture	1 (0.1)	3 (0.1)
Lumbar vertebral fracture	0	2 (0.1)
Meniscus lesion	0	2 (0.1)
Joint dislocation	2 (0.2)	1 (0.0)

Source: ISS Tables 20.7-1 and 20.7-15

To assess whether these injuries were occurring with seizures, the Sponsor submitted further analyses on June 7, 2012 in response to the Division's information request. Not only were there more injuries per subject in perampanel subjects than placebo (1.84 vs 1.57), there were more injuries that occurred without seizure events (35.5% vs 20.8%).

Table 77. Incidence of Injuries by Absence of Seizures, Epilepsy Phase 3 DB

	Placebo		Perampanel	
	n (%)	total	n (%)	total
Accidents and Injuries SMQ	49 (11.1)	442	135 (13.0)	1038
Number of injuries per subject	1.57		1.84	
Injuries without seizure event	16 (20.8)	77	88 (35.5)	248

Source: Safety information amendment June 7, 2012, Tables 23.9-25

Further analyses were performed by the Sponsor to calculate the exposure-adjusted event rates of falls and the TEAEs in the SMQ Accident and Injury. After stratifying the events by the presence or absence of seizures, there were larger differences between the perampanel and placebo groups (for both falls and the SMQ) for the events without concurrent seizures than the events with seizures. Specifically, there were higher incidence rate ratios of perampanel subjects compared to placebo experiencing falls and TEAEs in the Accident SMQ in the absence of seizures (3.0 for falls and 2.63 for the SMQ) than with concurrent seizures (1.57 for falls and 1.19 for the SMQ).

Therefore, there is an association between perampanel use and falls/injuries that are not confounded by seizures.

Table 78. Exposure-Adjusted Event Rate of TEAEs in the Accident/Injury SMQ with and without Seizures, Epilepsy Phase 3 DB Pool

MedDRA Preferred Term	Placebo NAE	Perampanel NAE (rate per 100 subject-months)				
		<4 mg	4 mg	>4-8 mg	>8-12 mg	Total
# Subjects	442	180	172	431	255	1038
Subject-months	1830.4	971.0	852.2	1724.6	620.2	4167.9
Events with seizure						
PT Fall	13 (0.7)	3 (0.3)	5 (0.6)	26 (1.5)	13 (2.1)	47 (1.1)
SMQ accident/injury	59 (3.2)	13 (1.3)	24 (2.8)	77 (4.5)	43 (6.9)	157 (3.8)
Events without seizure						
PT Fall	3 (0.2)	1 (0.1)	4 (0.5)	15 (0.9)	4 (0.6)	24 (0.6)
SMQ accident/injury	16 (0.8)	8 (0.8)	11 (1.3)	53 (3.1)	16 (2.6)	88 (2.1)

Source: Safety information amendment June 7, 2012, Tables 23.9-28.1, 23.9-28.2

NAE = the number of TEAEs and Dose groups = Actual dose at onset of TEAE

In conclusion, there is reasonable evidence of a causal relationship between perampanel use and dizziness/coordination, somnolence/fatigue, and falls/injuries. These are all clinically significant adverse reactions: potentially fatal (there were deaths due to fall-related complications in perampanel subjects), serious (all associated with SAEs), and could be mitigated through the appropriate use of the drug (closer monitoring during the titration period and with high risk subgroups such as the elderly). Therefore, I recommend that these 3 adverse reactions be included in the Warnings and Precautions section of perampanel labeling.

There is also reasonable evidence of a causal relationship (to a lesser degree) between perampanel use and cognitive dysfunction (dysarthria), paresthesias, and visual changes (vision blurred, diplopia, visual impairment). I recommend that these adverse reactions be included in the Adverse Reactions section of perampanel labeling.

7.3.4.3 Metabolic Changes

The following metabolic changes will be analyzed in this section: weight gain, hyperlipidemia, hyperglycemia, and hypertension. To further assess for the metabolic effects of perampanel, the Sponsor submitted the following analyses in the Safety Information Amendment dated July 27, 2012 in response to the Division's information request.

Weight Gain

In the epilepsy Phase 3 DB pool, adult perampanel subjects gained an average of 1.12 kg compared to an average 0.30 kg weight gain in placebo subjects with a median exposure of 19.0 weeks. More than twice as many perampanel subjects than placebo subjects had gained $\geq 7\%$ of baseline weight (9.1% vs 4.5%) and $\geq 15\%$ of baseline weight (0.9% vs 0.2%). The differences between perampanel and placebo subjects in

weight gain occurred to a lesser degree in adolescents. Adolescent perampanel subjects gained an average of 1.98 kg compared to an average 1.41 kg weight gain in placebo subjects with a median exposure of 19.0 weeks. There were no subjects who discontinued due to the TEAE of weight gain. The following table summarizes weight gain in the epilepsy Phase 3 DB pool.

Table 79. Weight Gain, Epilepsy Phase 3 Pool

	Placebo	Perampanel
Number of subjects with weight assessments at baseline and end of treatment	438	1033
Adults (>16 years old)	401	961
Adolescents (≤16 years old)	37	72
Median exposure (weeks)		
Adults	19.0	19.0
Adolescents	18.9	19.0
Mean change in weight from baseline (kg)		
Adults	0.30 kg	1.12 kg
Adolescents	1.41 kg	1.98 kg
Subjects (%) who gained ≥7% of baseline wt		
Adults	18 (4.5%)	87 (9.1%)
Adolescents	7 (18.9%)	17 (23.6%)
Subjects (%) who gained ≥15% of baseline wt		
Adults	1 (0.2%)	9 (0.9%)
Adolescents	1 (2.7%)	2 (2.8%)
Subjects (%) who gained ≥25% of baseline wt		
Adults	0	1 (0.1%)
Adolescents	0	0
Subjects (%) who discontinued due to wt gain	0	0

Source: Safety Information Amendment (7/27/12) Table 23.12-13

Comment: Other drugs associated with weight gain are Zyprexa®, Abilify®, and Geodon®. Weight gain is listed in the Warnings section of the Zyprexa® and Abilify® labeling and in the Adverse Reactions section of the Geodon® labeling. Zyprexa®-treated adults gained an average of 2.6 kg compared to a 0.3 kg weight loss in placebo subjects with a median exposure of 6 weeks (adolescents, 4.6 kg vs 0.3 kg). Abilify®-treated adults gained an average of 1.7 kg compared to a 0.4 kg in placebo subjects after an exposure of 6 weeks (adolescents, 5.8 kg vs 1.4 kg at 24 weeks). Geodon®-treated subjects had a median weight gain of 0.5 kg compared to no weight gain in placebo subjects in a pool of four 4- and 6- week trials.

The following table summarizes the mean change in weight (kg) from baseline to the end of treatment in each of the DB pooled groups. The mean change in weight for adults was at least 3 times higher (up to 18 times higher) in the total perampanel group than placebo in all of the DB pooled groups. The differences between perampanel and placebo subjects in weight gain occurred at a lesser degree in adolescents. A dose response was observed for most of the DB pooled groups with the highest mean change in weight occurring with the highest dose group(s). In the 4 mg dose group

(across indications), the average weight increase for adults was 0.65 to 1.51 kg. In the >4-8 mg dose group (across indications), the average weight increase for adults was 1.23 to 1.77 kg.

Table 80. Mean Change in Weight (kg) from Baseline to End of Treatment

Pooled Group	Placebo	Perampanel				Total
		<4 mg	4 mg	>4-8 mg	>8-12mg	
Epilepsy Phase 3 DB Pool*						
Adults	n=401	n=166	n=162	n=398	n=235	n=961
	0.31	0.38	0.96	1.23	1.57	1.12
Adolescents	n=37	n=14	n=9	n=31	n=18	n=72
	1.41	0.59	1.33	2.80	1.97	1.98
Epilepsy Phase 2 DB Pool	n=68	n=12	n=99		n=38	n=149
	0.15	1.02	0.86 [^]		0.44	0.77 [^]
Parkinson's DB Pool	n=818	n=689	n=716	n=54		n=1459
	0.03	0.37	0.65	1.77		0.56
Neuropathic Pain DB Pool	n=118	n=70	n=68	n=225		n=363
	0.19	0.58	1.51	1.30		1.20
Nonepilepsy DB Pool	n=1049	n=878	n=784	n=279		n=1941
	0.06	0.46	0.75	1.55		0.69

Source: ISS Tables 20.12-1, Safety Information Amendment (7/27/12) Table 23.12-15.1

*Randomized dose groups 2 mg, 4 mg, 8 mg, 12 mg

[^]with the value of subject with the erroneous maximum change of 152.1 kg excluded.

To assess for outliers, subjects were categorized into different intervals of the amount of weight gained. The following tables summarize the percentages of subjects in each weight gain category by randomized dose group for adults and adolescents. For the category of weight loss or no weight changes, there were fewer perampanel subjects than placebo subjects. For every category of weight gain for adults, there were more perampanel subjects than placebo subjects. A dose response was observed for most of the weight gain categories. For adolescents, there were conflicting results between the 0 to ≤5 kg and >5 to ≤10 kg weight gain categories and there was no dose-response.

Table 81. Weight Change Categories, Adults in Epilepsy Phase 3 DB Pool

Amount Gained (kg) from baseline	Placebo n (%)	Perampanel n (%)				Total
		2 mg	4 mg	8 mg	12 mg	
Total subjects	n=401	n=166	n=162	n=398	n=235	n=961
≤0	202 (50.4)	85 (51.2)	66 (40.7)	154 (38.7)	78 (33.2)	383 (39.9)
0 to ≤5	187 (46.6)	75 (45.2)	85 (52.5)	208 (52.3)	132 (56.2)	500 (52.0)
>5 to ≤10	11 (2.7)	6 (3.6)	11 (6.8)	32 (8.0)	22 (9.4)	71 (7.4)
>10 to ≤15	0	0	0	3 (0.8)	1 (0.4)	4 (0.4)
>15 to ≤20	1 (0.2)	0	0	1 (0.3)	2 (0.9)	3 (0.3)
>20 to ≤25	0	0	0	0	0	0

Source: Safety Information Amendment (7/27/12) Table 23.12-18.1

Table 82. Weight Change Categories, Adolescents in Epilepsy Phase 3 DB Pool

Amount Gained (kg) from baseline	Placebo n (%)	Perampanel n (%)				
		2 mg	4 mg	8 mg	12 mg	Total
Total subjects	n=37	n=14	n=9	n=31	n=18	n=72
≤0	10 (27.0)	6 (42.9)	3 (33.3)	4 (12.9)	5 (27.8)	18 (25.0)
0 to ≤5	22 (59.5)	8 (57.1)	6 (66.7)	22 (71.0)	11 (61.1)	47 (65.3)
>5 to ≤10	5 (13.5)	0	0	4 (12.9)	2 (11.1)	6 (8.3)
>10 to ≤15	0	0	0	1 (3.2)	0	1 (1.4)
>15 to ≤20	0	0	0	0	0	0

Source: Safety Information Amendment (7/27/12) Table 23.12-18.3

In the nonepilepsy DB pool, there were similar results with less perampanel subjects than placebo without any weight gain (45.4% vs 55.2%) and more perampanel subjects than placebo with weight gain of >0 to ≤5 kg (49.6% vs 42.6%), >5 to ≤10 kg (4.5% vs 1.7%), and >10 to ≤15 kg (0.4% vs 0.2%) (Safety Information Amendment 7/27/12 Table 23.12-19.1). A dose response was observed for the weight gain categories.

To assess for the effects of baseline BMI, the mean weight gain was stratified by the baseline BMI categories for both adults and adolescents. For adult perampanel subjects, weight gain was observed across all baseline BMI categories, while in placebo subjects weight loss or clinically insignificant weight gain were observed. For adolescent perampanel subjects, weight gain was observed across all baseline BMI categories, while there were inconsistent results for the placebo subjects.

Table 83. Mean Weight Change by Baseline BMI, Adults in Epilepsy Phase 3 DB Pool

Baseline BMI	Placebo	Perampanel (modal dose groups)				Total
		<4 mg	4 mg	>4-8 mg	>8-12mg	
< 25 kg/m ²	0.47	0.55	0.91	1.25	1.53	1.07
25-30 kg/m ²	-0.14	-0.29	0.94	0.93	1.13	0.75
30-40 kg/m ²	0.67	0.95	1.05	2.49	1.77	1.91
>40 kg/m ²	-0.51	10.0		1.08	4.05	3.41

Source: Safety Information Amendment (7/27/12) Table 23.12-16.1

Table 84. Mean Weight Change by Baseline BMI, Adolescents in Epilepsy Phase 3 DB Pool

Baseline BMI	Placebo	Perampanel (modal dose groups)				Total
		<4 mg	4 mg	>4-8 mg	>8-12mg	
< 25 kg/m ²	1.94	0.81	1.34	2.77	1.88	1.93
25-30 kg/m ²	-1.58	-1.00	-0.40	1.60	1.63	0.96
30-40 kg/m ²	0.10	4.50		3.80		3.94

Source: Safety Information Amendment (7/27/12) Table 23.12-16.2

In the epilepsy all treated pool after including the OLE studies, the mean weight gain at the end of treatment in the total perampanel group was 1.5 kg for adults and adolescents 5.2 kg (Safety Information Amendment 7/27/12 Table 23.12-14). The median exposure time was 71.2 weeks for adults and 75.9 weeks for adolescents. The

percentages of adult subjects who gained at least 7%, 15%, or 25% of their baseline body weight were 18.4%, 4.8%, 1.1%, respectively. The percentages of adolescent subjects who gained at least 7%, 15%, or 25% of their baseline body weight were 46.6%, 24.3%, 9.7%, respectively. Discontinuations due to the TEAE of weight gain occurred in 0.5% of adults and 1.0% of adolescents.

In the nonepilepsy all treated pool, the mean weight gain at the end of treatment in the total perampanel group was 0.39 kg with 10.0% of the subjects experiencing a weight increase of at least 7% of baseline and 7.9% experiencing a weight decrease of at least 7% (ISS Tables 200, 20.12-30).

The following table summarizes the mean weight change over time for adults and adolescents in the epilepsy and nonepilepsy all treated pools. In the epilepsy all treated pool, for adolescents, progressively larger increases in weight occurred up to 24 months (with the small sample size limiting further analysis beyond 24 months). For adults, in the epilepsy all treated pool, progressively larger increases in weight occurred up to 24 months (with smaller sample sizes limiting any further analyses beyond 24 months).

Table 85. Mean Weight Change from Baseline to End of 6, 12, 24, 36, 48, 60 months, All Treated Pools

	6 months	12 months	24 months	36 months	48 months	60 months
Adolescents (≤16 yrs)						
Epilepsy All Treated	n=89	n=69	n=38	n=2	n=0	n=0
Weight (kg)	2.99	4.59	7.50	4.85		
Weight (% change)	5.82	9.01	14.56	8.68		
Adults (>16 years)						
Epilepsy All Treated	n=1214	n=952	n=427	n=55	n=44	n=14
Weight	1.64	1.81	1.96	0.56	0.75	2.10
Weight (% change)	2.39	2.69	3.04	0.94	1.21	3.08
Nonepilepsy All Treated	n=1470	n=767	n=71	n=46	n=0	n=0
Weight	0.48	0.04	-0.17	-0.13		
Weight (% change)	0.62	0.11	-0.22	-0.16		

Source: Safety Information Amendment (7/27/12) Table 23.12-12

The following tables summarize the percentages of perampanel subjects in each weight change category over time for adults and adolescents in the epilepsy all treated pool. There were progressively higher percentages of perampanel subjects in the higher weight gain categories at the end of 6, 12, and 24 months.

Table 86. Weight Gain from Baseline to End of 6, 12, 24, 36, 48, 60 months, Adults in Epilepsy All Treated Pool

Amount Gained (kg)	6 months	12 months	24 months	36 months	48 months	60 months
Total subjects	n=1213	n=953	n=435	n=59	n=47	n=12
≤0	414 (34.1)	348 (36.5)	167 (38.4)	27 (45.8)	23 (48.9)	5 (41.7)
0 to ≤5	630 (51.9)	433 (45.4)	167 (38.4)	24 (40.7)	15 (31.9)	3 (25.0)
>5 to ≤10	148 (12.2)	141 (14.8)	73 (16.8)	7 (11.9)	6 (12.8)	4 (33.3)
>10 to ≤15	16 (1.3)	22 (2.3)	21 (4.8)	0	2 (4.3)	0
>15 to ≤20	4 (0.3)	6 (0.6)	3 (0.7)	0	1 (2.1)	0
>20 to ≤25	1 (0.1)	2 (0.2)	0	0	0	0
>25 to ≤30	0	1 (0.1)	4 (0.9)	1 (1.7)	0	0
>30 to ≤35	0	0	0	0	0	0

Source: Safety Information Amendment (7/27/12) Table 23.12-20.1

Table 87. Weight Gain from Baseline to End of 6, 12, 24, 36, 48, 60 months, Adolescents in Epilepsy All Treated Pool

Amount Gained (kg)	6 months	12 months	24 months	36 months	48 months
Total subjects	n=89	n=71	n=38	n=2	n=0
≤0	12 (13.5)	10 (14.1)	6 (15.8)	0	0
0 to ≤5	58 (65.2)	33 (46.5)	7 (18.4)	1 (50.0)	0
>5 to ≤10	15 (16.9)	21 (29.6)	14 (36.8)	1 (50.0)	0
>10 to ≤15	3 (3.4)	5 (7.0)	9 (23.7)	0	0
>15 to ≤20	1 (1.1)	1 (1.4)	1 (2.6)	0	0
>20 to ≤25	0	0	0	0	0
>25 to ≤30	0	1 (1.4)	0	0	0
>30 to ≤35	0	0	0	0	0
>35 to ≤40	0	0	0	0	0
>40	0	0	1 (2.6)	0	0

Source: Safety Information Amendment (7/27/12) Table 23.12-20.2

I performed additional analyses for weight and appetite related TEAEs that were reported in the trials. In the epilepsy Phase 3 studies, the TEAE of weight increased was reported by more perampanel subjects (3.8%) than placebo (1.4%), along with the TEAE of increased appetite (1.2% vs 1.1%). None of these events were SAEs. One perampanel subject discontinued the study due to the TEAE of increased appetite (vs 0 placebo). Interestingly, the TEAE of decreased appetite was also reported as a TEAE more frequently in perampanel subjects (2.2%) than placebo subjects (1.6%). However, the TEAE of weight decreased was reported less frequently in perampanel subjects than placebo (0.2% vs 0.9%) and decreased appetite and weight decreased led to discontinuation less frequently in perampanel subjects than placebo.

In the nonepilepsy DB pool, the TEAE of weight increased was reported by more perampanel subjects (1.2%) than placebo (0.5%), along with the TEAE of increased appetite (0.4% vs 0.2%). None of these events were SAEs. Five perampanel subjects discontinued the study due to the TEAE of weight increased (vs 0 placebo subjects).

Weight decreased (0.5% vs 0.6%) and decreased appetite (0.4% vs 0.6%) were both less common in perampanel subjects than placebo.

In the Phase 1 studies, both increased appetite and decreased appetite were reported. However, there was a greater difference between the percentages of perampanel and placebo subjects reporting increased appetite, food craving, and weight increased (1.5%) than with the reporting of decreased appetite (1.1%) in the multiple dose studies. The Phase 1 single-dose studies reported similar results.

Hyperlipidemia and Hyperglycemia

Total cholesterol, triglyceride, and blood glucose levels were measured in the perampanel studies (subjects were not required to fast before having blood drawn for laboratory evaluations). HDL levels were not measured.

The following tables summarize the percentages of adults and adolescents with clinically significant increases or shifts in total cholesterol, triglyceride, or glucose levels. In both adults and adolescents, perampanel subjects had higher incidences of total cholesterol increases and shifts than placebo subjects. For triglycerides and glucose, adult perampanel subjects had similar increases and shifts as placebo. While there were no adolescent subjects who had shifts to abnormal values of glucose, there were conflicting results for shifts in triglycerides; a higher percentage of adolescent perampanel subjects than placebo had shifts from normal to high triglycerides and a much lower percentage of adolescent perampanel subjects than placebo had shifts from borderline to high triglycerides.

Comment: Of note, total cholesterol measurements are typically not significantly changed by fasting status (as opposed to triglyceride measurements). Therefore, the lack of the effect of perampanel on triglyceride values (compared to placebo) may be due to the variability in fasting status when triglyceride measurements were obtained in the epilepsy trials.

Table 88. Increases and Shifts in Lipids and Glucose Values, Adults in Epilepsy Phase 3 DB Pool

Laboratory Evaluation	Placebo n (%)	Perampanel n (%)				
		2 mg	4 mg	8 mg	12 mg	Total
Total cholesterol	n=397	n=165	n=160	n=391	n=228	n=944
Increase ≥50 mg/dL*	11 (2.8)	7 (4.2)	6 (3.8)	30 (7.7)	18 (7.9)	61 (6.5)
Increase ≥100 mg/dL*	0	1 (0.6)	0	4 (1.0)	0	5 (0.5)
Shift from Normal to borderline (<200 to ≥200 and <240)	62 (15.6)	24 (14.5)	30 (18.8)	77 (19.7)	33 (14.5)	164 (17.4)
Shift from Normal to High (<200 to ≥240)	2 (0.5)	2 (1.2)	2 (1.3)	11 (2.8)	4 (1.8)	19 (2.0)
Shift from Borderline to High (≥200 and <240 to ≥240)	31 (7.8)	10 (6.1)	11 (6.9)	37 (9.5)	22 (9.6)	80 (8.5)
Triglycerides	n=397	n=165	n=160	n=391	n=228	n=944
Increase ≥50 mg/dL*	111 (28)	43 (26.1)	47 (29.4)	116 (30)	72 (31.6)	278 (29.4)
Increase ≥100 mg/dL*	44 (11.1)	21 (12.7)	19 (11.9)	42 (10.7)	30 (13.2)	112 (11.9)
Shift from Normal to borderline (<150 to ≥150 and <200)	64 (16.1)	22 (13.3)	20 (12.5)	67 (17.1)	40 (17.5)	149 (15.8)
Shift from Normal to High (<150 to ≥200)	43 (10.8)	12 (7.3)	11 (6.9)	28 (7.2)	23 (10.1)	74 (7.8)
Shift from Borderline to High (≥150 and <200 to ≥200)	20 (5.0)	7 (4.2)	11 (6.9)	24 (6.1)	8 (3.5)	50 (5.3)
Shift from Normal to Very High (<150 to ≥500)	1 (0.3)	0	0	1 (0.3)	0	1 (0.1)
Shift from Borderline to Very High (≥150 and <200 to ≥500)	0	0	0	1 (0.3)	0	1 (0.1)
Glucose (nonfasting)	n=397	n=165	n=160	n=391	n=228	n=944
Shift normal to borderline (<140 mg/dL to ≥140 and <200)	12 (3.0)	2 (1.2)	5 (3.1)	11 (2.8)	6 (2.6)	24 (2.5)
Shift normal to high (<140 to ≥200 mg/dL)	2 (0.5)	1 (0.6)	0	2 (0.5)	1 (0.4)	4 (0.4)
Shift borderline to high (≥140 and <200 to ≥200)	2 (0.5)	0	1 (0.6)	1 (0.3)	0	2 (0.2)

Source: Safety Information Amendment (7/27/12) Table 23.11-16.1

*Number (%) of Subjects with at least one post-baseline measurement that crossed the specified thresholds of abnormalities

Table 89. Increases and Shifts in Lipids and Glucose Values, Adolescents in Epilepsy Phase 3 DB Pool

Laboratory Evaluation	Placebo n (%)	Perampanel n (%)				
		2 mg	4 mg	8 mg	12 mg	Total
Total cholesterol	n=34	n=14	n=9	n=31	n=18	n=72
Increase ≥40 mg/dL*	1 (2.9)	2 (14.3)	1 (11.1)	2 (6.5)	1 (5.6)	6 (8.3)
Increase ≥100 mg/dL*	1 (2.9)	0	0	0	0	0
Shift from Normal to borderline (<170 to ≥170 and <200)	3 (8.8)	5 (35.7)	2 (22.2)	4 (12.9)	6 (33.3)	17 (23.6)
Shift from Normal to High (<170 to ≥200)	1 (2.9)	2 (14.3)	1 (11.1)	1 (3.2)	0	4 (5.6)
Shift from Borderline to High (≥170 and <200 to ≥200)	1 (2.9)	1 (7.1)	0	4 (12.9)	1 (5.6)	6 (8.3)
Triglycerides	n=34	n=14	n=9	n=31	n=18	n=72
Increase ≥50 mg/dL*	15 (44.1)	3 (21.4)	2 (22.2)	8 (25.8)	4 (22.2)	17 (23.6)
Increase ≥100 mg/dL*	3 (8.8)	1 (7.1)	1 (11.1)	4 (12.9)	0	6 (8.3)
Shift from Normal to borderline (<90 to ≥90 and ≤130)	9 (26.5)	5 (35.7)	3 (33.3)	8 (25.8)	2 (11.1)	18 (25.0)
Shift from Normal to High (<90 to >130)	3 (8.8)	2 (14.3)	2 (22.2)	4 (12.9)	0	8 (11.1)
Shift from Borderline to High (≥90 and ≤130 to >130)	7 (20.6)	0	0	5 (16.1)	2 (11.1)	7 (9.7)
Glucose (nonfasting)	n=34	n=14	n=9	n=31	n=18	n=72
Shift normal to borderline (<140 mg/dL to ≥140 and <200)	0	0	0	0	0	0
Shift normal to high (<140 to ≥200 mg/dL)	0	0	0	0	0	0
Shift borderline to high (≥140 and <200 to ≥200)	0	0	0	0	0	0

Source: Safety Information Amendment (7/27/12) Table 23.11-16.3

*Number (%) of Subjects with at least one post-baseline measurement that crossed the specified thresholds of abnormalities

Additionally in the nonepilepsy DB pool, perampanel subjects had higher incidences of total cholesterol increases and shifts than placebo subjects. However, perampanel subjects also had higher incidences of increases and shifts to high triglyceride values and shifts to high nonfasting glucose values. Shifts to high fasting glucose were similar in perampanel and placebo subjects (Safety Information Amendment 7/27/12 Table 23.11-17.1).

Hypertension

The following table summarizes the shifts to abnormal blood pressure categories in the epilepsy Phase 3 DB pool. There was a shift toward higher blood pressure categories observed in the perampanel group compared with placebo, which was most evident in shifts from normal (<120/80 mmHg) to Stage 2 hypertension (≥ 160/100 mmHg), although the numbers were small.

Table 90. Shifts in Blood Pressure Categories, Epilepsy Phase 3 DB Pool

BP Category on Treatment →	Stage 1 Hypertension 140-159/90-99 mmHg		Stage 2 Hypertension ≥ 160/100 mmHg	
	Placebo n=438	Perampanel n=1034	Placebo n=438	Perampanel n=1034
Normal BP (<120/80 mmHg)	16 (3.7)	41 (4.0)	0	6 (0.6)
Pre-hypertension: 120-139/80-89 mmHg	54 (12.3)	137 (13.2)	12 (2.7)	13 (1.3)

Source: Safety Information Amendment (7/27/12) Table 23.12-10

The following table summarizes the number (%) of subjects with an increase from baseline in SBP and DBP by different categories of mmHg change and study periods. At the end of week 6 and 12, treatment with perampanel was associated with higher percentages of subjects with increases of 5 to 10 mmHg in both SBP and DBP. By the end of the study, perampanel subjects had even greater increases in both SBP and DBP (11-15 mmHg and 16-20 mmHg) than placebo. By the end of the study, 16.2% vs 14.2% (perampanel vs placebo) subjects had SBP increases of >10 mmHg.

Table 91. Increase from Baseline in SBP and DBP by Study Period, Epilepsy Phase 3 DB Pool

	Systolic BP		Diastolic BP	
	Placebo	Perampanel	Placebo	Perampanel
End of Titration Period (Week 6)				
	n=413	n=949	n=413	n=949
Increase 5 - 10 mm Hg	67 (16.2)	174 (18.3)	77 (18.6)	203 (21.4)
Increase 11 - 15 mm Hg	24 (5.8)	59 (6.2)	23 (5.6)	47 (5.0)
Increase 16 - 20 mm Hg	24 (5.8)	44 (4.6)	14 (3.4)	29 (3.1)
Increase > 20 mm Hg	11 (2.7)	39 (4.1)	2 (0.5)	18 (1.9)
Maintenance Period (Week 12)				
	n=395	n=885	n=395	n=885
Increase 5 - 10 mm Hg	62 (15.7)	160 (18.1)	67 (17.0)	171 (19.3)
Increase 11 - 15 mm Hg	24 (6.1)	60 (6.8)	23 (5.8)	44 (5.0)
Increase 16 - 20 mm Hg	26 (6.6)	35 (4.0)	14 (3.5)	26 (2.9)
Increase > 20 mm Hg	15 (3.8)	32 (3.6)	5 (1.3)	16 (1.8)
End of Treatment				
	n=438	n=1034	n=438	n=1034
Increase 5 - 10 mm Hg	92 (21.0)	202 (19.5)	80 (18.3)	218 (21.1)
Increase 11 - 15 mm Hg	27 (6.2)	72 (7.0)	16 (3.7)	55 (5.3)
Increase 16 - 20 mm Hg	19 (4.3)	53 (5.1)	12 (2.7)	41 (4.0)
Increase > 20 mm Hg	16 (3.7)	42 (4.1)	12 (2.7)	17 (1.6)

Source: Safety Information Amendment (7/27/12) Table 23.12-11.1

Blood pressure data was also analyzed for the opposite effects of decreases in SBP/DBP from baseline (see following table). There were no differences between

perampanel and placebo subjects. By the end of the study, 34.0% vs 33.3% (perampanel vs placebo) subjects had SBP decreases of ≥ 5 mmHg.

Table 92. Decrease from Baseline in SBP and DBP by Study Period, Epilepsy Phase 3 DB Pool

	Systolic BP		Diastolic BP	
	Placebo	Perampanel	Placebo	Perampanel
End of Titration Period (Week 6)				
	n=413	n=949	n=413	n=949
Decrease 5 - 10 mm Hg	82 (19.9)	202 (21.3)	89 (21.5)	193 (20.3)
Decrease 11 - 15 mm Hg	21 (5.1)	53 (5.6)	30 (7.3)	43 (4.5)
Decrease 16 - 20 mm Hg	27 (6.5)	41 (4.3)	9 (2.2)	20 (2.1)
Decrease > 20 mm Hg	14 (3.4)	22 (2.3)	4 (1.0)	11 (1.2)
Maintenance Period (Week 12)				
	n=395	n=885	n=395	n=885
Decrease 5 - 10 mm Hg	78 (19.7)	163 (18.4)	89 (22.5)	179 (20.2)
Decrease 11 - 15 mm Hg	26 (6.6)	62 (7.0)	23 (5.8)	40 (4.5)
Decrease 16 - 20 mm Hg	14 (3.5)	48 (5.4)	10 (2.5)	28 (3.2)
Decrease > 20 mm Hg	24 (6.1)	25 (2.8)	9 (2.3)	13 (1.5)
End of Treatment				
	n=438	n=1034	n=438	n=1034
Decrease 5 - 10 mm Hg	86 (19.6)	207 (20.0)	90 (20.5)	201 (19.4)
Decrease 11 - 15 mm Hg	21 (4.8)	62 (6.0)	19 (4.3)	54 (5.2)
Decrease 16 - 20 mm Hg	17 (3.9)	47 (4.5)	15 (3.4)	30 (2.9)
Decrease > 20 mm Hg	22 (5.0)	36 (3.5)	6 (1.4)	12 (1.2)

Source: Safety Information Amendment (7/27/12) Table 23.12-11.2

To further evaluate the concurrent metabolic effects of perampanel, the number of subjects who had weight gain (categorized as >5%, >7%, and >10%) was stratified by the number of subjects who also newly developed other metabolic effects (triglycerides ≥ 150 mg/dL, blood pressure $\geq 130/85$ mmHg, and BMI >30 kg/m²) during the study and at the end of treatment. Across all weight gain categories, there were more perampanel subjects than placebo subjects who developed metabolic syndrome values of triglycerides, blood pressure, and BMI.

Table 93. Incidence of Metabolic Effects by Weight Gain Category, Epilepsy Phase 3 DB Pool

Metabolic Syndrome Value	Weight Gain	Placebo	Perampanel
Triglycerides \geq 150 mg/dl	n	430	1015
	> 5%	29 (6.7)	97 (9.6)
	> 7%	10 (2.3)	53 (5.2)
	> 10%	3 (0.7)	25 (2.5)
Blood Pressure \geq 130/85 mmHg	n	438	1033
	> 5%	19 (4.3)	72 (7.0)
	> 7%	9 (2.1)	39 (3.8)
	> 10%	2 (0.5)	16 (1.5)
Body Mass Index $>$ 30 kg/m ²	n	433	1026
	> 5%	12 (2.8)	65 (6.3)
	> 7%	3 (0.7)	34 (3.3)
	> 10%	1 (0.2)	13 (1.3)
All of above	n	425	1008
	> 5%	5 (1.2)	24 (2.4)
	> 7%	2 (0.5)	13 (1.3)
	> 10%	1 (0.2)	7 (0.7)

Source: Safety Information Amendment (7/27/12) Table 23.12-22

In conclusion, there is reasonable evidence of a causal relationship between perampanel use in adults and weight gain, increases in lipids (particularly total cholesterol), and blood pressure elevations. The Framingham Risk Score which estimates the 10-year cardiovascular risk of an individual is calculated by the individual's total cholesterol, systolic blood pressure, HDL cholesterol, age, gender, and use of tobacco and antihypertensives.⁸ Although an increase in cardiovascular events was not seen in perampanel subjects compared to placebo (see Section 7.3.5.3 of this review), it is difficult to make long-term conclusions regarding cardiovascular risk with data from the epilepsy Phase 3 DB studies with a median exposure of only 19 weeks. Finally, weight gain, increases in total cholesterol, and blood pressure elevations that are associated with perampanel use are clinically significant adverse reactions (with the potential to lead to increased cardiovascular risk with chronic use). Therefore, I recommend that these adverse reactions (grouped together as metabolic effects) be included in the Warnings and Precautions section of perampanel labeling.

7.3.4.4 Tendon/Ligament Ruptures

In the preclinical studies, the Sponsor has reported that perampanel binds to elastin with a very slow turnover. Therefore, there could be a possibility that long term accumulation might cause damage of fibrous tissues such as tendons and ligaments in humans. Tendon ruptures (partial or complete tears of the tendon) and ligament

⁸ National Heart Lung and Blood Institute. National Cholesterol Education Program. Risk Assessment Tool for Estimating Your 10-year Risk of Having a Heart Attack. <http://hp2010.nhlbihin.net/atp/iii/calculator.asp> (accessed August 13, 2012).

ruptures were experienced by subjects in this safety database. The Sponsor did not address this issue of tendon or ligament rupture in their ISS (or 120-day Safety Update). In response to the Division’s information request, the Sponsor provided additional information regarding the cases coded to the AE of tendon rupture (n=5) and ligament rupture (n=3). The Sponsor stated that there were no additional cases of tendon rupture in those subjects who reported other tendon disorder TEAEs (tendonitis, tendon injury, and tendon disorder).

Comment: However, after I independently reviewed the verbatim terms of these cases of tendinopathy, I found one additional case of tendon rupture (subject 218-2047-1003 in placebo group with the reported AE of “Achilles tear” which was coded to tendon injury). Therefore, the following table summarizes the correct number of subjects who experienced tendon rupture or tears.

Table 94. Tendon and Ligament TEAEs

MedDRA PT	Epilepsy DB Pool		Nonepilepsy DB Pool	
	Placebo	Perampanel	Placebo	Perampanel
All Subjects	510	1189	1079	2013
Tendonitis	1 (0.2)	1 (0.1)	4 (0.4)	2 (0.1)
Tendon ruptures	0	0	1 (0.1)	3 (0.1)
Tendon injury	0	0	1 (0.1)	1 (0.0)
Tendon disorder	0	0	0	2 (0.1)
Ligament rupture	0	1 (0.1)	0	0
Ligament injury	0	0	0	1 (0.0)
TOTAL SUBJECTS	1 (0.2)	2 (0.2)	4 (0.4)	9 (0.4)
	Epilepsy All Treated Pool		Nonepilepsy All Treated	
All Subjects	1651		2717	
Tendonitis	4 (0.2)		5 (0.2)	
Tendon ruptures	0		5 (0.2)*	
Tendon injury	0		3 (0.1)	
Tendon disorder	0		2 (0.1)	
Ligament rupture	2 (0.1)		1 (0.0)	
Ligament injury	1 (0.1)		1 (0.0)	
TOTAL SUBJECTS	7 (0.4)		17 (0.6)	

Source: ISS Tables 20.5-2, 20.5-28, 20.5-36, 20.5-54, 120-day Safety Update Table 20.5-75.1
*2 SAEs (1 leading to DC)

In the nonepilepsy DB pool, while a similar percentage of perampanel subjects (0.1%) and placebo (0.1%) experienced tendon ruptures, a lower percentage of perampanel subjects (0.2%) experienced tendon ruptures together with tendonitis than placebo subjects (0.4%). In the epilepsy DB pool, a lower percentage of perampanel subjects (0.1%) experienced tendonitis than placebo subjects (0.2%). While there were no subjects who experienced tendon ruptures, there was one perampanel subject who experienced a ligament rupture (vs 0 placebo subjects). An additional 2 tendon ruptures and 2 ligament ruptures occurred in perampanel subjects during the OLE studies.

Table 95. Tendon Ruptures and Ligament Ruptures

Subject #	Age, Sex, Race	Study: Treatment, Dose	Study Day	Tendon (or Ligament) / Trauma
Tendon Tears/Ruptures				
0412-0009	78, F, W	DB 302: Pera 4 mg	Day 31	Tendon in "left knee" / "accident at home" (history of L knee replacement >10 yrs)
1314-1021	53, M, W	DB 227: Pera 6 mg	Day 110	Tendon of "left leg" / No trauma reported
The tendon rupture occurred 22 days after perampanel was discontinued due to somnolence. <i>Of note, even though the drug was mostly likely cleared after 22 days (5 elimination half-lives), if perampanel binds to elastin then it may have been still present in fibrous connective tissues such as tendons.</i>				
0101-0005	40, M, W	DB 301: Pera 2 mg	Day 175	*Achilles tendon / "while playing football"
0105-0004	54, M, W	DB 214: Pera 2 mg OLE 220: Pera 6 mg	Day 355	Vastus lateralis tendon (L knee) / Fall
0128-0005	71, M, W	DB 301: Pera 4 mg OLE 303: Pera 4 mg	Day 482	*Tendon not specified / Fall on staircase
2047-1003	72, F, W	DB 218: Placebo	Day 58	"Achilles tear" coded to Tendon Injury
This subject had a previous AE of tendonitis and treated with oral prednisone from Day 35 to 41.				
Ligament Ruptures				
2455-6004	69, M, W	DB 306: Pera 8 mg	Day 77	Ligament not specified /no trauma reported (same day as epicondylitis)
2457-6006	58, F, W	DB 306: Pera 2 mg OLE 307: Pera 6 mg	OLE Day 46	L shoulder ligament / no trauma reported
2021-1003	65, F, W	DB 218: Pera 4 mg OLE 228: Pera 2 mg	Day 105	L shoulder ligament / no trauma reported

Source: Created by the reviewer using narratives provided by the Sponsor in the Safety Information Updates dated 6/21/12 and 8/03/12

*2 SAEs

In the nonepilepsy DB pool, 1 placebo subject, aged 72 years old, developed a partial rupture of the Achilles tendon after receiving oral prednisone for tendonitis. This subject did not have diabetes mellitus, renal disease, or take fluoroquinolones.

In the nonepilepsy all treated pool, 5 perampanel subjects with a mean age of 59 years developed tendon ruptures with a mean onset of 231 days (range 31 to 482 days). Although most occurred during a traumatic event, there was one case of possible spontaneous tendon rupture. The ruptured tendons included the Achilles tendon (1), vastus lateralis tendon (1), "left leg" tendon (1), "left knee" tendon (1), and unknown (1). None of the subjects had a history or concurrent events of tendinitis, tendon injury, or tendon disorder. None of these subjects were taking oral steroids (1 taking fluticasone, route not specified) or fluoroquinolones. Two subjects had a history of diabetes mellitus. In the nonepilepsy all treated pool, the incidence of tendon rupture in perampanel subjects was 0.18% (5/2717) while 0.37% (10/2717) experienced either tendon rupture or tendonitis.

Comment: Fluoroquinolones are associated with an increased risk of tendinitis and tendon rupture. Risk factors for fluoroquinolone-induced tendon disorders include older age (>60 years), corticosteroid use, renal failure, strenuous physical activity, and previous tendon disorders such as rheumatoid arthritis. The Achilles tendon is most frequently involved. A review by Khaliq Y and Zhanel GG reported a mean onset of tendon rupture after initiation of fluoroquinolone therapy was 25.6 days (median 6 days).⁹ Tendon injury occurred as early as 2 hours after the first dose of fluoroquinolone to as late as 6 months after discontinuation of treatment. The mean age was 59.0 ± 16.0 years (range 28 to 92 yrs). Although the exact incidence is not known, one study reported the incidence of fluoroquinolone-induced tendon rupture as 0.012% (4/33620) and after including tendonitis as 0.036% (12/33620).¹⁰ Other studies report the incidence of fluoroquinolone-induced tendon injury (tendon rupture and tendonitis) ranged from 0.14% to 0.40%.¹¹ Other authors have estimated the incidence of fluoroquinolone-induced tendinopathy (tendon rupture and tendonitis) to be 15 to 20 per 100,000 treated patients or 0.015% to 0.020%.¹² The pathophysiology of fluoroquinolone-associated tendon disorders is still unclear but a mismatch in tendon cell breakdown and repair has been implicated.¹³

Discussion

There were similar incidences of total tendon and ligament disorders between perampanel and placebo subjects. Some of the tendon ruptures occurred in subjects at higher risk (older, history of diabetes mellitus, possible debility with Parkinson's disease, corticosteroid use, trauma). Even though the mean age of these tendon rupture cases was similar to fluoroquinolone-induced tendon ruptures, they typically developed later in the course of therapy (mean onset 231 days vs 25.6 days).

It appears that the overall incidence of tendon rupture in the nonepilepsy perampanel population (0.18%) is within the range or higher than for fluoroquinolones. In fluoroquinolone labeling, the risk for tendon rupture and tendinitis is included in a boxed warning. However, interestingly, the incidence of tendonitis and tendon rupture in the placebo nonepilepsy population (4/1079 or 0.37%) is also within the range of or higher than the incidence of fluoroquinolone-induced tendinopathy (ruptures + tendonitis). There are many limitations to the reported incidences for fluoroquinolone-induced tendinopathy (based on observational data and differ among studies). Furthermore,

9 Khaliq Y and Zhanel GG. Fluoroquinolone-Associated Tendinopathy: A Critical Review of the Literature. *Clinical Infectious Diseases*. 2003; 36: 1404-10.

10 Wilton LV et al. A comparison of ciprofloxacin, norfloxacin, ofloxacin, azithromycin and cefixime examined by observational cohort studies. *Br J Clin Pharmacol*. 1996; 41: 277-84.

11 Khaliq Y and Zhanel GG. Fluoroquinolone-Associated Tendinopathy: A Critical Review of the Literature. *Clinical Infectious Diseases*. 2003; 36: 1404-10.

12 Harrell RM. Fluoroquinolone-Induced Tendinopathy. *Southern Medical Journal*. 1999; 92 (6): 622-5.

13 Hall MM et al. Musculoskeletal Complications of Fluoroquinolones: Guidelines and Precautions for Usage in the Athletic Population. *PM&R*. 2011; 3: 132-142.

there is a need for accurate incidence rates that control for the length of exposure. Antibiotics are typically taken for short periods of time while the perampanel exposure in this safety database was much longer (1251 subjects on perampanel for >6 months in the nonepilepsy population).

Additionally, this finding was not replicated in the epilepsy population. The lack of tendon rupture cases in this population may be due to the younger age of this pool (mean age 34.9 years) and lack of significant comorbidities such as diabetes mellitus (more restrictive exclusion criteria). However, there were cases of other fibrous connective tissue injuries such as ligament rupture seen in the epilepsy (n=2) population mainly in older subjects (mean age 64 years).

In conclusion, it is difficult to attribute the high incidence of tendon ruptures in the nonepilepsy population (compared to other medications associated with tendinopathy) solely 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. Furthermore, tendonitis and an Achilles' tendon tear also occurred in placebo subjects at similar rates as seen with perampanel subjects. However, it is concerning that if perampanel covalently binds to elastin for such a prolonged time, subjects may be developing tendinopathy long after the drug is discontinued. Therefore, I recommend postmarketing surveillance to continue to investigate the effects of perampanel exposure on the fibrous connective tissues, tendons and ligaments in humans.

7.3.5 Submission Specific Primary Safety Concerns

In the next four subsections (7.3.5.1 to 7.3.5.4), I will discuss my analyses along with the Sponsor's analyses of the following major organ systems: hepatobiliary, skin/immune system, cardiac, renal/urinary, endocrine, gastrointestinal, and respiratory.

7.3.5.1 Hepatobiliary Disorders

Cholelithiasis

In the epilepsy Phase 3 DB pool, a higher number of perampanel subjects (n=3) than placebo subjects (0) developed cholelithiasis. In the entire epilepsy population, a total of 8 subjects (0.5%) reported TEAEs of cholelithiasis (including 1 subject with bile duct stone/acute pancreatitis). These were SAEs in 5 perampanel subjects in the all treated pool (2 perampanel subjects vs 0 placebo in the Phase 3 DB pool, see following table).

In the nonepilepsy DB pool, a similar percentage of perampanel subjects (0.1% with cholelithiasis) and placebo subjects (0.1% with bile duct stone) developed these TEAEs. In the nonepilepsy all treated pool, a total of 7 subjects (0.3%) reported TEAEs of cholelithiasis. Some of the same subjects also reported cholecystitis and acute pancreatitis. These TEAEs were SAEs in 3 perampanel subjects.

Table 96. SAEs in Hepatobiliary Disorders SOC, DB pools

MedDRA Preferred Term	Placebo	Perampanel
Epilepsy Phase 3 DB Pool	n = 442	n = 1038
Cholelithiasis	0	2 (0.2)
Nonepilepsy DB Pool	n = 1079	n = 2013
Cholelithiasis	0	1 (0.0)
Biliary colic	0	1 (0.0)
Bile duct stone	1 (0.1)	0
Jaundice	1 (0.1)	0

Source: ISS Tables 20.7-1 and 20.7-15

Comment: Of note, there were no AEs for lipase elevation in the safety population. There was one additional placebo patient who developed acute pancreatitis (SAE in the nonepilepsy pool). It was not reported in the narrative that the etiology was due to cholelithiasis so this subject was excluded from the following table.

Table 97. Subjects with Cholelithiasis/Choledocholithiasis

Subject #	Age, Sex, Race	Study: Treatment, Dose	Adverse event (Preferred Term)	Study day	BMI (kg/m ²)
Epilepsy Studies:					
1001-4001	28, F, W	DB 304: Pera 12 mg	Cholelithiasis	DB 6	22.7
5101-4001	55, F, W	DB 304: Pera 8 mg	Cholelithiasis - SAE	DB 70	23.8
4003-6001	31, M, W	DB 306: Pera 4 mg	Cholelithiasis - SAE	DB 72	23.1
2803-5002	72, M, W	DB 305: Pera 8 mg OLE 307: Pera 12 mg	Cholelithiasis – SAE (h/o cholelithiasis)	Day 328	25.7
5158-4002	54, F, W	DB 304: Placebo OLE 307: Pera 12 mg	Cholelithiasis	Day 331	23.6
5139-4011	43, F, W	DB 304: Pera 12 mg OLE 307: Pera 12 mg	Cholelithiasis - SAE	Day 404	42.7
4004-6007	36, F, W	DB 306: Pera 4 mg OLE 307: Pera 12 mg	Cholelithiasis	Day 662	22.7
1702-4001	43, F, W	DB 304: Pera 12 mg OLE 307: Pera 8 mg	Pancreatitis acute/ Bile duct stone - SAE	Day 810	31.5
Nonepilepsy Studies:					
1319-1013	66, F, B	DB 227: Pera 2 mg	Cholelithiasis	DB 29	36.7
1301-1002	67, M, W	DB 227: Pera 8 mg	Cholelithiasis/ Pancreatitis acute - SAE	DB 84	27.7
0129-0010	77, F, W	DB 301: Placebo	Bile duct stone	DB 33	21.2
1314-1011	53, F, W	DB 227: Pera 6 mg OLE 228: Pera 4 mg	Cholelithiasis	Day 160	20.6
0131-0009	64, M, W	DB 301: Placebo OLE 303: Pera 4 mg	Cholelithiasis	Day 291	31.5
0601-0003	71, M, W	DB 204: Placebo OLE 205: Pera 2 mg	Cholelithiasis -SAE	Day 387	29.1

1805-1001	88, F, W	DB 227: Pera 6 mg OLE 228: Pera 6 mg	Cholelithiasis	Day 498	25.3
0211-0006	70, M, W	DB 301: Pera 2 mg OLE 303: Pera 4 mg	Cholecystitis/ Cholelithiasis - SAE	Day 587	27.4

Source: Created by the reviewer using the epilepsy and nonepilepsy ADAE, ADSL, ADVS datasets

Important risk factors for developing gall bladder disease are obesity and age over 40 years old. After excluding the cases that occurred in subjects with a prior history (n=1) or too early in the study (n=1), there are 2 subjects in the epilepsy DB studies and 4 subjects in the OLE studies with cholelithiasis. Of these, most were females in their 40s and 50s and some were obese (BMI>30, n=2). In the nonepilepsy studies, most of the subjects were overweight (BMI>25).

In conclusion, it is difficult to determine whether there is a signal for in the perampanel database. The assessment of the role of perampanel is difficult. Exploration of this signal should be continued during the post-marketing phase. Furthermore, it is reassuring that the serious sequelae of cholelithiasis, such as cholecystitis and pancreatitis, was rare in the safety population (0.06%, 3/ 5284 or 0.76 cases per 1000 subject-years, 3/3933.4 subject-years).

Drug-Induced Liver Injury

The Sponsor 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 Sponsor 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.

The following table summarizes the percentages of perampanel and placebo subjects in the Hepatobiliary disorders SOC and SMQs. A higher percentage of perampanel subjects compared to placebo developed TEAEs in the liver-related investigations SMQ (but not the drug related hepatic disorders – severe events SMQ).

Table 98. Hepatobiliary disorders SOC and SMQs, Epilepsy Phase 3 DB Pool

MedDRA SOC, SMQ	Placebo n = 442	Perampanel n = 1038
SOC Hepatobiliary disorders	0	*4 (0.4)
SMQs (broad):		
(1) Hepatic disorders	3 (0.7)	13 (1.3)
(2) Drug related hepatic disorders -Comprehensive search	3 (0.7)	13 (1.3)
(3) Drug related hepatic disorders -Severe events only	0	0
(3) Liver related investigations, signs and symptoms	3 (0.7)	13 (1.3)

Source: Created by the reviewer using MAED (MedDRA-based Adverse Event Diagnostic) service
 *3 cholelithiasis and 1 hepatic function abnormal

None of the liver-related TEAEs were SAEs (the SAEs of cholelithiasis are discussed earlier this section). The following table summarizes the discontinuations due to liver-

related AEs in the Investigations SOC. There were no discontinuations in perampanel subjects in the epilepsy Phase 2 and 3 DB pools (and only rare discontinuations in the other DB pools) due to liver-related TEAEs.

Table 99. Discontinuations in Investigations SOC, DB pools

MedDRA Preferred Term in SOC Investigations	Placebo	Perampanel
Epilepsy Phase 3 DB Pool	n = 442	n = 1038
	0	0
Epilepsy Phase 2 DB Pool	n = 68	n = 151
ALT increased	1 (1.5)	0
AST increased	1 (1.5)	0
Nonpilepsy DB Pool	n = 1079	n = 2013
ALT increased	0	3 (0.1)
AST increased	0	1 (0.0)
GGT increased	0	1 (0.0)
Hepatic enzyme increased	1 (0.1)	0
Phase 1 Multiple Dose Pool	n = 116	n = 343
ALT increased	0	1 (0.3)
Hepatic enzyme increased	0	1 (0.3)

Source: ISS Tables 20.7-1 and 20.7-15

The following table summarizes the liver related lab test outlier results for the epilepsy and nonpilepsy DB pools. In both the epilepsy and nonpilepsy DB pools, the incidence of liver related lab result elevations was similar for subjects receiving perampanel and those receiving placebo. There were no cases where subjects had transaminase elevations greater than 3x upper limit of normal (ULN) associated with total bilirubin >2xULN.

Table 100. Liver Test Result Outliers, DB Pools

Test/Cutoff threshold	Epilepsy DB Pool		Nonpilepsy DB Pool	
	Placebo	Perampanel	Placebo	Perampanel
ALT	n=498	n=1166	n=1049	n=1934
ALT >3xULN	2 (0.4)	3 (0.3)	2 (0.2)	5 (0.3)
ALT >5xULN	0	0	1 (0.1)	1 (0.1)
AST	n=498	n=1165	n=1048	n=1932
AST >3xULN	2 (0.4)	5 (0.5)	1 (0.1)	6 (0.3)
AST >5xULN	0	0	1 (0.1)	3 (0.2)
Total bilirubin	n=499	n=1167	n=1049	n=1935
Total bilirubin >2xULN	0	1 (0.1)	2 (0.2)	5 (0.3)
ALP	n=499	n=1167	n=1049	n=1935
ALP >3xULN	0	1 (0.1)	1 (0.1)	1 (0.1)

Source: ISS Tables 20.11-8, 20.11-59

The following table summarizes the liver related lab test outlier results for the epilepsy and nonpilepsy all treated pools. Elevations in each of the liver tests occurred in very few perampanel subjects (generally <0.5%). There were no cases where subjects had transaminase elevations greater than 3x ULN associated with total bilirubin >2xULN.

Table 101. Liver Test Result Outliers, All Treated Pools

Test/Cutoff threshold	Epilepsy All Treated Pool n=1651	Nonepilepsy All Treated Pool n=2717
ALT >3xULN	9 (0.6)	11 (0.4)
>5xULN	3 (0.2)	0
AST >3xULN	8 (0.5)	8 (0.3)
>5xULN	1 (0.1)	3 (0.1)
Total bilirubin >2xULN	2 (0.1)	10 (0.4)
ALP >3xULN	1 (0.1)	3 (0.1)
>5xULN	0	1 (0.0)

Source: ISS Table 20.11-90 and 120-day Update Table 20.11-140.1

Perampanel subjects with elevated liver labs either had elevated pretreatment values (subjects 206-0062-0091, 208-3019-1034, 306-2502-6003, and subject 206-0061-0150 had AST value 10xULN at baseline), high baseline values (subjects 305-5201-5007, 306-1502-6003, 207-3018-1015, and 306-3003-6003), elevated values with subsequent normal values (subjects 206-0077-0145, 208-3011-1019, 304-1015-4005, 306-1502-6008, 306-1806-6002, 306-1806-6013), other medical diagnoses (subject 305-2705-5005 with viral hepatitis A and subject 307-2704-5009 with viral infection), or developed elevations in ALT and AST with normal bilirubin after prolonged perampanel treatment (subject 304-1601-4002 on Study Day 733 and 306-2759-6005 on Study Day 584).

In the nonepilepsy all treated pool, the following 4 subjects discontinued due to increased hepatic enzymes.

Subject 301-0242-0008: On Study Day 28, elevation of ALT >3x ULN and AST >2x ULN with normal bilirubin. Perampanel was discontinued and follow up labs were normal.

Subject 227-1321-1011: On Study Day 1, mild elevation of ALT 1-2x ULN. Perampanel was discontinued and follow up labs were normal.

Subject 227-1900-1009: On Study Day 44, elevation of ALT >2x ULN and AST >2x ULN with normal bilirubin. Perampanel was discontinued and follow up labs were close to the normal range.

Subject 227-1900-1012: On Study Day 1, mild elevation of ALT 1-2x ULN. Perampanel was discontinued and follow up labs were normal.

Other perampanel subjects experienced an elevation in one liver parameter only (subject 302-0433-0001 with bilirubin >2x ULN), had high baseline values (subjects 204-0405-0011, 303-0442-0006, 303-0216-0005), or a single elevated post-baseline value (subjects 301-0218-0009, 302-0402-0002, 301-0261-0010 with bilirubin >2x ULN, subject 227-1307-1001 with ALT >5x ULN, subject 210-0061-6133 with AST >3x ULN, subject 302-0575-0011 with AST >5x ULN, subject 301-0122-0007 with AST >5x ULN and ALT >3x ULN).

In the Phase 1 single-dose study pool, no subjects had values for bilirubin that were >2x ULN. The Sponsor reported that the elevations of either ALT or AST > 5 x ULN occurred in two subjects, one with an isolated elevation of AST followed by normal values, and another who had elevated levels of AST and ALT at several evaluations,

decreasing toward normal by the final evaluation. No placebo subjects had ALT or AST values > 5x ULN.

In the Phase 1 multiple-dose study pool, no subjects had values for AST that were > 5x ULN. The Sponsor reported that the perampanel subject with values for ALT that were > 5x ULN also had elevated AST values (not >5x ULN) with both elevations resolving during the study. Four (1.2%) perampanel subjects and one (0.9%) placebo subject had values for bilirubin that were > 2x ULN. In all five cases, the Sponsor reported that the subjects had bilirubin elevations at screening and throughout treatment. No placebo subjects had ALT or AST values > 5x ULN.

Table 102. Liver Test Result Outliers, Phase 1 Studies

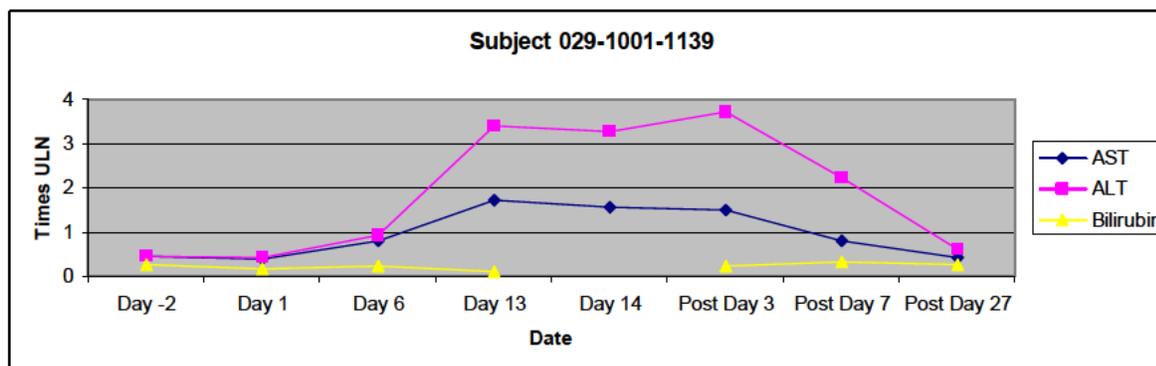
Test/Cutoff threshold	Single Dose		Multiple Dose	
	Placebo n=45	Perampanel n=544	Placebo n=116	Perampanel n=343
ALT >3xULN	0	1 (0.2)	0	3 (0.9)
>5xULN	0	1 (0.2)	0	1 (0.9)
AST >3xULN	0	1 (0.2)	0	0
>5xULN	0	2 (0.4)	0	0
Total bilirubin >2xULN	0	0	1 (0.9)	4 (1.2)
ALP >3xULN	0	0	0	0

Source: ISS Tables 22.5-109, 22.5-110

Narratives for the Phase 1 subjects who discontinued due to hepatic enzyme increases are provided below. It is difficult to make any conclusions regarding these cases due to the lack of bilirubin measurements on the key days with elevations in ALT and AST.

Subject 029-1001-1139, a 41-year-old Asian female healthy volunteer who experienced the AE of hepatic enzyme increased on Study Day 13. The subject received daily doses of 4 mg perampanel for the first 7 days followed by daily doses of 8 mg perampanel. The following chart summarizes the hepatic laboratory changes for this subject. Alkaline phosphatase levels were normal throughout the study. Of note, the bilirubin value was not reported for Day 14. Of note, other than lethargy, the subject did not report any liver-related AEs such as nausea, vomiting, abdominal pain, jaundice, or anorexia. The subject recovered from the transaminitis 27 days after the last dose of perampanel.

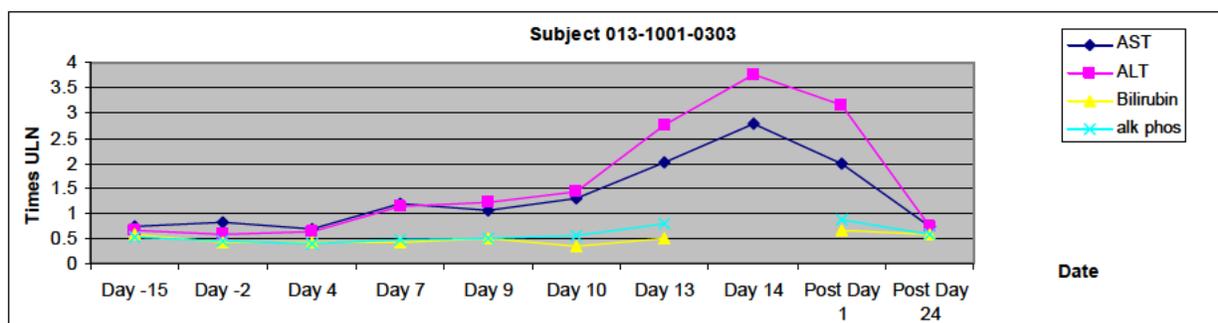
Figure 4. Liver Test Results, Subject 029-1001-1139



Source: Created by reviewer using the Phase 1 ADLB dataset

Subject 013-1001-0303, a 54 year-old white female who experienced increased liver enzymes. She received perampanel 6 mg for 7 days, then 8 mg and 10 mg for 1 day each, and then 12 mg for 4 days. The subject experienced the TEAEs of dizziness, fatigue, and mental status changes. On Study Day 7, the subject's ALT increased to 46 U/L (baseline 27) and AST increased to 50 U/L (baseline 31). On Day 9, the bilirubin increased to 10.26 $\mu\text{mol/L}$ (baseline 8.55) without an increase in alkaline phosphatase levels. On Study Day 14, the ALT increased to 150, AST increased to 117, and bilirubin increased to 13.68. Perampanel was discontinued and the transaminitis resolved in 3 weeks. The following chart summarizes the hepatic laboratory changes for this subject. Of note, the bilirubin and alkaline phosphatase labs were not reported for Day 14.

Figure 5. Liver Test Results, Subject 013-1001-0303



Source: Created by reviewer using the Phase 1 ADLB dataset*

*In a Safety Information Amendment dated March 23, 2012, in response to the Division's request to investigate whether there were any other liver enzyme results that were obtained on Study Day 14, the Sponsor clarified that based on the Study Day 13 elevated values, "additional" assessments of only ALT and AST were conducted on November 13, 2007 (Study Day 14); alkaline phosphatase, bilirubin and albumin were not requested as all were within normal ranges on Study Day 13.

In the Phase 1 Study 006, the effect of carbamazepine was evaluated on the PK, safety, and tolerability of perampanel. The Sponsor reported that among subjects with elevations in ALT, AST, or GGT, 7 subjects had elevated values in at least two of these enzymes. One subject had elevations at the poststudy assessment only (Day 49). In another subject, 2 of 3 elevations were noted poststudy (both on Day 49) and 1 elevation on Day 41, 9 days after the perampanel 2 mg single dose and 17 days after initiation of carbamazepine dosing. The 5 other subjects had at least one elevation occurring during the carbamazepine treatment period prior to perampanel dosing. Therefore, the Sponsor concluded that the subjects having elevations in more than one enzyme in Study 006 were likely attributed to carbamazepine instead of perampanel.

In conclusion, the evidence presented by the Sponsor does not suggest that perampanel use is associated with liver injury. Although patients experienced elevated liver parameters while exposed to perampanel, the risks for these elevations were similar for perampanel and placebo patients in the epilepsy Phase 2 and 3 trials and nonepilepsy trials. The Phase 1 trials did reveal that perampanel subjects had a higher incidence of liver parameter elevations than placebo subjects. However, elevated liver values were rare and sometimes in the setting of elevated baseline values. No SAEs were identified and the discontinuations had mild to moderate elevations of

transaminases. The safety database did not include any patients who developed transaminase elevations of greater than 3 times upper limit of normal that were associated with elevations of total bilirubin of greater than 2 times ULN.

7.3.5.2 Skin and Immune System Disorders

The following table summarizes the percentages of subjects reporting TEAEs in the SMQs Severe cutaneous adverse reactions, Anaphylactic reaction, Angioedema, and Neuroleptic malignant syndrome in the epilepsy Phase 3 DB pool. Perampanel subjects reported TEAEs in these SMQs at similar frequencies as placebo subjects. The preferred terms in the algorithmic or narrow SMQs (with the highest specificity to their respective clinical syndromes) were only reported by a small percentage of subjects (<0.5%) in both the placebo and perampanel groups.

Table 103. Skin and Immune System SMQs, Epilepsy Phase 3 DB Pool

SMQ	Placebo n = 442	Perampanel n = 1038
SMQ Severe cutaneous adverse reactions		
Narrow SMQ	0	0
Broad SMQ	3 (0.7)	4 (0.4)*
SMQ Anaphylactic reaction		
Algorithmic	2 (0.5)	3 (0.3)
Narrow SMQ	0	0
Broad SMQ	33 (7.5)	70 (6.7)
SMQ Angioedema		
Narrow SMQ	2 (0.5)	3 (0.3)
Broad SMQ	8 (1.8)	19 (1.8)
SMQ Neuroleptic malignant syndrome		
Narrow SMQ	0	0
Broad SMQ	32 (7.2)	81 (7.8)

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

*PTs blister (1), conjunctivitis (1), mouth ulceration (1), stomatitis (1) (no SAEs)

Additionally, in the epilepsy Phase 2 DB and nonepilepsy DB pools, perampanel subjects reported TEAEs in these SMQs at similar frequencies as placebo subjects. In the next few paragraphs, I will discuss skin disorders (including photosensitivity), anaphylactic reactions, angioedema, and drug reaction with eosinophilia and systemic symptoms (DRESS) in more detail.

Skin and subcutaneous tissue disorders

TEAEs coded to the preferred terms, Stevens-Johnson syndrome and toxic epidermal necrolysis, were not reported in perampanel subjects in the entire safety database. However, there was one case of Stevens-Johnson syndrome reported in a placebo subject in the nonepilepsy studies. The following table summarizes the TEAEs along with SAEs, discontinuations that were reported in perampanel subjects more often than placebo subjects in the epilepsy Phase 3 DB pool.

Table 104. SOC Skin and Subcutaneous Tissue Disorders: TEAEs Occurring in ≥ 2 Perampanel Subjects > Placebo, Epilepsy DB Pool

MedDRA SOC Skin and Subcut. tissue disorders	Placebo	Perampanel
Epilepsy Phase 3 Pool	33 (7.5)	84 (8.1)
Rash	7 (1.6)	23 (2.2)
Pruritus	2 (0.5)	11 (1.1)
Acne	1 (0.2)	7 (0.7)
Dry Skin	1 (0.2)	4 (0.4)
Hypoaesthesia facial	0	3 (0.3)
Rash Papular	0	3 (0.3)
Ecchymosis	0	2 (0.2)
Skin irritation	0	2 (0.2)
Epilepsy Phase 2 Pool	5 (7.4)	19 (12.6)
Rash	2 (2.9)	5 (3.3)
Palmar erythema	0	2 (1.3)
Skin ulcer	0	2 (1.3)

Source: ISS Tables 20.5-2, 20.5-28

Table 105. All SAEs and DCs in SOC Skin Disorders, Epilepsy Phase 2/3 DB Pool Combined

MedDRA SOC Skin and Subcut. tissue disorders	Placebo n=510	Perampanel n=1189
SAEs	0	1 (0.1)
Ecchymosis	0	1 (0.1)
Discontinuation TEAEs	0	10 (0.8)
Rash	0	7 (0.6)
Hypoaesthesia facial	0	1 (0.1)
Rash erythematous	0	1 (0.1)
Seborrhoeic dermatitis	0	1 (0.1)

Source: ISS Tables 20.7-1, 20.8-1, 20.8-15

In both of the epilepsy DB pools, a higher number of perampanel subjects than placebo subjects experienced adverse events related to skin disorders. Perampanel subjects reported rash more often than placebo subjects. Furthermore, only perampanel subjects (vs 0 placebo subjects) developed SAEs and discontinued from the study due to skin related TEAEs. After combining the epilepsy Phase 2 and 3 DB pools, there were 8 perampanel subjects (0.7%) who experienced a rash (7 rash, 1 rash erythematous) that led to drug discontinuation (vs 0 placebo subjects).

Comment: The narratives were reviewed for these 8 subjects. Most of these rashes were categorized as moderate in severity by the investigators. The mean day of onset was 43 days (range 4 to 119 days). The mean perampanel dose was 8 mg. The following treatments were reported: methylprednisolone (n=2) and antihistamines (n=1). After the discontinuation of perampanel, resolution occurred after average of 8.5 days (range 1 to 29 days) with 2 noted as ongoing. From the limited information

provided in the narratives, none of these cases reported widespread, exfoliative or bullous rashes involving the mucocutaneous areas.

In the epilepsy all treated pool, there were no additional perampanel subjects who developed skin related SAEs. There were 4 additional perampanel subjects who developed rashes that led to discontinuation with 1 “toxic skin eruption.”

Subject #306-3951-6008 developed a vesicular dermal rash on the upper torso and limbs on Day 69 of perampanel. Treatment included acyclovir, desloratadine, and quifenadine for the event of toxic skin eruption. Perampanel was discontinued on Day 80 and the event resolved one week later. Concomitant medications included levetiracetam and drospirenone with ethinyl estradiol.

In the nonepilepsy DB pool, skin related SAEs occurred only in the placebo group. In the nonepilepsy all treated pool, 1 subject developed the SAE of decubitus ulcer. In the nonepilepsy DB pool, more perampanel subjects (0.3%, n=7) developed rashes that led to discontinuation than placebo subjects (0.1%, 1 dermatitis allergic).

Comment: The narratives were reviewed for these 7 subjects (4 rash, 1 rash macular, 1 rash vesicular, 1 dermatitis allergic). Most were categorized as moderate in severity by the investigators. The mean day of onset was 45 days (range 4 to 120 days). The following treatments were reported: betamethasone/triamcinolone and topical silver diacetyltannin albuminate. After the discontinuation of perampanel, resolution occurred after average of 11 days (range 1 to 30 days) with 1 noted as resolving at the time of the report. From the limited information provided in the narratives, none of these cases reported widespread, exfoliative or bullous rashes. However, two cases reported involving the mucocutaneous areas: subject 210-0060-6017 who developed a moderate generalized rash on chest, legs, arms, and mouth on Day 53 which resolved the same day; subject 227-1804-1004 who developed a rash at the mouth on Day 14 which resolved 2 days after perampanel discontinuation.

Furthermore, there was one subject (204-0109-0002) who developed mild “inflammatory pustules” on the face, sternal, and dorsum that appeared to be an allergic skin eruption on Day 4. Perampanel was continued. On Day 32, her inflammatory pustules worsened and perampanel was discontinued. The event resolved one month later. No concomitant medications were reported. However, the subject had a history of “allergy against antibiotics.” This case fits the EuroSCAR criteria for “possible” acute generalized exanthematous pustulosis (AGEP; compatible pustules in a typical distribution on face/trunk with acute onset (≤ 10 days) without mucosal involvement).¹⁴ However, the subject did not have fever or neutrophilia, and the case lacked histopathological information to make a definitive diagnosis of AGEP.

In the Phase 1 studies, there were no perampanel subjects who developed skin related SAEs. One subject discontinued due to the TEAE rash pruritic. One subject (0017 in

¹⁴ Sidoroff et al. Acute generalized exanthematous pustulosis (AGEP): a clinical reaction pattern. J Cutan Pathol. 2001; 28:113-119.

Study 002) developed erythema multiforme on Day 12 confirmed by a dermatologist thought most likely due to an infectious etiology and treated with acyclovir. The subject completed the study, receiving his last dose of perampanel on Day 14. The event resolved one week later.

In conclusion, perampanel use is associated with an increased occurrence of rash and discontinuations due to rash than placebo use. Although, there were some cases of rash with mucocutaneous involvement, inflammatory pustules, and erythema multiforme, there were no definitive cases of any severe cutaneous adverse reactions associated with perampanel use.

Photosensitivity

In preclinical studies, the positive results for perampanel in the *in vitro* 3T3 neutral red uptake phototoxicity test and chromosomal aberration test with UV irradiation indicated that perampanel has the potential to cause phototoxicity. (The reader is referred to the Pharmacology/Toxicology review by Dr. Christopher Toscano for further details). Therefore, a photosensitivity questionnaire was added by protocol amendment to the epilepsy Phase 3 DB studies after enrollment had been ongoing for more than 6 months.

The following table summarizes the results of the photosensitivity questionnaire and photosensitivity reaction TEAEs. Positive responses to the question about skin rash, reaction, change in pigmentation, or skin complaint was higher in perampanel subjects (2.1%) than placebo subjects (1.2%). Furthermore, more perampanel subjects (1.0%) than placebo subjects (0.4%) had positive responses to the question about skin reacting to sunlight more than expected. A dose response was observed with highest percentage of positive responses to the first question in the 12 mg dose group (3.2%). However, after stratifying by study, a dose response was only observed in 1 out of the 3 studies (Study 304 CSR Table 14.3.8): placebo (1.5%), 8 mg (1.6%), and 12 mg (4.2%). In Study 305 (CSR Table 14.3.8), the following percentages reported positive responses: placebo (2.2%), 8 mg (4.9%), 12 mg (2.3%). The following are the results from Study 306 (CSR Table 14.3.8): placebo (0), 2 mg (0), 4 mg (1.4%), 8 mg (0).

Table 106. Results of Photosensitivity Questionnaire and Photosensitivity TEAEs

	Placebo n (%)	Perampanel n (%)				Total
		2 mg	4 mg	8 mg	12mg	
Yes to questions:	242	75	74	212	158	519
Skin rash/reaction/change in pigmentation/skin complaint	3 (1.2)	0	1 (1.4)	5 (2.4)	5 (3.2)	11 (2.1)
Skin reacted to sunlight more than expected	1 (0.4)	0	0	3 (1.4)	2 (1.3)	5 (1.0)
TEAEs:						
Epilepsy DB (Phase 2+3)	510	192	273	431	293	1189
Photosensitivity reaction	0	1 (0.5)	0	0	1 (0.4)	2 (0.2)
Sunburn	2 (0.4)	0	1 (0.4)	1 (0.2)	1 (0.3)	3 (0.3)
Nonepilepsy DB Pool	1079	908	814	291	0	2013
Photosensitivity reaction	1 (0.1)	0	2 (0.2)	0	0	2 (0.1)

Source: ISS Tables 20.14-1, 20.5-2, 20.5-28, 20.5-54

Of those who had positive responses to the first question, less perampanel subjects (45%, 5/11) had a prior history of dermatitis or skin complaints than placebo subjects (100%, 3/3). Of those who had positive responses to the first question, all of the placebo subjects and nine (81.8%) perampanel subjects had one or more skin-related TEAEs such as rash, sunburn, or dermatitis. None of these were SAEs or led to dose adjustment or discontinuation.

Additionally, I reviewed the safety database for AEs coded to preferred terms related to sun sensitivity or sun damage. In the epilepsy DB pool, while there were more perampanel subjects (0.2%) who reported photosensitivity reactions compared to placebo subjects (0), less perampanel subjects (0.3%) reported sunburn compared to placebo subjects (0.4%). In the nonepilepsy DB pool, a similar percentage of perampanel and placebo subjects reported photosensitivity reaction (no reports of sunburn). In the all treated pools, there were a total of 10 perampanel subjects with the PT photosensitivity reaction (5 epilepsy, 5 nonepilepsy).

Additional preferred terms describing conditions related to sun damage were reported by perampanel subjects in the nonepilepsy DB pool: actinic keratoses (1), basal cell carcinoma (4), and squamous cell carcinoma of the skin (1). No placebo subjects reported these TEAEs. In the nonepilepsy all treated pool, there were additional perampanel subjects reporting actinic keratoses (1) and lentigo maligna stage unspecified (1). No perampanel subjects reported any of these TEAEs in the epilepsy all treated pool. Melanoma was also reported by perampanel subjects (please see Section 7.6.1 of this review for further details).

In conclusion, it is difficult to attribute an increased risk of photosensitivity reaction with perampanel exposure. There were many limitations to the above findings: the subjective nature of the questionnaire which was only administered to half of the epilepsy Phase 3 DB pool and dose response only seen in 1 of the 3 studies.

Conclusions based on the TEAEs related to sun damage are also difficult to make in the higher risk older, white nonepilepsy population.

Anaphylactic reaction/Angioedema

In the epilepsy all treated pool, there were no perampanel subjects who reported anaphylaxis, angioedema, bronchospasm, stridor, laryngeal oedema, laryngospasm, or throat tightness. Perampanel subjects reported the following TEAEs: hypersensitivity (8), drug hypersensitivity (1), urticaria (3), gingival swelling (4), eye swelling/eye oedema/eyelid oedema (5), face oedema/swelling face (4), and allergic oedema (1). None of these TEAEs were SAEs. There was one subject who discontinued due to face oedema (subject 231-1008-1002 with mild facial edema on Day 37 which resolved 3 days after discontinuing perampanel. No rash, fever, or dyspnea were reported).

Of the 9 perampanel subjects who reported hypersensitivity (8) and drug hypersensitivity (1), the actual verbatim terms for the adverse events mostly included allergies. The verbatim terms for these AEs were as follows: allergic reaction (unknown source), non-specific allergic reaction, increase of allergies, environmental allergies (2), allergies (2), allergy to air conditioner, erythromycin hypersensitivity (drug hypersensitivity). These TEAEs occurred after study day 330 except for “increased of allergies” (Day 11), “allergy to air conditioner” (Day 32), and “allergies” (Day 44). [Of note, in a subject (304-1601-4001) receiving placebo, the AE of drug hypersensitivity was reported as “allergic reaction to study med” which led to study discontinuation].

In the nonepilepsy all treated pool, there were no perampanel subjects who reported anaphylaxis, laryngospasm, stridor, swollen tongue, or drug hypersensitivity. Perampanel subjects reported bronchospasm (3) and angioedema (2) (described in more detail below). In the nonepilepsy DB pool, perampanel subjects reported the following TEAEs at similar frequencies as placebo subjects: bronchospasm (0 vs 1), eyelid oedema (0 vs 1), face oedema (2 vs 1), hypersensitivity (2 vs 1), lip oedema (1 vs 0), lip swelling (0 vs 1), swelling face (4 vs 0), and urticaria (1 vs 2, respectively). None of these TEAEs were SAEs or led to drug discontinuation.

Comment: The 2 perampanel subjects who experienced the TEAE of hypersensitivity reported the following verbatim terms: environmental allergies and allergic reaction one day after cellulitis due to insect bites. The narratives to the following subjects were provided in response to the Division’s request in a Safety Information Amendment dated July 16, 2012. None of these cases represent cases of anaphylaxis or angioedema due to perampanel with resolution of the events with continued perampanel exposure.

The following 3 subjects experienced the TEAE of bronchospasm:

Subject 218-2046-1002 developed bronchospasm on OLE study day 130 and was continued on perampanel with resolution of the event and without recurrence.

Subject 302-0496-0002 developed bronchospasm on study day 139, concurrent with bronchitis. Perampanel was continued without recurrence.

Subject 302-0570-0016 developed bronchospasm after ~2 months of perampanel in the OLE study (also occurred while receiving placebo in DB study). Perampanel was continued for 6 more months.

The following 2 subjects experienced the TEAE of angioedema:

Subject 227-1321-1002 with a past history of angioedema who developed angioedema on study day 180 while in the OLE study 228

Subject 309-0214-0006 who developed angioedema on study day 226 which resolved within 1 day while continuing to take perampanel. Four days later, perampanel was discontinued because of the reason "other" (comment: sponsor decision).

In the Phase 1 studies, two subjects who discontinued from the multiple-dose studies reported pharyngolaryngeal pain/tongue hemorrhage and swollen tongue. The narratives are summarized below. The limited information provided in these narratives prevents definitive conclusions to be made regarding the causal association with perampanel exposure, although a role for perampanel cannot be ruled out.

Subject 013-1001-0021, a 40 year-old white female who experienced balance disorder and ataxia. She received perampanel 6 mg for 7 days, then 8 mg and 10 mg and 12 mg for 1 day each. While on 6 mg, the subject experienced balance disorder and dizziness. While on 8 mg, the subject experienced headache, paresthesia, and nasal congestion. While taking 10 mg, the subject experienced cold sweat, emotional disorder, dysarthria, and feeling drunk. While on 12 mg, the subject experienced chest pain, dyspnea, feeling hot, pharyngolaryngeal pain, tongue hemorrhage, increased respiratory rate, and rhinorrhea. On Study Day 11, perampanel was discontinued.

Subject 013-1001-0350, a 19 year-old white female who received 4 days of 6 mg of perampanel. The subject experienced nausea, vomiting, and retching along with sore throat, swollen glands, dizziness, epigastric tenderness, abdominal pain, and swollen tongue. No further information was reported in the narrative.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

There were no perampanel subjects with TEAEs coded to the MedDRA PTs, Drug rash with eosinophilia and systemic symptoms, hypereosinophilic syndrome, serum sickness, or pseudolymphoma. The 2 subjects (1 perampanel and 1 placebo subject) with the PT drug hypersensitivity were described earlier in this Section.

In response to the Division's information request, the Sponsor conducted a review of the entire perampanel database for subjects who met the search criteria for Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) using an extensive list of MedDRA PTs. Specifically, the search used the following European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) Project criteria for DRESS¹⁵:

Reaction suspected to be drug related with at least 3 of the following:

1. Acute skin rash
2. Involvement of at least one internal organ
3. Enlarged lymph nodes
4. One of the following blood count abnormalities (lymphocytes > or < than the lab limits, eosinophils > than the lab limits in % or absolute count, platelets < lab limits)
5. Fever above 38°Celsius

15 The European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) Project website: Drug Reaction with Eosinophilia and Systemic Symptoms <http://regiscar.uni-freiburg.de/diseases/dress/index.html> Accessed July 27, 2012.

To be certain of temporal proximity for the onset of an AE, the Sponsor set a window of 30 days and only those events that occurred within 30 days of each other were considered valid. This window was also limited to the period during which the subject was receiving treatment (i.e., treatment-emergent). The onset day of an AE was considered Day 1 of the 30 day window. This programmatic search initially identified a total of 6 subjects (2 placebo, 4 perampanel) as possible cases of DRESS. Each of the 6 possible cases was then further reviewed by the Sponsor, and 3 subjects were identified who met the specified criteria for DRESS.

Comment: I reviewed the narratives for the 6 subjects along with an independent review of each of the subject's laboratory and vital sign parameters. Although some of these subjects may have had more than 3 of the DRESS criteria listed above, it is unlikely that any of these subjects are true cases of DRESS. From the limited information provided in these narratives, there are no definite cases of DRESS associated with perampanel use.

Table 107. Perampanel Subjects Identified in the Search for DRESS

Subject #	Age, Sex, Race	Study: Treatment, Dose	AE PTs identified in FDA DRESS PT list	Lab abnormalities that fit the FDA DRESS criteria
Subjects who met the specified criteria for DRESS:				
0766-0025	33, M, A	309: Pera 2 mg	Pyrexia Rash Urticaria	Baseline high eosinophil count 2.5×10^9 (ULN 0.8×10^9) and high bilirubin 20.7 $\mu\text{mol/L}$ (reference 1.7-18.8)
Subject with a history of Parkinson's disease who developed pyrexia on DB Day 83 while on perampanel 2 mg. Treatment included paracetamol and the event resolved the next day. On Day 85, the subject experienced a skin rash over his left thigh (mild in severity). Treatment included topical ketoconazole and oral albendazole (antihelmintic). Perampanel was continued. The rash resolved a month later prior to completing the study. At baseline and during the study, both eosinophil and bilirubin values were elevated (no elevation of AST/ALT). Concomitant medications included pramipexole and carbidopa/levodopa.				
0021-0019	36, M, W	DB 206: Pera 3 mg	Hypersensitivity Rash Decreased lymphocytes	Low lymphocytes 810 cells/ mm^3 (reference 1000-4000)
Subject with a history of epilepsy who developed an increase of "allergies" (coded as hypersensitivity) in DB Day 11 while on 1 mg of perampanel. Treatment included diphenhydramine and the event resolved the next day. On Day 15, low values for lymphocytes were reported (810 cells/ mm^3). Perampanel was continued. Lymphocytes returned to normal by the next measurement on Day 29 (1160 cells/ mm^3). On Day 37, while on 3 mg of perampanel during the titration phase, the subject experienced a rash (moderate in severity). No treatment was reported. Perampanel was discontinued and the rash resolved the following day. There was no evidence of eosinophilia, transaminitis, or pyrexia. Concomitant medications included carbamazepine, glycopyrronium, and omeprazole.				

1007-4015	34, M, W	DB 304: Placebo	Lymphocytopenia Fever Testicular dermatitis	Low lymphocytes 1.0×10^9 (reference $1.02-3.36 \times 10^9$)
Subject with a history of complex partial seizures who developed low lymphocytes levels (1.01×10^9) on Study Day 43 while on placebo. The next day, the subject experienced dermatitis and then pyrexia (temperature not reported). Treatment included ibuprofen and topical econazole. The events of pyrexia and dermatitis resolved. The subject entered the OLE Study 307 on Study Day 133 and was started on perampanel. Lymphocytes continued to be low. However, there were no recurrences of dermatitis or pyrexia. Concomitant medications included topiramate, oxcarbazepine, and clobazam.				
Subjects identified in initial screen but were not considered cases of DRESS by the Sponsor:				
4702-6003	45, F, A	DB 306: Pera 8 mg	Seborrheic dermatitis Eosinophil ct increased	High eosinophil ct 0.59×10^9 (reference 0-0.56)
This subject did not meet at least 3 criteria (met more than one criterion as a result of the same event of eosinophilia as a TEAE and a laboratory abnormality).				
0001-0007	42, M, B	008: Pera 2 mg	Rash Thrombocytopenia	Low platelet count 133×10^9 (reference 140-440)
This subject did not meet at least 3 criteria (met more than one criterion as a result of the same event of thrombocytopenia as a TEAE and a laboratory abnormality).				
0187-0004	70, M, W	DB 301: placebo	Fever Dermatitis diaper Lymphopenia	Low lymphocyte 9.3% (reference 15.4-48.5%)
This subject met at least 3 criteria. However, the Sponsor concluded that this subject did not meet the criteria for DRESS because the absolute lymphocyte count was normal at 1.50 (reference $0.8-3.0 \times 10^9$ cells/L). (However, the RegiSCAR criteria states that either the % or absolute count can be used for blood count abnormalities).				

Source: Created by the reviewer using narratives provided by the Sponsor and review of ADLB, ADAE, ADVS datasets.

7.3.5.3 Cardiac Disorders

In addition to the SOC Cardiac disorders, the following MedDRA SOCs contain terms relevant to cardiac adverse events: Investigations (cardiac lab/vitals/ECG abnormalities) and Nervous system disorders (syncope and loss of consciousness). The following table summarizes the cardiac-related TEAEs experienced by perampanel and placebo subjects. In both the epilepsy Phase 3 DB and nonepilepsy DB pools, a lower percentage of perampanel subjects than placebo experienced cardiac-related TEAEs. In the epilepsy all treated pool, one perampanel subject died due to cardiac arrest (discussed in Section 7.3.1). Perampanel subjects in the nonepilepsy all treated pool had a higher incidence of death, SAEs, discontinuations, and TEAEs than the epilepsy all treated pool. This is likely due to the older population (mean age 62.3 years vs 35.6 years) with more comorbidities (see Section 7.2.1.2 Demographics).

Table 108. Summary of Cardiac-related TEAEs, SAEs, DCs

Cardiac-related TEAEs	Epilepsy Phase 3 DB Pool		Nonepilepsy DB Pool	
	Placebo	Perampanel	Placebo	Perampanel
	n=442	n=1038	n=1079	n=2013
Deaths	0	0	4 (0.4)	5 (0.2)
SAEs	0	0	12 (1.0)	18 (0.9)
Discontinuations (DCs)	0	2 (0.2)	12 (1.0)	20 (1.0)
TEAEs	13 (2.9)	26 (2.5)	59 (5.5)	106 (5.3)
	Epilepsy All Treated Pool		Nonepilepsy All Treated	
	n=1651		n=2717	
Deaths	1 (0.1)		9 (0.3)	
SAEs	12 (0.7)*		47 (1.7)	
Discontinuations (DCs)	9 (0.5)		34 (1.3)	
TEAEs	97 (5.9)		202 (7.4)	

Source: ISS Table 153, 158, 159 and 120-day Safety Update Table 26

*These subjects are described in more detail later in this section.

In the epilepsy Phase 2 DB pool, there was also a lower incidence of cardiac TEAEs in the total perampanel group (1.3%) than placebo (2.9%) (ISS Table 154). None occurred in more than 1 subject. There were no cardiac deaths, SAEs, or events that led to discontinuation of treatment (ISS Tables 115, 20.7-9, 20.8-16).

The following 2 tables provide a closer look at the TEAEs that were experienced by at least 2 perampanel subjects and greater than placebo in both the epilepsy Phase 3 DB pool and nonepilepsy DB pool. The MedDRA HLT and HLGs are provided for each of the cardiac PTs. Furthermore, I performed an analysis of cardiac SMQs and report the SMQs that had a higher percentage of perampanel subjects than placebo.

Table 109. Cardiac-related TEAEs in ≥ 2 Perampanel Subjects > Placebo, Epilepsy Phase 3 DB Pool

Epilepsy Phase 3 DB	Placebo	Perampanel
	n = 442	n = 1038
SOC Cardiac disorders	10 (2.3)	18 (1.7)
HLGT Coronary artery disorders		
HLT Ischaemic coronary artery disorders		
PT Angina pectoris	0	2 (0.2)
HLT Rate and rhythm disorders NEC		
PT Tachycardia	1 (0.2)	4 (0.4)
SOC Investigations		
PT Electrocardiogram QT prolonged	0	3 (0.3)
SOC Nervous system disorders		
PT Syncope	0	3 (0.3)
SMQ Ischaemic heart disease – broad	7 (1.6)	21 (2.0)
Ischaemic heart disease – narrow	0	2 (0.2)
SMQ Cardiac failure – broad	2 (0.5)	14 (1.4)
SMQ Torsade/QT prolongation – broad*	0	6 (0.6)
Torsade/QT prolongation – narrow*	0	3 (0.3)

Source: ISS Table 20.5-2

SMQ analysis performed by reviewer using MAED (MedDRA-based Adverse Event Diagnostic) service.

*Broad SMQ includes the 3 electrocardiogram QT prolonged and 3 syncope (narrow SMQ) PTs. (Specifically there were no ECGs in the database that revealed torsades de pointes).

In the epilepsy Phase 3 DB pool, there were only 4 cardiac PTs identified (that occurred in ≥ 2 perampanel subjects and >placebo). These PTs each occurred in very few perampanel subjects (<0.5%). The 2 narrow SMQs (ischaemic heart disease and QT prolongation) with a higher percentage of perampanel subjects than placebo correlate with some of the 4 PTs (angina pectoris and ECG QT prolonged). Again, these narrow SMQs represent very few perampanel subjects (<0.5%).

There were 3 cases of electrocardiogram QT prolonged. None of these events were SAEs. One subject was withdrawn from the study (narrative described below). I reviewed the ECG parameters for the other 2 subjects who had only minimal increases in QTcF. One subject had one single value of QTcF=451 msec, a change of 33 msec from baseline. The other subject had a borderline value of QTcF=441 msec, a change of only 14 msec from baseline.

Syncope was experienced in 3 perampanel subjects (vs 0 placebo) while no subjects experienced loss of consciousness. The verbatim terms for these 3 events were vasovagal syncope, fainted, and fainting. None of these events were SAEs or resulted in discontinuations. Conversely, in nonepilepsy DB pool, syncope was experienced in a lower percentage of perampanel subjects (0.6%) than placebo (0.8%). Syncope was an SAEs in the same percentage of perampanel (0.1%) and placebo subjects (0.1%). Loss of consciousness was also experienced at the same frequency (0.1% vs 0.1%).

Table 110. Cardiac-related TEAEs in ≥ 2 Perampanel Subjects > Placebo, Nonepilepsy DB Pool

Nonepilepsy Double-blind Pool	Placebo n = 1079	Perampanel n = 2013
SOC Cardiac disorders	46 (4.3)	86 (4.3)
HLGT Cardiac arrhythmias		
HLT Cardiac conduction disorders		
PT Atrioventricular block first degree	3 (0.3)	9 (0.4)
PT Atrioventricular block	0	2 (0.1)
PT Bundle branch block left	0	2 (0.1)
HLT Supraventricular arrhythmias		
PT Sinus bradycardia	2 (0.2)	8 (0.4)
PT Supraventricular extrasystoles	0	3 (0.1)
PT Sinus tachycardia	0	2 (0.1)
HLT Rate and rhythm disorders NEC		
PT Tachycardia paroxysmal	0	2 (0.1)
HLT Ventricular arrhythmias/cardiac arrest		
PT Ventricular extrasystoles	0	5 (0.2)
SOC Investigations		
PT Electrocardiogram QT prolonged	7 (0.6)	15 (0.7)
PT Electrocardiogram abnormal	2 (0.2)	7 (0.3)
PT Blood pressure systolic increased	0	2 (0.1)
PT Cardiac murmur	0	2 (0.1)
SMQ Cardiac arrhythmias – broad	49 (4.5)	101 (5.0)
Cardiac arrhythmias – narrow	24 (2.2)	58 (2.9)
SMQ Torsade/QT prolongation – narrow*	7 (0.7)	15 (0.8)

Source: ISS Table 20.5-54

SMQ analysis performed by reviewer using MAED (MedDRA-based Adverse Event Diagnostic) service.

*Specifically there were no ECGs in the database that revealed torsades de pointes.

In the nonepilepsy DB pool, perampanel subjects experienced more TEAEs in the HLGT cardiac arrhythmias than placebo. The 2 narrow SMQs (cardiac arrhythmias and QT prolongation) with a slightly higher percentage of perampanel subjects than placebo correlate with these PTs. Looking more closely at these arrhythmia PTs, they are disparate events with both conduction disorders and supraventricular arrhythmias (with both bradycardia and tachycardia) with rare ventricular extrasystoles.

In terms of ventricular proarrhythmias, there were notably no TEAEs coded to the PTs ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia, ventricular tachycardia, or torsade de pointes. One perampanel subject experienced the TEAE ventricular arrhythmia (narrative was provided by the Sponsor on 7/27/12 in response to the Division's information request).

Subject 206-0016-0075 was reported to have ventricular arrhythmia on Day 60 while on 4 mg of perampanel. No ECG was reported. Two prior ECGs were read as "abnormal" (with normal QTc intervals) while 7 prior ECGs were reportedly normal. The event was considered moderate and treatment included metoprolol. Perampanel was continued until the end of the study, 7 days later.

It is difficult to make any conclusions regarding this case as the ECG results for Day 60 were not reported. However, it is reassuring that all of the prior ECGs had normal QTc intervals.

None of these TEAEs (ventricular extrasystoles, ventricular arrhythmia) were SAEs. One subject with the TEAE ventricular extrasystole withdrew from the study.

Subject 302-0424-0001 with a history of HTN and atrioventricular block who developed ventricular extrasystole 15 days after first exposure to study drug which resolved 19 days later without any treatment recorded.

The reported term for this AE was “increased ventricular premature beats” which occurred on Study Day 168 according to the nonepilepsy ADAE dataset. PVCs are common and were not likely due to perampanel.

The following table summarizes the cardiac SAEs (in SOCs Cardiac disorders, Investigations, Vascular disorders) that occurred in at least 2 perampanel subjects and greater than placebo. There was only 1 subject with a cardiac SAE in the epilepsy Phase 2 and Phase 3 DB pools (aortic stenosis in the Vascular disorders SOC, see narrative below). There were 2 perampanel subjects who discontinued due to tachycardia (1) and electrocardiogram QT prolonged (1, see narrative below).

Subject 305-2904-5004, a 47-year-old female with no relevant medical history was assigned to the 8 mg/d group and completed the double blind treatment phase on Day 99. On Day 100, an ECG revealed a QTcF of 462 msec (an increase of 34 msec from baseline value of 428 msec). Repeat ECGs performed on the same day had a QTcF value of 442 msec. The subject was withdrawn from the study because of this event.

The prolonged QT interval was likely due to normal variation and unlikely related to perampanel as the QTcF value on the repeat ECG on the same was lower and only 14 msec above baseline.

In the nonepilepsy DB pool, perampanel subjects (0.8%) had a lower frequency of cardiac SAEs than placebo (1.0%). Furthermore, all of the ischemia-related PTs (coronary artery disease, myocardial infarction, and acute myocardial infarction) occurred less frequently in the perampanel group than placebo.

Table 111. Cardiac-related SAEs Occurring in at Least 2 Subjects > Placebo

MedDRA System Organ Class Preferred Term	Placebo	Perampanel
Epilepsy DB (Phase 3 + Phase 2)	n = 510	n = 1189
Cardiac disorders	0	0
Nonepilepsy Double-blind Pool	n = 1079	n = 2013
Cardiac disorders	11 (1.0)	17 (0.8)
Atrial fibrillation	0	4 (0.2)
Cardiac failure	0	2 (0.1)
Cardiac failure congestive	0	2 (0.1)
Tachycardia	0	2 (0.1)

Source: ISS Tables 20.7-1 and 20.7-15

In the Phase 1 single-dose studies, a lower percentage of perampanel subjects (0.4%) experienced cardiac TEAEs than placebo (0.7%) (ISS Table 22.4-9). However, for the multiple dose studies, the incidence was higher in the total perampanel group (3.2%) than in the placebo group (0%). Events that occurred in 2 or more subjects included

palpitations (n=4), cyanosis (n=2), heart rate increased (n=2), and tachycardia (n=2). While none of these 4 TEAEs were SAEs, 1 perampanel subject experienced the SAE of loss of consciousness (due to head trauma, narrative described in Section 7.3.2). Narratives for the 2 subjects who reported cyanosis were provided by the Sponsor (7/27/12) in response to the Division's information request.

Subject 026-1001-1005 developed cyanosis prior to study drug administration.

Subject 026-1001-1006 developed cyanosis immediately after the recording of EEG and after the measurement of saccadic eye movement. Both events resolved within 10 minutes and perampanel was continued.

These events were unlikely related to perampanel as they occurred prior to treatment or during likely vasovagal episodes.

There was 1 discontinuations due to the TEAE, electrocardiogram QT prolonged:

Subject 023-1001-9025, 33 yo Asian female with a history of recent use of LSD, cannabinoids, valium, and opioids who experienced prolonged QT at 23.5 hours after receiving perampanel 8 mg. Baseline QTc = 449 msec and at 23.5 hours, QTc=486 msec (change of 37 msec). Perampanel was withdrawn due to this AE. The next day, QTc was measured at 407 msec and 414 msec. One month later, QTc was measured at 443 msec.

This case is confounded by the use of both recreational substances and arrhythmogenic medications and therefore it is difficult to make any conclusions regarding the role of perampanel.

For both of the all treated pools, a dose response was not observed for cardiac events (see following table).

Table 112. Cardiac TEAEs, All Treated Pools

Category	Perampanel n (%)				
	<4 mg	4 mg	>4-8 mg	>8-12mg	Total
Epilepsy All Treated Pool	153	192	354	952	1651
Modal dose groups	5 (3.3)	11 (5.7)	22 (6.2)	59 (6.2)	97 (5.9)
Nonepilepsy All Treated Pool	1048	1441	188	40	2717
Modal dose groups	64 (6.1)	122 (8.5)	14 (7.4)	2 (5.0)	202 (7.4)

Source: ISS Table 20.9-72 and 120-day Update Table 20.9-165.1

In the epilepsy OLE studies, there were no cardiac SAEs experienced by more than 2 perampanel subjects. There were only 2 SAE events experienced by more than 1 perampanel subject (2 angina pectoris and 2 atrial fibrillation). The SAEs due to arrhythmias were either supraventricular (1 atrial fibrillation, 1 atrial flutter, 1 sick sinus syndrome) or bradycardic (1 bradycardia, 1 atrioventricular dissociation). There were no events of ventricular arrhythmias. The following table summarizes the narratives of these SAEs.

In the nonepilepsy all treated pool, the SAEs due to arrhythmias were mainly supraventricular (10 atrial fibrillation, 2 atrial flutter, 1 supraventricular tachycardia, 1 sick sinus syndrome) or tachycardic/bradycardic (1 tachycardia paroxysmal, 3 tachycardia 1 bradycardia, 1 arrhythmia). The one sudden cardiac death occurred in a 61-year old subject with prior cardiac history (coronary artery disease with previous coronary bypass surgery, hypertension, hypercholesterolemia). The narratives for the 5

perampanel subjects with the SAE of syncope were reviewed and revealed etiologies that were not due to arrhythmias (orthostatic hypotension, dehydration, hypertension, bowel obstruction, and infection).

Table 113. Cardiac-related SAEs, Epilepsy All Treated Pool

Subject #	Age, Sex, Race	Study: Treatment, Dose	Adverse event (Preferred Term)	Study day (with DB)	Phase of Study
0009-0176	48, F, W	DB 206: Pera 1 mg OLE 207: Pera 12 mg	Cardiac arrest	OLE 705 (797)	Maintenance
Death – please see narrative in Section 7.3.1					
1007-4011	24, M, W	DB 304: Pera 8 mg OLE 307: Pera 8 mg	Cardiac failure	OLE 512 (645)	Maintenance
Subject with a history of Down's syndrome, pulmonary hypertension, aortic valve disease, pneumonia who experienced cardiac failure during an episode of pneumonia and influenza. Treated with levofloxacin, oseltamivir, hydrocortisone, and furosemide. Resolved 7 days later. Study drug was continued. <i>The cardiac failure was likely a result of pneumonia rather than perampanel use.</i>					
5114-4007	56, M, W	DB 304: Pera 8 mg OLE 307: Pera 12 mg	Myocardial infarction	OLE 425 (558)	Maintenance
Subject with a history of brain lobectomy, hypervitaminosis, and osteopenia who experienced chest pain with diaphoresis and mild nausea on OLE Day 425. EKG was reported as having nonspecific ST/T wave changes. Labs reportedly revealed an increased troponin of 0.83 (units not reported) and CK-MB (result not reported). Coronary angiography revealed 100% blockage of the right coronary artery and 70% blockage of the left circumflex artery. A stent was placed in the right coronary artery. The subject experienced an inferior wall myocardial infarction with significant elevation of troponin I and CPK. A repeat coronary angiogram was performed with a stent placement in the left circumflex artery. The event of myocardial infarction resolved within 4 days on Day 429. Study drug was continued until OLE Day 751 when the subject was discontinued from the study because of inadequate therapeutic effect. Baseline BMI = 24.7 kg/m ² . Baseline BP = 144/77. Baseline total cholesterol was elevated at 6.4 mmol/L (normal range 3.37-5.18). <i>This patient had baseline risk factors for coronary artery disease (hypertension, hypercholesteremia, male, age>45). Therefore, it is difficult to ascertain perampanel's role in this case.</i>					
5139-4011	43, F, W	DB 304: Pera 12 mg OLE 307: Pera 12 mg	Angina pectoris	OLE 262	Maintenance
Subject with a history of obesity, hyperlipidemia, hypertension, and asthma who experienced chest pain on OLE Day 262. EKG reportedly showed normal sinus rhythm with no acute ST-T wave changes. Myocardial perfusion scan reportedly showed a small focal area of reversible ischemia involving the anterior wall of the left ventricle with normal systolic function. Serial cardiac enzymes were reportedly negative. Subsequent coronary angiography reportedly revealed no abnormalities. The subject was medically managed and the study drug was continued (most recent dose of perampanel received on OLE Day 366). Baseline BMI = 42.7 kg/m ² . Baseline total cholesterol was elevated at 6.19 mmol/L. <i>The chest pain was unlikely related to perampanel (or to a cardiac etiology) as there were no recurrences while continued on perampanel.</i>					
1105-5008	62, M, W	DB 305: Pera 8 mg OLE 307: Pera 10 mg	Acute coronary syndrome	OLE 220	Maintenance
Subject with a history of myocardial infarction (x2), HTN, respiratory disorder, and brain abscess who developed chest pressure and dyspnea on OLE Day 220. The subject was diagnosed with acute coronary syndrome and was hospitalized. Coronary angiography was performed without stent					

<p>placement (results were not reported). Serial troponin T values were within the normal ranges. The subject was medically managed and the study drug was discontinued one day later (OLE Day 221) because of "inadequate therapeutic effect." ECG results from OLE Day 201 revealed a prolonged PR interval of 210. Baseline BMI = 24.3 kg/m² and BP = 121/80 mmHg. <i>This was unlikely related to perampanel use given the subject's prior history of myocardial infarctions.</i></p>					
2806-5011	62, M, W	DB 305: Pera 12 mg OLE 307: Pera 12 mg	Angina unstable	OLE 23	Maintenance
<p>Subject with a history of HTN, hypothyroidism, hyperlipidemia, and adjustment disorder who developed "crushing" chest pain. The subject was diagnosed with unstable angina and was hospitalized. Serial troponin tests were reportedly negative and ECG reportedly showed normal sinus rhythm without ischemic changes. The subject was medically managed and the study drug was continued (as of the data cut-off point). Baseline BMI = 24.7 kg/m². Screening/baseline BP was elevated at 158/87-170/82 mmHg. Baseline total cholesterol was elevated at 6.35 mmol/L. <i>The chest pain was unlikely related to perampanel (or to a cardiac etiology with negative ECG and troponins) as there were no recurrences while continued on perampanel.</i></p>					
5165-5001	43, F, W	DB 305: placebo OLE 307: Pera 10 mg	Bradycardia/ Sick sinus syndrome/ Hypotension	OLE 166	Maintenance
<p>Subject with a history of a vagal nerve stimulator implantation and cocaine abuse experienced a complex partial seizure and was hospitalized on OLE Day 166. While in the emergency room, during another seizure, the subject became bradycardic. A permanent pacemaker was implanted due to bradycardia and sick sinus syndrome. The subject was also noted to be mildly hypotensive. The study drug was continued until OLE Day 198 when the subject discontinued from the study because of the event of drug abuse (cocaine use). Baseline BMI = 22.3 kg/m² and BP = 98/62-100/62. <i>The bradycardia and sick sinus syndrome were likely due to seizures and recreational drug use and unlikely due to perampanel.</i></p>					
5167-5008	64, M, W	DB 305: placebo OLE 307: Pera 10 mg	Angina pectoris/ Heart rate irregular/ Coronary artery stenosis	OLE 66/71/83	Conversion
<p>Subject with a history of mental retardation, cerebral palsy, and right bundle branch block who experienced angina pectoris on OLE Day 66. Treatment was not reported and the subject was continued in the study. Five days later, the subject experienced an irregular heart rate which was discovered during a visit with the primary medical doctor who scheduled a coronary angiogram. The angiogram revealed a >80% stenosis of the right posterior descending artery. A stent was placed. The study drug was continued until Day 203 when the subject discontinued from the study because of subject choice and inadequate therapeutic effect. Baseline BMI = 22.0 kg/m² and BP = 124/80. <i>It is difficult to ascertain perampanel's role in this case that lacks many details such as the specific ECG findings for the irregular heart rate. The coronary artery stenosis was unlikely due to perampanel with only 2 months' exposure to perampanel. It is reassuring that there no recurrences of these events while perampanel was continued until Day 203.</i></p>					
5204-5001	63, F, W	DB 305: Pera 8 mg OLE307: Pera 8 mg	Atrial fibrillation	OLE 209 (343)	Maintenance
<p>Subject with a history of hyperthyroidism, hypothyroidism, and paroxysmal hypertension who experienced atrial fibrillation on OLE Day 209 (previous events of atrial fibrillation were noted during the DB study). A cardiologist treated the subject with metoprolol and warfarin. The study drug dose was reduced. On OLE Day 218 the subject experienced a seizure and bradycardia (to 35 bpm). Atropine was administered and metoprolol was discontinued. The event of atrial fibrillation and bradycardia resolved and the study drug was continued until OLE Day 279. Baseline BMI = 30.1 kg/m². Baseline BP = 120/75 with intermittent increases to 140/60-160/75 (BP = 110/66 at the end of the study).</p>					

<i>It is difficult to ascertain perampanel's role in this case of atrial fibrillation. The case is confounded by a prior history of hyperthyroidism. It is reassuring that there were no recurrences while perampanel was continued until Day 279.</i>					
1505-6004	65, M, W	DB 306: Pera 2 mg OLE 307: Pera 10 mg	Cardiovascular insufficiency	OLE 578	Maintenance
Subject without any cardiac history who was hospitalized with severe pneumonia on OLE Day 578 and also diagnosed with cardiovascular insufficiency. The study drug was discontinued. <i>The cardiovascular insufficiency was likely due to the severe pneumonia rather than perampanel use.</i>					
2102-6004	38, M, W	DB 306: placebo OLE 307: Pera 12 mg	Atrial fibrillation/flutter	OLE 476	Maintenance
Subject with a history of psoriasis who experienced fatigue, elevated body temperature, "heavy feeling in the chest," and a "fast heartbeat" on OLE Day 476. The subject was hospitalized and developed atrial flutter at a rate of 250 bpm. The subject underwent a successful radio-frequency catheter ablation. The study drug was discontinued. Chest xray revealed bilateral lower lobe pneumonia. Baseline BMI = 34.5 kg/m ² and BP =125/80 mmHg. <i>This is unlikely related to perampanel as the atrial flutter developed only after prolonged exposure to perampanel (476 days).</i>					
2757-6004	50, F, A	DB 306: Pera 2 mg OLE 307: Pera 8 mg	Atrioventricular dissociation/ Hypertrophic CM	OLE 89 (223)	Maintenance
Subject with a history of asymptomatic sinus bradycardia who was hospitalized on OLE Day 89 for further workup of ECGs during the study that showed persistent bradycardia. An echocardiogram reportedly revealed evidence of a hypertrophic band resulting in tricuspid regurgitation and outflow obstruction. A cardiac stress test was positive for stress-induced myocardial ischemia and revealed atrioventricular-dissociation rhythm with sinus bradycardia. The subject was diagnosed with hypertrophic subaortic stenosis and intermittent atrioventricular dissociation. The subject was medically managed and the study drug was continued (as of the data-cut off point). One ECG on OLE Day 84 revealed an abnormal QTcF of 453 msec (screening QTcF = 450). Baseline BMI = 22.1 kg/m ² .					
1202-6003	68, M, W	DB 306: Pera 8 mg	Aortic stenosis (SOC Vascular disorders)	DB 41	Maintenance
Subject with a history of HTN, hypercholesterolemia, type 2 diabetes, and first degree AV block who was diagnosed with aortic stenosis by echocardiogram (mean gradient 68 mmHg). The subject was medically managed and the subject completed the study, receiving his last dose of perampanel on Study Day 133. <i>This is unlikely related to perampanel as the aortic stenosis was discovered too soon after perampanel initiation (Day 41).</i>					
2602-6002	48, F, W	DB 306: placebo OLE 307: Pera 12 mg	Hypertension	OLE 166	Maintenance
Subject with a history of hyperglycemia, anxiety/depression, and meningitis who was hospitalized for the event of hypertension on OLE Day 166. BP values not reported for this hospitalization. Subject was treated with perindopril 2 mg daily. Hypertension resolved and the subject was continued in the study until OLE Day 350 when she discontinued due to the event of paranoia. Baseline BMI = 31.2 kg/m ² . Baseline BP was elevated at 150/90 mmHg. Baseline total cholesterol and glucose were also elevated at 6.32 mmol/L and 8.5 mmol/L (normal range 3.6-7.7), respectively. <i>The hypertension was unlikely related to perampanel given the subject's elevated blood pressure at baseline and resolution of the event of hypertension while continued on perampanel.</i>					

5139-4006	45, M, W	DB 304: placebo OLE 307: Pera 12 mg	Syncope	OLE 712	Maintenance
<p>Subject with a history of anaplastic astrocytoma s/p chemotherapy, radiation therapy who experienced a syncopal episode on OLE Day 712. The subject accidentally ran into a wall and hit his head. Subsequently the subject became dizzy and was taken to the emergency room. While in the ER, the subject became diaphoretic with decreased BP and HR. The subject lost consciousness. A head CT was negative for any acute changes. Treatment included intravenous fluids. The event resolved that same day. The study drug was restarted the following day and the subject continued in the study.</p> <p><i>The syncopal episode was likely related to head trauma rather than perampanel use.</i></p>					

Source: Created by the reviewer using subject narratives and ISS ADLB and ADVS datasets.

Additionally, a cardiology consult was requested to review OLE Study 228 which revealed after 12 months of treatment a mean change from baseline of QTcF of 12.6 msec in the highest dose group (>8-12 mg/day). The review by Dr. Mónica Fizman dated July 27, 2012 from the Division of Cardiology and Renal Products QT Interdisciplinary Review Team concluded that it is unlikely that changes from baseline of QTc reported in study 228 are a QT signal for the following reasons:

- In the TQT study reviewed by QT-IRT, QTcF did not exceed the threshold of regulatory concern after a 12-mg dose.
- The 12-mg dose was tested during perampanel clinical program and data obtained from ECG monitoring in controlled trials in patients with epilepsy, Parkinson's disease and neuropathic pain do not show clinically relevant mean QTc values (i.e., QTcF > 500 ms).
- Incidence of TEAEs of concern as per ICH E14 Guidance did not differ significantly from placebo arms and no dose-dependent trend in QTc prolongation was observed in any of the studies.
- It is more likely that results from study 228 are related to variability/changes within the studied population (i.e., disease outcome, concomitant medication, etc.) difficult to elucidate without a comparator group.

In conclusion, although there were differences in cardiac TEAEs seen in perampanel subjects compared to placebo subjects, these differences were small and difficult to attribute to perampanel. The cardiac events in the OLE studies (particularly the nonepilepsy population with prior cardiac history) are difficult to interpret without a placebo group to compare. Furthermore, most of the cardiac SAEs in the epilepsy OLE studies were not related to perampanel use.

7.3.5.4 Other Organ Systems

Renal and Urinary Disorders

In the epilepsy Phase 3 and nonepilepsy DB pools, a similar percentage of perampanel subjects as placebo experienced TEAEs in the SOC Renal and Urinary disorders. Notably, there were no AEs of acute renal failure in perampanel subjects in the epilepsy all treated pool (one acute renal failure occurred in a placebo subject in the prandomization phase).

Table 114. TEAEs in SOC Renal and Urinary Disorders in ≥ 2 Perampanel Subjects and >Placebo

	Placebo	Perampanel
Epilepsy Phase 3 DB Pool	n = 442	n = 1038
SOC Renal and Urinary disorders	5 (1.1)	19 (1.8)
Pollakiuria	0	4 (0.4)
Haematuria	1 (0.2)	3 (0.3)
Enuresis	0	2 (0.2)
Nephrolithiasis	0	2 (0.2)
Nonepilepsy DB Pool	n = 1079	n = 2013
SOC Renal and Urinary disorders	34 (3.2)	55 (2.7)
Pollakiuria	4 (0.4)	11 (0.5)
Urinary incontinence	3 (0.3)	11 (0.5)
Haematuria	3 (0.3)	9 (0.4)
Proteinuria	2 (0.2)	7 (0.3)
Diabetic nephropathy	0	2 (0.1)
Neurogenic bladder	0	2 (0.1)
Renal failure acute	0	2 (0.1)
[Nephrolithiasis]	[3 (0.3)]	[2 (0.1)]

Source: ISS Tables 20.5-28, 20.5-54

The following table summarizes the SAEs in the SOC Renal and Urinary disorders occurring in perampanel subjects greater than placebo. There were very few SAEs occurring in this SOC in perampanel subjects.

Table 115. SAEs in Renal and Urinary Disorders SOC Occurring in Perampanel Subjects > Placebo

MedDRA System Organ Class Preferred Term	Placebo	Perampanel
Epilepsy Phase 3 DB Pool	n = 442	n = 1038
SOC Renal and Urinary disorders	0	3 (0.3)
Cystitis Haemorrhagic	0	1 (0.1)
Nephrolithiasis	0	1 (0.1)
Urinary Incontinence	0	1 (0.1)
Nonepilepsy Double-blind Pool	n = 1079	n = 2013
SOC Renal and Urinary disorders	4 (0.4)	4 (0.2)
Renal failure acute	0	2 (0.1)
Diabetic nephropathy	0	1 (0.0)
Haematuria	0	1 (0.0)
Nephrolithiasis	0	1 (0.0)
Urinary retention	0	1 (0.0)

Source: ISS Tables 20.7-1 and 20.7-15

There were no SAEs or discontinuation TEAEs in this SOC in the epilepsy Phase 2 pool or the Phase 1 studies. The TEAE of blood creatinine increased was not considered an SAE in the entire database.

In the epilepsy all treated pool, there were 3 subjects with the SAE of nephrolithiasis (one subject with a prior history of nephrolithiasis). In nonepilepsy all treated pool, 2 subjects experienced the SAE of nephrolithiasis (both subjects 309-0184-0002 and 302-0410-0003 with prior history). The following tables summarize the SAEs in the epilepsy and nonepilepsy all treated pools.

Table 116. SAEs in SOC Renal and Urinary Disorders, Epilepsy All Treated Pool

Subject #	Age, Sex, Race	Study: Treatment, Dose	Adverse event (Preferred Term)	Study day	Phase of Study
5118-4013	42, F, W	DB 304: Pera 8 mg OLE 307: Pera 12 mg	Nephrolithiasis	OLE 238	Maintenance
Subject with a history of anxiety/depression, right nephrectomy, and nephrolithiasis who was hospitalized for urinary tract infection and nephrolithiasis on OLE Day 238. Treatment included levofloxacin and hydromorphone. The subject passed the stones. Perampanel was continued. <i>This is unlikely related to perampanel given the patient's previous history of nephrolithiasis.</i>					
2904-5003	35, M, W	DB 305: Pera 8 mg OLE 307: Pera 6 mg	Nephrolithiasis	OLE 196	Maintenance
Subject without any medical history who experienced abdominal pain on OLE 196 and was hospitalized. The subject with diagnosed with gastritis, duodenal ulcer, and nephrolithiasis. Treatment included omeprazole. Perampanel was continued. <i>Perampanel's role in this case is unclear.</i>					
4402-6001	47, M, W	DB 306: Pera 2 mg	Nephrolithiasis	DB Day 4	Titration
Subject with a history of dermatitis who underwent a renal ultrasound which reportedly revealed right nephrolithiasis on Day 4. Perampanel was continued. Treatment included extracorporeal shock wave lithotripsy on Day 45. <i>This is unlikely related to perampanel as the nephrolithiasis developed too soon after initiation (Day 4).</i>					
2402-5015	61, F, W	DB 305: Pera 12 mg	Cystitis haemorrhagic	DB 17	Titration
Subject with a history of depression was hospitalized for cystitis hemorrhagic on Day 17. Treatment included distigmine and tamulosin. Perampanel was continued until day 43 when the subject was discontinued from the study because of dizziness and gait disturbance. Renal labs remain within normal limits. Concomitant medications included levetiracetam and oxcarbazepine. <i>This is unlikely related to perampanel as symptoms did not reoccur when perampanel was continued.</i>					
2402-5013	66, F, W	DB 305: Pera 12 mg	Urinary incontinence	DB 6	Titration
Subject with a history of gastritis who experienced status epilepticus on Day 6. The subject also had abdominal pain caused by an "overfull bladder" which was relieved with an indwelling catheter. The subject also developed constipation. Perampanel was discontinued. Constipation and urinary incontinence [more appropriately labeled as urinary retention] resolved. <i>This is unlikely related to perampanel and likely due to the event of status epilepticus.</i>					

Source: Created by the reviewer using narratives provided by the Sponsor

Table 117. Acute Renal Failure SAEs, Nonepilepsy All Treated Pool

Subject #	Age, Sex, Race	Study: Treatment, Dose	Adverse event (Preferred Term)	Study day
1320-1003	57, M, W	DB 227: Pera 4 mg	Renal failure acute	DB Day 88
<p>Subject with a history of diabetes mellitus and hypertension who experienced acute renal failure and was hospitalized on Study Day 88. Creatinine value increased to 2.17 mg/dL (normal potassium values). Baseline Cr = 1.35 mg/dL (reference 0.5-1.3). The renal failure reportedly resolved by the next day. <i>(However, in the ADLB dataset, repeat creatinine values remained elevated 20 days later at 1.48 mg/dL and 47 days later at 1.61 mg/dL).</i> The study drug was continued and the subject completed the study without any other events. No significant preceding TEAEs (tinea infection, peripheral edema, and bursitis). Vital signs remained within normal limits. Concomitant medications included hydrochlorothiazide, lisinopril, metformin, gabapentin, and topiramate.</p> <p><i>This is unlikely related to perampanel as the patient had an abnormal Cr value at baseline and the acute renal failure resolved within one day and did not reoccur when perampanel was continued.</i></p>				
1301-1002	67, M, W	DB 227: Pera 8 mg	Renal failure acute	DB Day 86
<p>Subject began experiencing the SAE of severe pancreatitis acute on Study Day 84 with severe diarrhea, nausea, and vomiting. Three days later, the subject began experiencing the SAEs of severe renal failure acute. Perampanel was discontinued. The subject died 2 months later.</p> <p><i>The acute renal failure was likely due to severe pancreatitis and unlikely related to perampanel.</i></p>				

Source: Created by the reviewer using narratives provided by the Sponsor

In conclusion, perampanel is not associated with any renal or urinary disorders in this database. Perampanel was not associated with an increase in TEAEs in the renal and urinary SOC. There were only rare SAEs with most cases unlikely related to perampanel. Furthermore, perampanel was not associated with an increase in renal laboratory parameters (creatinine PCS changes, mean changes, or shifts to high values) (see Section 7.4.2.2).

Endocrine disorders

A higher percentage of perampanel subjects than placebo developed thyroid-related disorders in the epilepsy DB pool. However, these findings are not replicated in the nonepilepsy DB pool. In the epilepsy all treated pool, 0.8% (n=14) perampanel subjects developed thyroid-related disorders: goitre (6), hypothyroidism (6), hyperthyroidism (1), thyroid neoplasm (1), thyroid neoplasm (1), and thyroid cancer (1). Five (36%, 5/14) of these subjects had a past history of thyroid disorders.

Table 118. Thyroid-related TEAEs, SOCs Endocrine Disorders and Neoplasms

MedDRA PT	Epilepsy DB Pool		Nonepilepsy DB Pool	
	Placebo	Perampanel	Placebo	Perampanel
All Subjects	510	1189	1079	2013
Goitre	0	2	2	1
Hyperthyroidism	0	1	2	3
Hypothyroidism	1	2	2	1
Thyroid mass	0	0	0	1
Thyroiditis	0	0	0	0
Thyroid neoplasm	0	0	1	1
Thyroid cancer	0	0	0	0
TOTAL SUBJECTS	1 (0.2)	5 (0.4)	6 (0.6)	6 (0.3)
	Epilepsy All Treated Pool		Nonepilepsy All Treated	
All Subjects	1651		2717	
Goitre	6		2	
Hyperthyroidism	1		4	
Hypothyroidism	6		1	
Thyroid mass	0		1	
Thyroiditis	0		1	
Thyroid neoplasm	1		2	
Thyroid cancer	1		0	
TOTAL SUBJECTS	14 (0.8)		10 (0.4)	

Source: ISS Tables 20.5-2, 20.5-28, 20.5-36, 20.5-54, 120-day Safety Update Table 20.5-75.1

The following table summarizes the narratives for the SAEs and discontinuations due to thyroid-related TEAEs in the Endocrine disorders and Neoplasm SOCs in the epilepsy and nonepilepsy all treated pools. Two of these subjects had a past history of thyroid disorders.

Table 119. Thyroid-related SAEs & DCs, Epilepsy & Nonepilepsy All Treated Pool

Subject #	Age, Sex, Race	Treatment, Dose	Adverse event	Study day
2454-6004	32, M, W	DB 306: Pera 4 mg OLE 307: Pera 12 mg	Goitre	OLE 212
Subject with a history of leukemia, intracranial hemorrhage, and meningioma, experienced a goiter on OLE Day 212. Subject was hospitalized and underwent surgical resection of the thyroid gland. Study drug was continued. <i>Perampanel's role in this case is unclear.</i>				
2454-6003	40, M, W	DB 306: Pera 2 mg	Goitre	DB 74
Subject with a history of hypertension and struma (1999) experienced a goiter on Study Day 74 (July 14, 2009). Subsequently on Day 86, the subject was hospitalized and underwent a radical strumectomy. <i>This is unlikely related to perampanel with the patient's previous history of struma.</i>				
0121-0003	61, F, W	DB 301: Pera 2 mg	Hyperthyroidism	DB 141
Subject with a history of "mild thyroideal hypertrophy" who experienced hyperthyroidism on Day 141. Treatment included carbimazole. Perampanel was discontinued on Day 174. Earlier in the study, the subject experienced allergic dermatitis and bradykinesia. <i>This is unlikely related to perampanel with the patient's previous history of thyroid abnormalities.</i>				
0466-0015	70, F, W	DB 302: Pera 2 mg OLE 303: Pera	Hyperthyroidism	OLE 96
Subject with a history of Parkinson's disease who experienced lethargy and momentarily unresponsive the morning of OLE Day 96. Subject was hospitalized with hyperthyroidism and urinary tract infection. TSH was reportedly low at 0.01. Neurology consult diagnosed the subject with having encephalopathy which may have been related to PD. Treatment included atenolol for hyperthyroidism and ciprofloxacin for urinary tract infection. Perampanel was discontinued on Day 95. <i>Perampanel's role in this case is unclear.</i>				
1305-5003	28, F, W	DB 305: placebo OLE 307: Pera 12 mg	Thyroid cancer (new diagnosis)	OLE 519

Source: Created by the reviewer using narratives provided by the Sponsor.

In conclusion, perampanel is not associated with thyroid disorders in this database. Although there was a small signal for thyroid-related disorders in the epilepsy DB pool, this was not replicated in the nonepilepsy DB pool. Furthermore, there were only rare SAEs and many subjects had previous history of thyroid disorders.

Gastrointestinal Disorders

In the epilepsy Phase 3 DB pool, in the SOC Gastrointestinal disorders, the TEAEs that occurred in >1% perampanel subjects and greater than placebo were nausea (5.2% vs 4.5%), toothache (1.4% vs 0.7%), and abdominal discomfort (1.1% vs 0.2%). There were 2 SAEs in perampanel subjects: nausea (1) and omental infarction (1). The following TEAEs that led to drug discontinuation occurred more frequently in perampanel subjects than placebo subjects: nausea (0.4% vs 0), vomiting (0.4% vs 0.2%), constipation (0.2% vs 0), abdominal pain (0.1% vs 0), and omental infarction (0.1% vs 0).

In the epilepsy Phase 2 DB pool, the TEAEs in this SOC that occurred in >1% perampanel subjects and greater than placebo were diarrhea (4.6% vs 4.4%), constipation (2.6% vs 0), and abdominal discomfort (1.3% vs 0). There were no SAEs. One perampanel subject discontinued due to dry mouth.

Comment: In the epilepsy OLE studies, there were young perampanel subjects who developed the SAEs of colitis, colitis collagenous, and ileitis (see summaries of narratives in the following table). However, there is a higher incidence of inflammatory bowel disease in ages 20-30 years old (bimodal age distribution) in the general population.

In the nonepilepsy DB pool, the TEAEs in this SOC that occurred in >1% perampanel subjects and greater than placebo were vomiting (2.0% vs 1.6%) and abdominal pain upper (1.2% vs 1.0%). There were no SAEs that occurred in more than 2 perampanel subjects and greater than placebo. The following TEAEs that led to drug discontinuation occurred more frequently in perampanel subjects than placebo subjects: nausea (0.5% vs 0.3%), vomiting (0.3% vs 0.2%), diarrhoea (0.3% vs 0.2%), and abdominal pain upper (0.2% vs 0.1%),

Table 120. Select SAEs in SOC GI Disorders, Epilepsy All Treated Pool

Subject #	Age, Sex, Race	Treatment, Dose	Adverse event	Study day	Phase
1604-4008	28, F, W	DB 304: Pera 8 mg OLE 307: Pera 8 mg	Colitis collagenous	OLE 114	Conversion
Subject with a history of psoriasis, asthma, anemia, and GERD experienced colitis collagenous on OLE Day 114. Treatment included mesalazine and domperidone. Perampanel was discontinued in response to this event. At the time of discontinuation from the study, the subject had rash as an ongoing adverse event. Eosinophils mildly elevated at $0.61 \times 10^9/L$ on DB Day 44 (screening value=0.5, ULN=0.56) <i>The colitis is unlikely related to perampanel as the subject has an extensive history of other autoimmune diseases.</i>					
2502-6006	37, M, Chinese	DB : placebo OLE 307: Pera 12 mg	Colitis	OLE 468	Maintenance
Subject with a history of encephalitis, carcinoma of testis, fatty liver who experience rectal bleeding and hospitalized. Colonoscopy revealed mucus in the colon with multiple patchy colitis changes with superficial erosions. Biopsy results revealed nonspecific ileitis, colitis, and proctitis. Stool cultures were negative. Treatment included mesalazine. Study drug was continued. <i>This is unlikely related to perampanel as the colitis occurred after prolonged exposure to perampanel (468 days) and perampanel was continued.</i>					
3003-1039	38, M, W	DB 208: Pera 6 mg OLE 207: Pera 12 mg	Ileitis	OLE 1500	Maintenance
Subject with a history of traumatic brain injury who experienced abdominal pain and diarrhea on OLE Day 1500. A computed tomography scan revealed ileitis. Treatment included levofloxacin and the event of ileitis resolved on OLE Day 1517. Perampanel was continued. <i>This is unlikely related to perampanel as the ileitis occurred after prolonged exposure to perampanel (1500 days) and resolved even with the continuation of perampanel.</i>					

5115-4002	42, M, W	DB 304: Pera 12 mg	Omental infarction	DB 33	Titration
<p>Subject with a history of occludent digital dysplasia syndrome, glaucoma, traumatic brain injury, GERD, PUD, BPH who developed abdominal pain, nausea, and vomiting on Day 20. Perampanel was discontinued. On Day 33, an exploratory laparotomy revealed omental infarction.</p> <p><i>Perampanel's role in this case is unclear. However, likely due to subject's previous history (?occludent digital dysplasia syndrome).</i></p>					
5162-5002	64, F, W	DB 305: Pera 8 mg OLE 307: Pera 12 mg	Colitis ischaemic	OLE 45	Conversion
<p>Subject with a history of hypercholesterolemia and asthma who experienced a fall and an ankle fracture on OLE Day 19. While awaiting surgical repair, the subject sustained an ankle infection and developed septic shock. Perampanel was discontinued on Day 37. On Day 45, the subject experience ischemic colitis with perforation. An exploratory laparotomy was performed with subtotal colectomy and an ileostomy and drainage of a left upper quadrant sub-splenic abscess.</p> <p><i>The ischemic colitis was likely a result of hypotension from septic shock and unlikely related to perampanel.</i></p>					
5133-4001	66, M, W	DB 304: placebo OLE 307: Pera 10 mg	Large intestinal perforation	OLE 294	Maintenance
<p><i>This is unlikely related to perampanel given that the perforation occurred during a colonoscopy.</i></p>					

Source: Created by the reviewer using narratives provided by the Sponsor.

In conclusion, perampanel use is associated with nausea, vomiting, and abdominal pain. Although there were subjects who developed colitis and ileitis, these cases were unlikely related to perampanel use.

Respiratory Disorders

In the epilepsy Phase 3 DB pool, in the SOC Respiratory, thoracic and mediastinal disorders, the TEAEs that occurred in >1% perampanel subjects and greater than placebo were oropharyngeal pain (1.7% vs 1.4%) and epistaxis (1.1% vs 0.5%). Dyspnoea was experienced by perampanel subjects less often than placebo (0.3% vs 0.5%). There were no SAEs or TEAEs that led to discontinuations in the SOC Respiratory, thoracic and mediastinal disorders.

In the epilepsy Phase 2 DB pool, the TEAEs in this SOC that occurred in >1% perampanel subjects and greater than placebo were oropharyngeal pain (4.0% vs 1.5%) and sinus congestion (3% vs 0). No subjects reported dyspnoea (dyspnoea exertional was reported by 1 perampanel subject). There were no SAEs or TEAEs that led to discontinuations in the SOC Respiratory, thoracic and mediastinal disorders.

In the nonepilepsy DB pool, there were no TEAEs in this SOC that occurred in >1% perampanel subjects and greater than placebo. Dyspnoea was experienced by perampanel subjects less often than placebo (1.4% vs 1.7%). The following SAEs were reported in 2 or more perampanel subjects (and greater than placebo): dyspnoea (0.2% vs 0) and pulmonary embolism (0.1% vs 0). Discontinuations due to dyspnoea occurred more frequently in perampanel subject than placebo (0.5% vs 0.2%).

In conclusion, perampanel is not associated with important respiratory disorders in this database. There may be a small signal for oropharyngeal pain but not for dyspnea. It is reassuring that there were no SAEs or TEAEs leading to discontinuation in this SOC in the epilepsy DB pool.

Hyperthermia

In the epilepsy DB pool, 1 perampanel subject experienced the TEAE hyperthermia (vs 0 placebo subjects). In the epilepsy all treated pool, there were a total of 3 perampanel subjects who experienced the TEAE hyperthermia. There was one SAE (described below). The other 2 subjects developed hyperthermia on Day 67 (however recorded temperature values were in the normal range) and on Day 827 (no temperature values recorded on that day). In the nonepilepsy all treated pool, there were no TEAEs coded to hyperthermia.

Subject 306-3951-6006, 35 yo white male with a history of hypertension, increased intracranial pressure, renal disorder who experienced hyperthermia on OLE Day 199 while on perampanel 12 mg. Despite taking antipyretics, the subject's temperature increased to 40 degrees Celsius. Blood pressure was reportedly 160/129 (baseline BP=125/80). Treatment included metamizole (antipyretic) and enalapril. Perampanel was discontinued. Events resolved 14 days later. Concomitant medications included clonazepam, topiramate, and carbamazepine.

This is unlikely related to perampanel as hyperthermia occurred after prolonged exposure to perampanel (199 days). An infectious etiology (particularly viral) could have caused the same clinical syndrome.

In conclusion, perampanel is not associated with hyperthermia in this database. Although there were rare AEs coded to hyperthermia in the epilepsy population, these cases were unlikely related to perampanel use. Furthermore, there were no AEs coded to hyperthermia in the nonepilepsy population.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the epilepsy all treated pool, the overall incidence of treatment-emergent AEs (TEAEs) was 90.1%. The TEAEs occurred most frequently within the SOC of Nervous system disorders, followed by Infections/infestations, General disorders, and Psychiatric disorders. In the total perampanel group, the most common TEAEs ($\geq 10\%$) were dizziness (46.6%), somnolence (21.2%), headache (18.1%), fatigue (12.9%), irritability (11.5%), and weight increased (10.9%) (120-day Safety Update Table 36). Exposure adjusted rates were lower in the epilepsy all treated pool (12.5 per 1000 subject-weeks) than in the epilepsy Phase 3 double-blind pool (44.7 per 1000 subject-weeks), suggesting no increase in the incidence of these events with longer exposure to treatment.

After adjusting for exposure, the incidence rate of TEAEs was two times higher in the nonepilepsy pool (25.0 per 1000 subject-weeks) than the epilepsy pool (12.5 per 1000

subject-weeks). There were also differences in the SOC distribution between the epilepsy and nonepilepsy pools likely due to the underlying diseases and comorbidities. The most commonly occurring TEAEs in the epilepsy studies also occurred in the nonepilepsy studies.

Table 121. TEAEs by System Organ Class – All Treated Subjects

	Epilepsy All Treated		Nonepilepsy All Treated	
Total number of subjects	1651		2717	
Subjects with any TEAE	1487		2156	
Incidence per number of subjects	90.1%		79.4%	
Total exposure (subject-weeks)	118920.0		86176.1	
Incidence per 1000 subject-weeks	12.5		25.0	
MedDRA SOC	n	per 1000 subj-wks	n	per 1000 subj-wks
Nervous System Disorders	1177	9.90	1298	15.1
Infections and Infestations	576	4.84	588	6.82
General Disorders and Administration Site	556	4.68	453	5.26
Psychiatric Disorders	475	3.99	501	5.81
Gastrointestinal Disorders	474	3.99	534	6.20
Injury, Poisoning and Procedural Complications	430	3.62	454	5.27
Investigations	320	2.69	383	4.44
Musculoskeletal and Connective Tissue Disorders	299	2.51	558	6.48
Skin and Subcutaneous Tissue Disorders	244	2.05	220	2.55
Eye Disorders	205	1.72	132	1.53
Respiratory, Thoracic and Mediastinal Disorders	197	1.66	222	2.58
Metabolism and Nutrition Disorders	161	1.35	171	1.98
Ear and Labyrinth Disorders	139	1.17	117	1.36
Blood and Lymphatic System Disorders	85	0.71	52	0.60
Reproductive System and Breast Disorders	84	0.71	56	0.65
Vascular Disorders	83	0.70	252	2.92
Cardiac disorders	76	0.64	158	1.83
Renal and Urinary Disorders	68	0.57	124	1.44
Immune System Disorders	28	0.24	9	0.10
Neoplasms Benign, Malignant and Unspecified	24	0.20	61	0.71
Endocrine disorders	13	0.11	10	0.12
Hepatobiliary Disorders	11	0.09	15	0.17
Surgical and Medical Procedures	6	0.05	8	0.09
Pregnancy, Puerperium and Perinatal Conditions	4	0.03	0	0
Social circumstances	2	0.02	4	0.05
Congenital, Familial and Genetic Disorders	2	0.02	0	0

Source: ISS Tables 20.8-7 and 20.8-21 and 120-day Safety Update Table 9

The following table summarizes the number of subjects with TEAEs, SAEs, and TEAEs leading to discontinuation for each different DB pool. In nearly every DB pool, a dose response relationship is present with the number of TEAEs increasing with increasing perampanel dose. In every DB pool, adverse event incidences were similar in the placebo and lower dose groups, but much higher than placebo in the highest dose groups. However, due to the pooling of these studies, the differences in the AE profile across the dose groups may be partly due to differences in demographics, underlying

diseases, concomitant medications, and other baseline characteristics (discussed in more detail in Section 7.2.1).

Table 122. TEAEs, SAEs, DCs by Randomized Treatment Groups

Category	Placebo n (%)	Perampanel n (%)				
		<4 mg	4 mg	>4-8 mg	>8-12mg	Total
Epilepsy Phase 3 DB Pool*	442	180	172	431	255	1038
TEAEs	294 (66.5)	111 (62)	111 (65)	350 (81)	227 (89)	799 (77.0)
Serious TEAEs (SAEs)	22 (5.0)	6 (3.3)	6 (3.5)	24 (5.6)	21 (8.2)	57 (5.5)
TEAE leading to withdrawal	21 (4.8)	12 (6.7)	5 (2.9)	33 (7.7)	49 (19.2)	99 (9.5)
Epilepsy Phase 2 DB Pool	68	12	101		38	151
TEAEs	47 (69.1)	8 (66.7)	65 (64.4)		32 (84.2)	105 (69.5)
Serious TEAEs (SAEs)	3 (4.4)	0	2 (2.0)		1 (2.6)	3 (2.0)
TEAE leading to withdrawal	4 (5.9)	0	5 (5.0)		2 (5.3)	7 (4.6)
Parkinson's DB Pool	845	717	745	55		1517
TEAEs	543 (64.3)	461 (64)	547 (73)	50 (91)		1058 (70)
Serious TEAEs (SAEs)	60 (7.1)	46 (6.4)	54 (7.2)	8 (14.5)		108 (7.1)
TEAE leading to withdrawal	92 (10.9)	83 (11.6)	113 (15)	15 (27.3)		211 (13.9)
Neuropathic Pain DB Pool	121	72	69	236		377
TEAEs	79 (65.3)	45 (62.5)	44 (63.8)	193 (82)		282 (74.8)
Serious TEAEs (SAEs)	4 (3.3)	2 (2.8)	2 (2.9)	25 (10.6)		29 (7.7)
TEAE leading to withdrawal	10 (8.3)	7 (9.7)	11 (15.9)	78 (33.1)		96 (25.5)
Nonepilepsy DB Pool	1079	908	814	291		2013
TEAEs	706 (65.4)	596 (66)	591 (73)	243 (84)		1430 (71)
Serious TEAEs (SAEs)	65 (6.0)	49 (5.4)	56 (6.9)	33 (11.3)		138 (6.9)
TEAE leading to withdrawal	106 (9.8)	97 (10.7)	124(15.2)	93 (32.0)		314 (15.6)

Source: ISS Tables 46, 47, 49, 50, 51

*Randomized treatment groups used for Epilepsy Phase 3 DB Pool: 2 mg, 4 mg, 8 mg, and 12 mg
For each row category, a subject with two or more adverse events in that category is counted only once.

In terms of severity, most of the TEAEs in the epilepsy Phase 3 DB pool were considered mild or moderate. Mild TEAEs occurred more frequently in the placebo group than the total perampanel group. Although moderate and severe TEAEs also occurred more frequently in the placebo group than the lower dose groups (2 mg and 4 mg), they both occurred more frequently in the higher dose groups (8 and 12 mg) than placebo. A dose-response relationship is strongest for severe TEAEs. The 12-mg group also displayed a higher incidence of adverse events that were rated as possibly or probably related to the study treatment (ISS Table 58).

Table 123. Severity of TEAEs, Epilepsy Phase 3 DB Pool

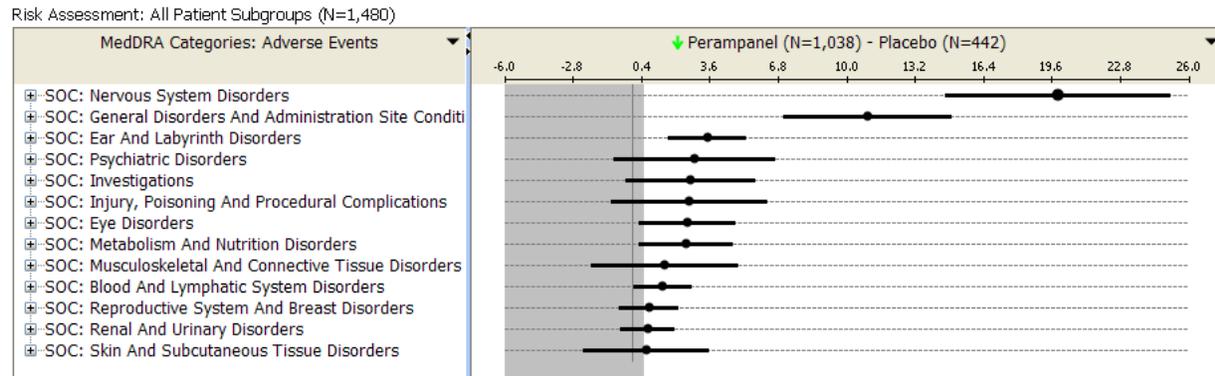
Severity of TEAE	Placebo n (%)	Perampanel n (%)				
		2 mg	4 mg	8 mg	12mg	Total
Subjects with any TEAEs	294 (100)	111 (100)	111 (100)	350(100)	227(100)	799 (100)
Mild	164 (55.8)	71 (64)	78 (70.3)	167 (48)	82 (36.1)	398 (49.8)
Moderate	106 (36.1)	37 (33.3)	28 (25.2)	136 (39)	108 (48)	309 (38.6)
Severe	24 (8.2)	3 (2.7)	5 (4.5)	47 (13)	37 (16.3)	92 (11.5)

Source: ISS Table 57

For each row category, a subject with two or more adverse events in that category is counted only once.

The largest differences between the total perampanel and placebo groups were in the incidences of TEAEs in the following SOCs: Nervous system, General, Ear/Labyrinth, and Psychiatric disorders.

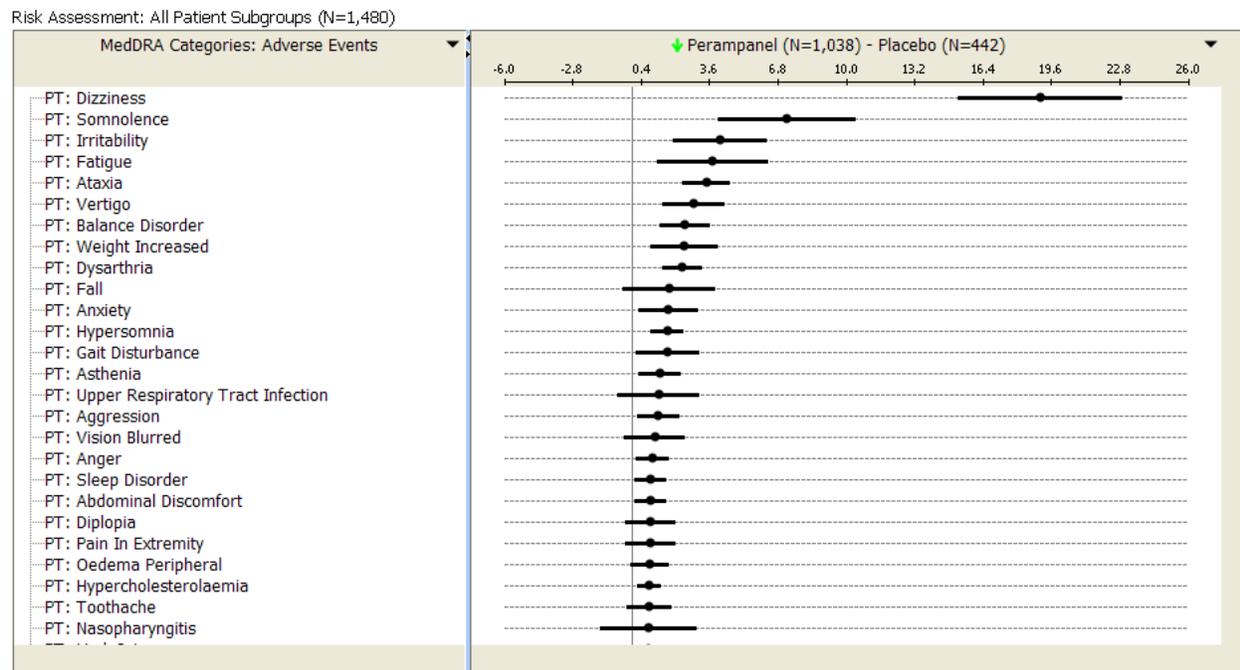
Figure 6. TEAE Risk Difference (per 100) by SOC, Total Perampanel vs Placebo, Epilepsy Phase 3 DB Pool



Source: Created by the reviewer using JReview and Epilepsy ADAE, ADSL datasets

The largest differences between the total perampanel and placebo groups were in the incidences of the following PTs: dizziness, somnolence, irritability, fatigue, ataxia, vertigo, balance disorder, weight increased, dysarthria, fall, anxiety, hypersomnia, and gait disturbance.

Figure 7. TEAE Risk Difference (per 100) by PT, Total Perampanel vs Placebo, Epilepsy Phase 3 DB Pool



Source: Created by reviewer using JReview and Epilepsy ADAE, ADSL datasets

The following table summarizes the TEAEs that occurred in at least 2% of the subjects and more frequently than placebo in any dose group for the epilepsy Phase 3 DB pool.

Table 124. Adverse Reactions, Epilepsy Phase 3 DB Pool (Events ≥ 2% of subjects and more frequent than placebo in any dose group)

MedDRA System Organ Class Preferred Term	Placebo n=442 %	Perampanel %				Total n=1038
		2 mg n=180	4 mg n=172	8 mg n=431	12 mg n=255	
Subjects with any TEAE	67	62	65	81	89	77
Ear and Labyrinth Disorders	2	3	5	6	6	5
Vertigo	1	3	4	3	5	4
Eye Disorders	4	2	5	7	9	6
Diplopia	1	1	1	1	3	2
Vision blurred	1	0	1	3	4	2
Gastrointestinal Disorders	19	13	9	20	22	17
Constipation	2	1	2	2	3	2
Nausea	5	2	3	6	8	5
Vomiting	3	3	2	3	4	3
General Disorders and Administration Site Conditions	12	14	15	24	32	23
Asthenia	1	1	1	2	2	2
Fatigue	5	4	8	8	12	8
Gait disturbance	1	1	1	4	4	3

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Irritability	3	4	4	7	12	7
Pyrexia	2	3	1	3	1	2
Infections and Infestations	21	19	17	22	20	20
Bronchitis	1	1	2	2	1	1
Nasopharyngitis	4	4	5	5	4	5
Pharyngitis	1	3	1	0	1	1
Upper respiratory tract infection	3	6	3	3	4	4
Injury, Poisoning and Procedural Complications	12	8	6	14	24	14
Contusion	1	1	0	2	2	1
Fall	3	1	2	5	10	5
Head injury	1	1	1	1	3	1
Skin laceration	1	1	0	2	2	1
Investigations	7	6	8	10	13	10
Weight increased	1	2	4	4	4	4
Metabolism & Nutrition disorders	3	4	1	6	11	6
Decreased appetite	2	1	1	2	4	2
Increased appetite	1	1	0	1	3	1
Musculoskeletal, CT disorders	10	7	8	12	16	12
Arthralgia	1	1	0	3	2	2
Back pain	2	1	2	2	5	2
Myalgia	2	1	1	1	3	2
Pain in extremity	1	1	0	2	3	2
Nervous system disorders	31	30	32	57	69	51
Ataxia	0	0	1	3	8	3
Balance disorder	1	0	0	5	3	3
Dizziness	9	10	16	32	43	28
Dysarthria	0	0	1	3	4	2
Headache	11	9	11	11	13	11
Hypersomnia	0	1	1	2	3	2
Hypoaesthesia	1	1	0	0	3	1
Paraesthesia	1	1	0	1	2	1
Somnolence	7	12	9	16	18	14
Psychiatric disorders	12	9	6	17	22	15
Aggression	1	1	1	2	3	2
Anger	0	0	0	1	3	1
Anxiety	1	2	2	3	4	3
Respiratory, Thoracic and Mediastinal Disorders	9	2	6	7	9	7
Cough	3	1	1	1	4	2
Oropharyngeal pain	1	1	2	2	2	2
Skin, Subcutaneous disorders	7	4	8	10	8	8
Rash	2	1	2	3	2	2

Source: Safety Information Amendment (February 6, 20120) Table 20.5-3.2-1

The Sponsor defined adverse drug reactions (ADRs) as TEAEs for which there is some basis to believe a causal relationship exists between the occurrence of the TEAE and the use of perampanel. The Sponsor assessed the AEs that occurred in at least 2% of the subjects in the total perampanel group and at a rate higher than the placebo group as possible ADRs (Table 58, Summary of Clinical Safety page 155). However, the

Sponsor did not include the AEs that occurred with the 2 mg dose (not considered an effective dose) and if difference between placebo were small or showed no dose response.

From the clinical evaluation of the epilepsy studies, the following PTs were considered ADRs by the Sponsor (shown in order of decreasing frequency in the total perampanel group): dizziness, somnolence, fatigue, irritability, fall, nausea, ataxia, weight increased, vertigo, balance disorder, gait disturbance, anxiety, vision blurred, dysarthria, back pain, decreased appetite, aggression, diplopia, anger, and increased appetite. Additionally, confusional state was added to the list based on the clinical evaluation of the nonepilepsy studies.

Comment: I agree with these adverse drug reactions. However, I would also include paraesthesia/hypoaesthesia, asthenia, hypersomnia, oropharyngeal pain, vomiting (nonepilepsy perampanel subjects 2.0% vs placebo 1.6% with dose response), and pain in extremity (2.0% vs 1.7% with dose response in nonepilepsy). These adverse drug reactions are already included in the table above.

Phase 1 Studies

The following tables summarize the TEAEs that occurred in at least 2% of the total perampanel administrations and at least 5% of the total perampanel group in the single-dose and multiple-dose studies, respectively. Of note, the high incidence of euphoric mood occurred in the single-dose Studies 023 and 024 that were specifically designed to assess abuse potential in multiple-drug users receiving perampanel doses up to 36 mg.

Table 125. TEAEs Occurring in \geq 2% of the Total Perampanel Administrations - Phase 1 Single Dose Pool

MedDRA Preferred Term	Perampanel (N=922)
Administrations with any TEAE	541 (58.7)
Dizziness	227 (24.6)
Somnolence	178 (19.3)
Headache	98 (10.6)
Fatigue	81 (8.8)
Euphoric mood	54 (5.9)
Nausea	38 (4.1)
Vision blurred	24 (2.6)
Hypoaesthesia oral	22 (2.4)
Gait disturbance	19 (2.1)

Source: ISS Table 22.4-16

N=number of single dose administrations

Table 126. TEAEs Occurring in \geq 5% of the Total Perampanel Population - Phase 1 Multiple Dose Pool

MedDRA Preferred Term	Perampanel (n=343)
Administrations with any TEAE	304 (88.6)
Dizziness	180 (52.5)
Headache	98 (28.6)
Somnolence	84 (24.5)
Nausea	53 (15.5)
Fatigue	41 (12.0)
Positive Rombergism	41 (12.0)
Dysarthria	39 (11.4)
Feeling drunk	39 (11.4)
Oropharyngeal pain	28 (8.2)
Insomnia	26 (7.6)
Vision blurred	24 (7.0)
Ataxia	21 (6.1)
Diarrhoea	19 (5.5)
Lethargy	19 (5.5)
Balance disorder	18 (5.2)
Epistaxis	18 (5.2)
Fall	18 (5.2)
Vomiting	18 (5.2)
Asthenia	17 (5.0)
Coordination abnormal	17 (5.0)

Source: ISS Table 22.4-41
 n= number of subjects

Other TEAEs occurring in \geq 2% (but $<$ 5%) of the total perampanel population included the following PTs: rash, paraesthesia, visual impairment, poisoning, constipation, contusion, memory impairment, irritability, hypoaesthesia, orthostatic hypotension, chest pain, dyspnoea, mental status changes, agitation, dysgeusia, emotional disorder, erythema, euphoric mood, nightmare, sedation, and speech disorder.

7.4.2 Laboratory Findings

In their NDA presentation, the Sponsor separately summarized hematology and chemistry (hepatobiliary, renal, and electrolyte) results. For the epilepsy and nonepilepsy pools, the Sponsor identified potentially clinically significant (PCS) changes (treatment-emergent markedly abnormal results, an increase in NCI grade to \geq Grade 2, in subjects with normal values at baseline) and provided shift tables and mean change from baseline analyses. This approach was acceptable to the reviewer.

7.4.2.1 Hematology

The following table summarizes the potentially clinically significant changes (for subjects with normal values at baseline) in hematology parameters for the epilepsy Phase 3 DB pool and the nonepilepsy DB pool. In both of the DB pools, the incidences of PCS hematology changes were similar between the placebo and perampanel groups.

Table 127. Potentially Clinically Significant Changes in Hematology Parameters for Subjects Normal at Baseline

Parameter	Epilepsy Phase 3 DB Pool				Nonepilepsy DB Pool			
	Placebo		Perampanel		Placebo		Perampanel	
	n	#PCS (%)	n	#PCS (%)	n	#PCS (%)	n	#PCS (%)
Hemoglobin <100g/L	405	0	945	2 (0.2)	975	3 (0.3)	1772	6 (0.3)
WBC <3.0x10 ⁹ /L	378	5 (1.3)	901	5 (0.6)	1009	3 (0.3)	1877	7 (0.4)
Platelets <75x10 ⁹ /L	401	0	965	0	997	0	1846	0
Lymphocytes <0.8x10 ⁹ /L	399	9 (2.3)	930	10 (1.1)	927	21 (2.3)	1744	43 (2.5)
Neutrophils <1.5x10 ⁹ /L	382	12 (3.1)	915	20 (2.2)	765	14 (1.8)	1387	17 (1.2)

Source: ISS Tables 20.11-51.1, 20.11-51.2, 20.11-112.1, 20.11-112.2

Potentially clinically significant change = an increase in NCI grade to ≥ Grade 2 from baseline.

In the epilepsy Phase 3 DB pool, only 2 (0.2%) perampanel subjects had PCS changes in hemoglobin from normal baseline values. Both subjects were females and both had a single occurrence of a PCS change followed by either subsequent normal values (one subject) or subsequent values of NCI Grade 1 (the other subject). This last subject was receiving perampanel 12 mg and on Study Day 43, the subject's hemoglobin level was 88 g/L (baseline=124 g/L, normal range=116-162 g/L). No treatment for the event was reported. Perampanel was continued with subsequent hemoglobin values approaching the normal range: Day 71, 101 g/L; Day 102, 107 g/L; Day 130, 112 g/L. Concomitant medications included carbamazepine, levetiracetam, and topiramate.

In the epilepsy Phase 3 DB pool, the majority of the subjects reporting markedly abnormal low values of hemoglobin (n=14) had abnormal baseline hemoglobin values (n=12). All of these 12 subjects had an increase of 1 NCI grade from a baseline NCI Grade of 1. Eight of these subjects concomitantly took valproic acid, phenytoin, or both.

In the epilepsy Phase 2 DB pool, no perampanel subjects with normal baseline values had a hemoglobin or platelet result that met the low PCS criteria (ISS Table 20.11-61.1). One (0.7%) perampanel subject had a PCS low WBC result (vs none in placebo). Three (2.3%) perampanel subjects had a PCS low neutrophil results (vs none in placebo).

In the Phase 1 single-dose studies, markedly abnormal low leukocytes occurred in 5 (0.7%) of the perampanel administrations along with 9 low neutrophils (1.5%) and 3 low lymphocytes (0.5%) (ISS Tables 22.5-25 and 22.5-35). In the Phase 1 multiple-dose studies, 1 (0.3%) and 4 (1.6%) perampanel subjects developed markedly abnormal low leukocytes and low neutrophils, respectively (ISS Tables 22.5-30 and 22.5-40). There

were no markedly abnormal values reported for any of the other hematology parameters. No placebo subjects developed any treatment-emergent markedly abnormal values.

The following table summarizes the mean changes from baseline to the end of treatment for the hematology parameters. The mean values were within normal ranges at baseline and the end of treatment for all treatment groups. The mean changes tended to be small and of unknown clinical significance. The mean changes were similar in the perampanel and placebo groups.

Table 128. Mean Change from Baseline to End of Treatment for Hematology Labs

Parameter	Epilepsy Phase 3 DB				Nonepilepsy DB Pool			
	Placebo		Perampanel		Placebo		Perampanel	
	n	mean Δ	n	mean Δ	n	mean Δ	n	mean Δ
RBC (x10 ¹² /L)	431	-0.023	1018	-0.010	1046	-0.017	1935	0.013
Hematocrit (%)	427	-0.001	1010	0.001	1046	-0.003	1929	0.001
Hemoglobin (g/L)	431	-0.8	1017	-0.5	1046	-0.6	1935	0.2
WBC (x10 ⁹ /L)	431	-0.162	1018	-0.137	1046	-0.009	1935	0.039
Platelet (x10 ⁹ /L)	427	-2.9	1012	-2.9	1033	-1.4	1917	0.2

Source: ISS Tables 20.11-1.1, 20.11-1.2, 20.11-103.1, 20.11-103.2

Additionally, in the epilepsy Phase 2 DB pool, the mean changes tended to be small and of unknown clinical significance (ISS Table 20.11-52.1). The mean changes were similar in the perampanel and placebo groups.

The following table summarizes the percentages of subjects who shifted from normal or high values at baseline to low values for hematology parameters. In the epilepsy Phase 3 DB pool, the incidences of shifts to low values were higher in the perampanel group than placebo for hemoglobin (5.0% vs 3.5%) and neutrophils (6.5% vs 4.4%). However, the shifts to low values were similar for RBC count, hematocrit, and WBC count. Furthermore, there were no dose response relationships seen in the shift results. In the nonepilepsy DB pool, shifts to low values were similar in the perampanel and placebo groups for all of the hematology parameters except for lymphocytes (4.9% vs 3.4%).

Table 129. Shifts to Low (from Normal/High at Baseline) for Hematology Parameters

Parameter	Epilepsy Phase 3 DB				Nonepilepsy DB Pool			
	Placebo		Perampanel		Placebo		Perampanel	
	n	# shift (%)	n	#shift (%)	n	# shift (%)	n	#shift (%)
RBC low	431	20 (4.6)	1018	45 (4.4)	1046	23 (2.2)	1935	47 (2.4)
Hematocrit low	427	19 (4.4)	1010	45 (4.5)	1046	30 (2.9)	1929	57 (3.0)
Hemoglobin low	431	15 (3.5)	1017	51 (5.0)	1046	35 (3.3)	1935	51 (2.6)
WBC low	431	27 (6.3)	1018	70 (6.9)	1046	10 (1.0)	1935	31 (1.6)
Platelet low	427	17 (4.0)	1012	18 (1.8)	1033	13 (1.3)	1917	15 (0.8)
Lymphocytes low	430	11 (2.6)	1013	30 (3.0)	1029	35 (3.4)	1904	83 (4.9)
Neutrophils low	430	19 (4.4)	1013	66 (6.5)	789	9 (1.1)	1430	17 (1.2)

Source: ISS Tables 20.11-5.1, 20.11-5.2, 20.11-107.1, 20.11-107.2

In the epilepsy Phase 2 DB pool, shifts to low values were higher in the perampanel group than placebo for RBC count (7.9% vs 4.4%), hematocrit (2.7% vs 1.5%), hemoglobin (4.0% vs 2.9%), WBC count (6.0% vs 4.4%), and neutrophils (2.9% vs 0) (ISS Table 20.11-56.1, 20.11-56.2).

The following table summarizes the PCS changes in the epilepsy and nonepilepsy all treated pools after including the OLE studies. In general, PCS changes in hematology parameters occurred rarely in these populations. However, more than 4% of the total perampanel subjects had PCS changes from normal baselines in lymphocyte (nonepilepsy) and neutrophil counts (epilepsy). In the epilepsy all treated pool, only 11 subjects (0.8%) had neutrophil counts between 0.5 to 1.0 x10⁹/L, or Grade 3 toxicity (with 10 subjects having only single abnormal values) and only 1 subject (0.1%) had a single neutrophil count below 0.5 x10⁹/L (Grade 4 Toxicity).

Table 130. Potentially Clinically Significant Changes in Hematology Parameters in Subjects Normal at Baseline, All Treated Pools

Parameter	Epilepsy All Treated Pool		Nonepilepsy All Treated Pool	
	n	#PCS (%)	n	#PCS (%)
Hemoglobin <100g/L	1475	13 (0.9)	2364	9 (0.4)
WBC <3.0x10 ⁹ /L	1425	18 (1.3)	2521	18 (0.7)
Platelets <75x10 ⁹ /L	1517	3 (0.2)	2483	1 (0.0)
Lymphocytes <0.8x10 ⁹ /L	1440	32 (2.2)	2317	97 (4.2)
Neutrophils <1.5x10 ⁹ /L	1419	58 (4.1)	2026	25 (1.2)

Potentially clinically significant change = an increase in NCI grade to ≥Grade 2 from baseline.

Source: ISS Tables 20.11-45.1, 20.11-45.2 and 120-day Safety Update Tables 20.11-143.1.1, 20.11-143.1.2

Hematology-related TEAEs

The following table summarizes the TEAEs in the MedDRA SOC Blood and lymphatic system disorders. Incidences of TEAEs in this entire SOC were low (<5%) in both the perampanel and placebo groups.

Table 131. Hematology TEAEs in ≥ 2 Subjects in Perampanel Group > Placebo

MedDRA SOC, PT	Placebo	Perampanel
Epilepsy DB Pool (Phase 2 +Phase 3)	n = 510	n = 1189
SOC Blood and lymphatic system disorders	5 (1.0)	27 (2.3)
Anaemia	1 (0.2)	10 (0.8)
Neutropenia	0	7 (0.6)
Leukopenia	0	6 (0.5)
Eosinophilia	1 (0.2)	4 (0.3)
Thrombocytopenia	1 (0.2)	3 (0.3)
Epilepsy DB Pool (Phase 2)	n=68	n=151
SOC Investigations		
Activated PTT prolonged	1 (1.5)	4 (2.6)
Nonepilepsy Double-blind Pool	n = 1079	n = 2013
SOC Blood and lymphatic system disorders	13 (1.2)	28 (1.4)
Anaemia	5 (0.5)	16 (0.8)
Haemolysis	0	2 (0.1)
Poikilocytosis	0	2 (0.1)
[Leukopenia]	1 (0.1)	0
[Thrombocytopenia]	1 (0.1)	1 (0.0)
[Neutropenia]	0	0

Source: ISS Tables 20.5-28, 20.5-54

The TEAE of anemia occurred more frequently in perampanel subjects than placebo subjects in both of the DB pools. The majority of these subjects had abnormal values at baseline or history of anemia (described earlier in this Section under Table 127).

The TEAEs of neutropenia and leukopenia occurred in 7 (0.7%) and 6 (0.6%), respectively, of the perampanel-treated subjects (vs none in placebo). Three subjects had both neutropenia and leukopenia. Of the 7 subjects who had neutropenia, 5 subjects had baseline abnormalities, 1 subject had an associated viral infection (see narrative below), and 1 subject had single postbaseline markedly abnormal values with subsequent normal values. Of the 6 subjects with leukopenia, 2 subjects had baseline abnormalities (NCI Grade 1). One of these 2 subjects had a single markedly abnormal value with subsequent normal values. The rates of abnormally low neutrophil counts were higher in adolescents than adults in the total perampanel groups.

None of the hematology-related AEs resulted in death or was considered an SAE in perampanel subjects (although there was 1 SAE of thrombocytopenia in a placebo subject). Two events in the perampanel group led to discontinuation but were likely not related to perampanel use (neutropenia was likely secondary to an infectious etiology and thrombocytopenia was likely related to ITP):

Subject 304-1004-4001 experienced neutropenia. The subject's baseline value was $2.06 \times 10^9/L$ (normal range 1.8 to $8.0 \times 10^9/L$). On Study Day 7, the subject experienced the AE of bronchitis and was given levofloxacin. On Day 41, the neutrophil count was low at $1.67 \times 10^9/L$. On Study Day 139 while on 10 mg of perampanel, a markedly abnormal low neutrophil value was reported at $1.36 \times$

$10^9/L$. No treatment for the event was reported and perampanel was discontinued. Fourteen days later, the neutropenia improved ($1.5 \times 10^9/L$) with resolution at 44 days after discontinuation ($2.10 \times 10^9/L$). About 1 month later, the subject reported another episode of bronchitis which was treated with amoxicillin. Subsequent labs (performed 20 days later) revealed a recurrence of neutropenia ($1.64 \times 10^9/L$).

Subject 306-4409-6003 was randomized to receive perampanel 2 mg/day. On Study Day 99, the subject experienced an AE of thrombocytopenia and the platelet count was reported to be $29 \times 10^9/L$ (normal range $140-450 \times 10^9/L$). The subject had abnormally low values of platelets at screening ($47 \times 10^9/L$) and baseline ($54 \times 10^9/L$). Treatment for the event was not reported. Platelet count on other days was as follows: Study Day 43, $31 \times 10^9/L$; Study Day 71, $31 \times 10^9/L$; Study Day 111, $9 \times 10^9/L$; Study Day 146, $34 \times 10^9/L$. Concomitant medications at the time of the events included oxcarbazepine, levetiracetam, and clobazam.

In the epilepsy Phase 2 DB pool, activated PTT prolonged occurred more frequently in perampanel subjects than placebo. All 4 of the perampanel-treated subjects had baseline values (36.1 to 80.3 seconds) that were above the ULN (normal range, 24 to 36 seconds). The placebo subject had a baseline value (33.7 seconds) within the normal range.

In the non-epilepsy double-blind pool, none of the perampanel subjects had TEAEs of neutropenia or leukopenia. Only two events were SAEs in the hematology grouping (anemia in 1 placebo subject and 1 perampanel subject). Anemia led to discontinuation in one perampanel subject, while hemoglobin decreased and hematocrit decreased led to discontinuation of treatment in one placebo subject.

In conclusion, perampanel is not associated with changes in hematology parameters in this database. Although there was a small signal for neutropenia, lymphopenia, and anemia, there was a lack of dose response and replication among the other DB pools. Furthermore, most of these perampanel subjects had single abnormal values or baseline abnormalities in hematology parameters.

7.4.2.2 Chemistry

The following table summarizes the potentially clinically significant changes (for subjects with normal values at baseline) in chemistry parameters for the epilepsy Phase 3 and Phase 2 DB pool. In both of the DB pools, the only PCS chemistry change that occurred in at least 2% of perampanel subjects and greater than placebo was high CPK (4.1% vs 0) in the Phase 2 DB pool. Smaller differences between the perampanel and placebo subjects are noted for PCS high potassium, low calcium, and low glucose (discussed in more detail in Section 7.4.2.3).

Table 132. Potentially Clinically Significant Changes in Chemistry Parameters for Subjects Normal at Baseline, Epilepsy DB Pools

Parameter	Epilepsy Phase 3 DB Pool				Epilepsy Phase 2 DB Pool			
	Placebo		Perampanel		Placebo		Perampanel	
	n	#PCS (%)	n	#PCS (%)	n	#PCS (%)	n	#PCS (%)
Hepatobiliary								
ALT >3.0xULN	403	0	965	1 (0.1)	61	0	134	0
ALP >3.0xULN	375	0	871	0	57	0	123	0
AST >3.0xULN	412	0	975	3 (0.3)	65	0	148	0
Bilirubin >1.5xULN	417	0	976	2 (0.2)	67	0	151	0
GGT >3.0xULN	277	0	683	1 (0.1)	37	0	85	0
Renal								
Creatinine >1.5xULN	424	1 (0.2)	999	1 (0.1)	62	0	145	1 (0.7)
Electrolytes								
Bicarbonate ≤15mEq/dL	335	3 (0.9)	796	4 (0.5)	54	0	116	1 (0.9)
Potassium <3.0mmol/L	422	0	989	0	62	0	146	0
Potassium >5.5mmol/L	422	2 (0.5)	989	10 (1.0)	62	0	146	2 (1.4)
Sodium <130mmol/L	414	9 (2.2)	970	15 (1.5)	63	1 (1.6)	133	2 (1.5)
Sodium >150mmol/L	414	2 (0.5)	970	1 (0.1)	63	0	133	0
Other								
Calcium <2.0mmol/L	415	2 (0.5)	970	1 (0.1)	65	0	141	2 (1.4)
Calcium >2.9mmol/L	415	0	970	0	65	0	141	0
Glucose <3.0mmol/L	419	2 (0.5)	988	17 (1.7)	64	2 (3.1)	143	1 (0.7)
Glucose >8.9mmol/L	419	5 (1.2)	988	9 (0.9)	64	0	143	0
Cholesterol >7.75mmol/L	255	0	623	2 (0.3)	27	0	72	0
Triglycerides >2.5xULN	402	0	914	1 (0.1)	55	0	120	1 (0.8)
Creatine kinase >3xULN	389	18 (4.6)	922	19 (2.1)	53	0	122	5 (4.1)
LDH >3xULN	421	0	984	0	58	0	128	0
Magnesium ≤0.49 mmol/L	427	0	1009	1 (0.1)	10	0	38	0
Phosphate <0.6mmol/L	419	4 (1.0)	995	9 (0.9)	64	0	140	0

Source: ISS Tables 20.11-51.3, 20.11-51.4, 20.11-51.5, 20.11-51.6, 20.11-61.3, 20.11-61.4, 20.11-61.5, 20.11-61.6

Potentially clinically significant change = an increase in NCI grade to ≥Grade 2 from baseline.

In the nonepilepsy DB pool, PCS changes that occurred in at least 2% of the perampanel subjects and greater than placebo included high potassium (2.6% vs 1.7%), and high glucose (7.0% vs 2.7%) (ISS Tables 20.11-98.3, 20.11-112.4, 20.11-112.5, 20.11-112.6).

Comment: Of note, data for treatment-emergent markedly abnormal creatine kinase and lactate dehydrogenase values were not included in the ISS. In response to an information request, the Sponsor submitted this data on April 20, 2012.

In the Phase 1 studies, treatment emergent markedly abnormal lab results occurred in at least 2% of the perampanel group only for high potassium (2.0% of multiple dose perampanel subjects) (ISS Tables 22.5-45, 22.5-50, 22.5-55, 22.5-60, 22.5-65, 22.5-70, 22.5-75, 22.5-80).

The following table summarizes the mean changes from baseline to the end of treatment for the chemistry parameters. The mean values were within normal ranges at baseline and the end of treatment for all treatment groups. The mean changes tended to be small and of unknown clinical significance. The mean changes were similar in the perampanel and placebo groups.

Table 133. Mean Change from Baseline to End of Treatment for Chemistry Labs

Parameter	Epilepsy Phase 3 DB Pool				Epilepsy Phase 2 DB Pool			
	Placebo		Perampanel		Placebo		Perampanel	
	n	mean Δ	n	mean Δ	n	mean Δ	n	mean Δ
Hepatobiliary								
ALT IU/L	430	-0.37	1015	-0.72	68	-0.03	151	-0.48
ALP IU/L	431	-3.06	1016	-0.60	68	0.78	151	1.63
AST IU/L	430	-0.09	1013	-0.20	68	0.40	151	-2.39
Bilirubin μmol/L	431	-0.030	1016	-0.278	68	-0.222	151	-0.391
GGT IU/L	431	-1.0	1016	-3.8	62	-3.6	139	-1.5
Renal								
BUN mmol/L	431	0.064	1016	-0.039	68	-0.003	151	0.121
Cr μmol/L	431	-0.494	1016	-0.208	68	0.057	151	-0.885
Electrolytes								
Bicarbonate mmol/L	432	-0.48	1016	-0.45	66	0.28	151	0.30
Potassium mmol/L	430	-0.077	1016	-0.041	68	0.099	151	0.044
Sodium mmol/L	431	0.08	1017	0.40	68	0.16	151	-0.31
Other								
Calcium mmol/L	431	-0.011	1016	0.000	68	0.006	151	-0.012
Glucose mmol/L	431	-0.018	1016	0.044	68	0.026	151	0.103
Cholesterol mmol/L	431	-0.046	1016	0.035	68	-0.016	151	0.070
Triglycerides mmol/L	431	0.012	1016	0.082	68	-0.086	151	0.014
CPK IU/L	430	20.0	1015	4.9	62	-3.1	139	-144.9
LDH IU/L	429	1.6	1008	5.0	62	-0.4	139	0.0
Magnesium mmol/L	431	-0.011	1016	-0.010	10	0.014	38	0.003
Phosphate mmol/L	431	0.001	1015	-0.008	68	0.015	151	-0.057

Source: ISS Tables 20.11-1.3, 20.11-1.4, 20.11-1.5, 20.11-1.6, 20.11-52.3, 20.11-52.4, 20.11-52.5, 20.11-52.6

Additionally, in the nonepilepsy DB pool, the mean changes tended to be small and of unknown clinical significance (ISS Table 20.11-103.3, 20.11-103.4, 20.11-103.5, 20.11-103.6). The mean changes were similar in the perampanel and placebo groups.

The following table summarizes the shift results from normal or low at baseline to high for select chemistry parameters and the shift results from normal or high at baseline to low for other parameters. In the epilepsy Phase 3 DB pool, the incidences of shifts were higher in the perampanel group than placebo for high CPK (6.9% vs 4.2%) and phosphate (1.7% vs 0.7%). In the epilepsy Phase 2 DB pool, shifts in at least 2% of the perampanel group and twice that of placebo occurred for high potassium (4.0% vs 1.5%), low calcium (4.6% vs 1.5%), high cholesterol (8.6% vs 2.9%), and high CPK (14.4% vs 1.6%).

Table 134. Shift Results for Chemistry Parameters, Epilepsy DB Pools

Parameter	Epilepsy Phase 3 DB Pool				Epilepsy Phase 2 DB Pool			
	Placebo		Perampanel		Placebo		Perampanel	
	n ^b	# shift (%)	n ^b	# shift (%)	n ^b	# shift (%)	n ^b	# shift (%)
Hepatobiliary								
ALT High	430	11 (2.6)	1015	17 (1.7)	68	2 (2.9)	151	1 (0.7)
ALP High	431	9 (2.1)	1016	23 (2.3)	68	1 (1.5)	151	2 (1.3)
AST High	430	7 (1.6)	1013	11 (1.1)	68	2 (2.9)	151	3 (2.0)
Bilirubin High	431	0	1016	2 (0.2)	68	0	151	0
GGT High	431	19 (4.4)	1016	24 (2.4)	68	4 (6.5)	151	3 (2.2)
Renal								
BUN High	431	1 (0.2)	1016	7 (0.7)	68	1 (1.5)	151	4 (2.6)
Cr High	431	4 (0.9)	1016	5 (0.5)	68	0	151	2 (1.3)
Electrolytes								
Bicarbonate Low	432	36 (8.3)	1016	70 (6.9)	66	8 (12.1)	151	12 (7.9)
Bicarbonate High	432	16 (3.7)	1016	43 (4.2)	66	5 (7.6)	151	6 (4.0)
Potassium High	430	0	1016	1 (0.1)	68	1 (1.5)	151	6 (4.0)
Potassium Low	430	5 (1.2)	1016	8 (0.8)	68	1 (1.5)	151	1 (0.7)
Sodium High	431	2 (0.5)	1017	7 (0.7)	68	1 (1.5)	151	0
Sodium Low	431	7 (1.6)	1017	17 (1.7)	68	2 (2.9)	151	5 (3.3)
Other								
Calcium High	431	3 (0.7)	1016	7 (0.7)	68	0	151	1 (0.7)
Calcium Low	431	3 (0.7)	1016	8 (0.8)	68	1 (1.5)	151	7 (4.6)
Glucose High	431	5 (1.2)	1016	10 (1.0)	68	2 (2.9)	151	3 (2.0)
Glucose Low	431	9 (2.1)	1016	26 (2.6)	68	3 (4.4)	151	5 (3.3)
Cholesterol High	431	36 (8.4)	1016	70 (6.9)	68	2 (2.9)	151	13 (8.6)
Triglycerides High	431	17 (3.9)	1016	39 (3.8)	68	2 (2.9)	151	6 (4.0)
CPK High	430	7 (4.2)	1015	29 (6.9)	62	1 (1.6)	139	20 (14.4)
LDH High	429	10 (2.3)	1008	14 (1.4)	62	2 (3.2)	139	4 (2.9)
Magnesium low	431	1 (0.2)	1016	1 (0.1)	10	0	38	0
Phosphate low	431	3 (0.7)	1015	17 (1.7)	68	1 (1.5)	151	2 (1.3)

Source: ISS Tables 20.11-5.3, 20.11-5.4, 20.11-5.5, 20.11-5.6, 20.11-56.3, 20.11-56.4, 20.11-56.5, 50.11-56.6

In the nonepilepsy DB pool, shifts in at least 2% of the perampanel group and greater than placebo occurred for high CPK (8.3% vs 5.9%), and high LDH (2.7% vs 0.8%) (ISS Tables 20.11-107.4, 20.11-127.3, 20.11-107.5, 20.11-107.6). For the hepatobiliary parameters, ALT, AST, and bilirubin, shifts to high values occurred less frequently or similarly in the perampanel group compared to the placebo group.

In the Phase 1 studies, shifts in at least 2% of the perampanel group occurred for high ALT (2.3% single dose and 2.4% multiple dose) and bilirubin (4.5% multiple dose) (ISS Tables 22.5-89, 22.5-90, 22.5-91, 22.5-92, 22.5-93, 22.5-94, 22.5-95, 22.5-96). Drug-induced liver injury is discussed in Section 7.3.5.1 of this review.

The following table summarizes the PCS changes in the epilepsy and nonepilepsy all treated pools after including the OLE studies. In general, PCS changes in chemistry parameters occurred rarely in these populations. However, $\geq 2\%$ of the total

perampanel subjects had PCS outliers of high potassium, high CPK, low glucose, high glucose (only in nonepilepsy pool), and low sodium (only in epilepsy pool). Of note, the nonepilepsy studies included subjects who had diabetes mellitus and subjects were not required to fast before laboratory tests were performed. Therefore, elevated glucose values were not unexpected in this population.

Table 135. Potentially Clinically Significant Changes in Chemistry Parameters for Subjects Normal at Baseline, All Treated Pools

Parameter	Epilepsy All Treated Pool		Nonepilepsy All Treated Pool	
	n	#PCS (%)	n	#PCS (%)
Hepatobiliary				
ALT >3.0xULN	1508	8 (0.5)	2306	8 (0.3)
ALP >3.0xULN	1369	0	2239	3 (0.1)
AST >3.0xULN	1544	7 (0.5)	2453	7 (0.3)
Bilirubin >1.5xULN	1546	3 (0.2)	2500	5 (0.2)
GGT >3.0xULN	1041	7 (0.7)	1943	11 (0.6)
Renal				
Creatinine >1.5xULN	1566	8 (0.5)	2448	3 (0.1)
Electrolytes				
Bicarbonate ≤15 mEq/dL	1228	7 (0.6)	902	3 (0.3)
Potassium <3.0 mmol/L	1565	4 (0.3)	2486	4 (0.2)
Potassium >5.5 mmol/L	1565	40 (2.6)	2486	79 (3.2)
Sodium <130 mmol/L	1519	36 (2.4)	2465	8 (0.3)
Sodium >150 mmol/L	1519	5 (0.3)	2465	12 (0.5)
Other				
Calcium <2.0 mmol/L	1542	8 (0.5)	2532	5 (0.2)
Calcium >2.9 mmol/L	1542	0	2532	0
Glucose <3.0 mmol/L	1547	39 (2.5)	2110	42 (2.0)
Glucose >8.9 mmol/L	1547	23 (1.5)	2110	146 (6.9)
Cholesterol >7.75 mmol/L	958	2 (0.2)	1528	12 (0.8)
Triglycerides >2.5xULN	1419	5 (1.4)	2063	8 (0.4)
Creatine kinase >3xULN	1419	55 (3.9)	520	17 (3.3)
LDH >3xULN	1530	0	661	0
Magnesium ≤0.49 mmol/L	1564	24 (1.5)	799	1 (0.1)
Phosphate <0.6 mmol/L	1439	1 (0.1)	2483	7 (0.3)

Source: ISS Table 20.11-98.3, 20.11-98.4, 20.11-98.5, 20.11-98.6 and 120-day Safety Update Tables 20.11-143.1.3, 20.11-143.1.4, 20.11-143.1.5, 20.11-143.1.6
Potentially clinically significant change = an increase in NCI grade to ≥Grade 2 from baseline.

7.4.2.3 Additional Analyses for Chemistry Parameters

In this section, I will present additional analyses for CPK, hyponatremia, hyperkalemia, hypocalcemia, and hypoglycemia. Comprehensive analyses of perampanel's effects on metabolic parameters (total cholesterol, triglycerides, hyperglycemia) are presented in Section 7.3.4.3 of this review.

Creatine Phosphokinase (CPK)

The following table summarizes the CPK test outlier and SMQ results for the epilepsy and nonepilepsy DB pools. In the epilepsy DB pool, a lower percentage of perampanel subjects than placebo developed extremely high CPK values (3 to 5 times ULN and >5x ULN). In the nonepilepsy DB pool, a similar percentage of perampanel and placebo subjects developed extremely high CPK values (3 to 5 times ULN and >5x ULN). No dose response was observed. In both pools, a similar percentage of perampanel and placebo subjects experienced TEAEs in the SMQ Rhabdomyolysis and Myopathy. There were no subjects with TEAEs in the narrow SMQ.

Table 136. CPK Outliers, DB Pools

Test/Cutoff threshold	Epilepsy DB Pool		Nonepilepsy DB Pool	
	Placebo	Perampanel	Placebo	Perampanel
	n=492	n=1154	n=289	n=603
CPK ≤3x ULN	465 (94.5)	1111 (96.3)	277 (95.8)	576 (95.5)
CPK >3x and ≤5x ULN	14 (2.8)	27 (2.3)	8 (2.8)	16 (2.7)
CPK >5x ULN	13 (2.6)	16 (1.4)	4 (1.4)	11 (1.8)
SMQ Rhabdomyolysis	n=510	n=1189	n=1038	n=2013
Broad	21 (4.1)	53 (4.5)	50 (4.6)	86 (4.3)
Narrow	0	0	0	0

Source: ISS Table 20.11-8, 20.11-59, 20.11-110

SMQ analysis performed by reviewer using MAED (MedDRA-based Adverse Event Diagnostic) service

There was only one subject coded to PT rhabdomyolysis in entire safety database. The increase in CPK was likely due to immobility and less likely caused by perampanel.

Subject 0109-0005, a 69 year-old white female was randomized to the 2 mg perampanel group in the Parkinson's Disease DB Study 214 and subsequently entered the OLE Study 220. On Study Day 60, the subject experienced somnolence and bradykinesia. The subject was hospitalized for further evaluation and recovered. On Day 75, the subject was rehospitalized for sedation and bradykinesia ("frozen state"). Labs revealed an elevated creatine phosphokinase (peak 2,007 U/L), and the subject was diagnosed with rhabdomyolysis. The subject was treated with valium, intravenous fluids, a decreased dose of carbidopa/levodopa, and quetiapine fumarate. Perampanel was discontinued. The patient recovered.

In conclusion, perampanel is not associated with significant elevations in creatine phosphokinase in this database. Perampanel use was not associated with an increased incidence of extremely high CPK values or TEAEs in the Rhabdomyolysis SMQ. There was only one AE coded to the PT rhabdomyolysis which was unlikely related to perampanel use.

Hyponatremia

The following table summarizes the incidences of potentially clinically significant sodium values, shifts from normal to low sodium, and consecutively low sodium values. In response to the Division's information request, the Sponsor performed an analysis of sodium values <125 mmol/L (Safety Information Amendment, 7/27/12).

Table 137. Hyponatremia

Category	Placebo n (%)	Perampanel n (%)				Total
		<4 mg	4 mg	>4-8 mg	>8-12mg	
Epilepsy Phase 3 DB Pool*	n=442	n=180	n=172	n=431	n=255	n=1038
Sodium <130 mmol/L [^]	9 (2.2)	2 (1.2)	2 (1.2)	5 (1.2)	6 (2.6)	15 (1.5)
Sodium <125 mmol/L [^]	0	0	1 (0.6)	0	1 (0.4)	2 (0.2)
Shift from normal to low	15 (3.5)	5 (2.8)	3 (1.8)	17 (4.0)	10 (4.1)	35 (3.4)
Consecutive Low ≥2 Visits [^]	4 (1.0)	0	0	5 (1.2)	5 (2.2)	10 (1.0)
Epilepsy Phase 2 DB Pool	n=68	n=12	n=101		n=38	n=151
Sodium <130 mmol/L [^]	1 (1.6)	0	1 (1.1)		1 (2.9)	2 (1.5)
Sodium <125 mmol/L [^]	0	0	0		1 (2.9)	1 (0.8)
Shift from normal to low	6 (8.8)	0	9 (8.9)		3 (7.9)	12 (7.9)
Consecutive Low ≥2 Visits [^]	2 (3.2)	0	1 (1.1)		2 (5.7)	3 (2.3)
Nonepilepsy DB Pool	n=1079	n=908	n=814	n=291		n=2013
Sodium <130 mmol/L [^]	1 (0.1)	1 (0.1)	2 (0.3)	1 (0.4)		4 (0.2)
Sodium <125 mmol/L [^]	0	1 (0.1)	0	0		1 (0.1)
Shift from normal to low	15 (1.4)	15 (1.7)	9 (1.2)	11 (3.9)		35 (1.8)
Consecutive Low ≥2 Visits [^]	2 (0.2)	0	1 (0.1)	3 (1.1)		4 (0.2)

Source: Safety Information Amendment 7/27/12 Table 23.11-18.1

*Randomized treatment groups: 2 mg, 4 mg, 8 mg, and 12 mg

[^]Subjects with normal values at baseline

A similar percentage of perampanel subjects and placebo developed potentially clinically significant sodium values (<130 mmol/L), shifts to low values, and consecutively low sodium values. There were only 4 subjects (all perampanel subjects) in these DB pools with a sodium value less than 125 mmol/L. These subjects were on concomitant therapy with either carbamazepine or oxcarbazepine (known to cause hyponatremia) except for the one subject in the nonepilepsy DB pool. In the epilepsy all treated pool, while there were 36 perampanel subjects (2.4%) who developed sodium values <130 mmol/L, only 8 (0.5%) developed sodium values <125 mmol/L.

The following table summarizes the narratives for the hyponatremia SAEs. There were 3 subjects in the entire safety population with the SAEs of hyponatremia. All of these subjects were in the epilepsy studies and concomitantly on oxcarbazepine or carbamazepine. Therefore, it is difficult to ascertain the causal role of perampanel for hyponatremia with such rare events of severe hyponatremia (<125 mmol/L) and the use of concomitant medications known to cause hyponatremia.

Table 138. Hyponatremia SAEs, Epilepsy All Treated Pool

Subject #	Age, Sex, Race	Study: Treatment, Dose	Adverse event (Preferred Term)	Study day	Phase of Study
5139-4007	65, F, W	DB 304: Pera 12 mg OLE 307: Pera 12 mg	Hyponatremia	DB 58	Maintenance
<p>Subject with a history of hyponatremia experienced convulsions on Day 56. Treatment included lorazepam and hydralazine. The subject was found to have hyponatremia with levels of 127 and 128 (baseline value was 133). Perampanel was continued. The subject had another seizure with a fall and head injury on Day 86. The subject was hospitalized with respiratory distress and hypertension (SBP 230 mmHg). Sodium value was 120. Perampanel was continued. On Day 112, the subject experienced another episode of convulsion and was hospitalized. Hyponatremia was found and treatment included sodium chloride. The subject entered the OLE study with no change to study drug dose. At the next assessment sodium level was 125 on Day 134. The investigator assessed the event as not related to study drug but rather to oxcarbazepine. Perampanel was continued and the subject received her most recent dose on Day 303.</p> <p>Concomitant medications included citalopram, zonisamide, metoprolol, and oxcarbazepine.</p>					
5201-5004	46, F, W	DB 305: Placebo OLE 307: Pera 6 mg	Hyponatremia	OLE 82	Conversion
<p>Subject with a history of head injury s/p neurosurgery, hypertension who was hospitalized for hyponatremia on OLE Day 82. Sodium value was 126 mmol/L. Baseline was 137 mmol/L (reference 132-147). No treatment was recorded. The event resolved 2 days later and perampanel was continued. Subsequent values were 134 on Day 92 and 139 on Day 211.</p> <p>Concomitant medications included ramipril, pregabalin, levetiracetam, and oxcarbazepine.</p>					
5127-4004	60, F, W	DB 304: Pera 12 mg OLE 307: Pera 12 mg	Hyponatremia	OLE 382	Maintenance
<p>Subject with a history of hypertension who experienced a seizure and a fall. The subject was hospitalized and hyponatremia was noted at 121 mmol/L. Baseline was 138 (reference 132-147 mmol/L). Head CT was negative for any acute changes. No treatment was recorded for the hyponatremia. Perampanel was continued. Subsequent values were 134 on Day 490, 134 on Day 575, and 135 on Day 603. Concomitant medications included carbamazepine, lamotrigine, lisinopril.</p>					

Source: Created by the reviewer using narratives provided by the Sponsor and the epilepsy ADLB and ADAE datasets

Hyperkalemia

The following table summarizes the incidences of potentially clinically significant potassium values, shifts from normal to high potassium, and consecutively high potassium values. A higher percentage of perampanel subjects than placebo developed markedly abnormal high potassium values in all of the DB pools. However, in the epilepsy studies, there was no dose response observed and very few subjects (n=3) developed high values on consecutive visits (≥ 2 visits). Furthermore, there were no SAEs or discontinuations due to hyperkalemia in the entire safety database.

Table 139. Hyperkalemia

Category	Placebo n (%)	Perampanel n (%)				
		<4 mg	4 mg	>4-8 mg	>8-12mg	Total
Epilepsy Phase 3 DB Pool*	430	179	169	422	246	1016
Potassium >5.5 mmol/L [^]	2 (0.5)	5 (2.8)	0	3 (0.7)	2 (0.8)	10 (1.0)
Shift from normal to high	0	1 (0.6)	0	0	0	1 (0.1)
Consecutive High ≥ 2 Visits [^]	0	1 (0.6)	0	0	0	1 (0.1)
Epilepsy Phase 2 DB Pool	68	12	101		38	151
Potassium >5.5 mmol/L [^]	0	0	2 (2.1)	0	0	2 (1.4)
Shift from normal to high	1 (1.5)	0	2 (2.0)		4 (10.5)	6 (4.0)
Consecutive High ≥ 2 Visits [^]	0	1 (8.3)	1 (1.0)	0	0	2 (1.3)
Nonepilepsy DB Pool	1047	877	771	279	0	1927
Potassium >5.5 mmol/L [^]	17 (1.7)	18 (2.1)	17 (2.3)	14 (5.2)	0	49 (2.6)
Shift from normal to high	22 (2.1)	15 (1.7)	20 (2.6)	4 (1.4)	0	39 (2.0)
Consecutive High ≥ 2 Visits [^]	9 (0.9)	7 (0.8)	5 (0.7)	2 (0.7)	0	14 (0.7)

Source: ISS Table 20.11-5.5, 20.11-2.6, 20.11-51.5, 20.11-53.5, 20.11-61.5, 20.11-32.5, 20.11-45.5, 20.11-112.6

*Randomized treatment groups: 2 mg, 4 mg, 8 mg, and 12 mg

[^]Subjects with normal values at baseline

In the epilepsy population, the elevated potassium values were mostly between 5.5-5.9 mmol/L (n=114) and 6.0-6.4 mmol/L (n=12). There were 12 values between 6.5-8.5 mmol/L; these values were either elevated at baseline or screening, 30 days after last dose, or on study days >300 days.

In conclusion, perampanel is not associated with hyperkalemia in this database. Although there were more potentially clinically significant potassium values in perampanel subjects than placebo population, these mostly represented single (nonconsecutive) elevated potassium values that did not result in SAEs or treatment discontinuations. There were rare cases of potassium values ≥ 6.5 mmol/L which were unlikely related to perampanel use as they occurred before treatment, 30 day after treatment, or after prolonged exposure to perampanel.

Hypocalcemia

The following table summarizes the incidences of potentially clinically significant calcium values, shifts from normal to low calcium, and consecutively low calcium values. A higher percentage of perampanel subjects than placebo developed shifts to low calcium in the epilepsy Phase 2 DB and nonepilepsy DB pools. However, this signal was not replicated in the epilepsy Phase 3 DB pool or for PCS changes and consecutively low values for the nonepilepsy DB pool. Furthermore, there were no SAEs or discontinuations due to hypocalcemia in the entire safety database.

Table 140. Hypocalcemia

Category	Placebo n (%)	Perampanel n (%)				
		<4 mg	4 mg	>4-8 mg	>8-12mg	Total
Epilepsy Phase 3 DB Pool*	431	179	169	422	246	1016
Calcium <2.0 mmol/L [^]	2 (0.5)	0	0	1 (0.3)	0	1 (0.1)
Shift from normal to low	3 (0.7)	1 (0.6)	1 (0.6)	4 (0.9)	2 (0.8)	8 (0.8)
Consecutive Low ≥2 Visits [^]	2 (0.5)	1 (0.6)	0	0	0	1 (0.1)
Epilepsy Phase 2 DB Pool	68	12	101		38	151
Calcium <2.0 mmol/L [^]	0	0	2 (2.2)	0	0	2 (1.4)
Shift from normal to low	1 (1.5)	0	6 (5.9)	0	1 (2.6)	7 (4.6)
Consecutive Low ≥2 Visits [^]	1 (1.5)	0	3 (3.0)	0	1 (2.6)	4 (2.6)
Nonepilepsy DB Pool	1047	877	771	279	0	1927
Calcium <2.0 mmol/L [^]	2 (0.2)	1 (0.1)	0	0	0	1 (0.1)
Shift from normal to low	3 (0.3)	1 (0.1)	3 (0.4)	8 (2.9)	0	12 (0.6)
Consecutive Low ≥2 Visits [^]	1 (0.1)	0	1 (0.1)	1 (0.4)	0	2 (0.1)

Source: ISS Table 20.11-5.5, 20.11-2.6, 20.11-51.5, 20.11-53.5, 20.11-61.5, 20.11-32.5, 20.11-45.5, 20.11-112.6

*Randomized treatment groups: 2 mg, 4 mg, 8 mg, and 12 mg

[^]Subjects with normal values at baseline

Hypoglycemia

The following table summarizes the incidences of potentially clinically significant glucose values, shifts from normal to low glucose, and consecutively low glucose values. A higher percentage of perampanel subjects than placebo developed PCS low glucose values in the epilepsy Phase 3 DB pool. I independently reviewed these PCS values in the Phase 3 pool: most (88% or 15/17) were single, nonconsecutive low values with subsequent normal values while continued on perampanel and none were above toxicity Grade 2. One perampanel subject had a history of diabetes mellitus. Furthermore, this signal was not replicated in the other DB pools and there were no SAEs of hypoglycemia in the epilepsy studies. In the nonepilepsy studies, there was 1 hypoglycemia SAE in a subject with a history of Type 1 diabetes mellitus on Day 77 when the subject was “sick with a cold” with blood glucose fluctuations (and 2 hyperglycemia SAEs). In conclusion, while perampanel may be associated with decreases in glucose levels, these cases were mostly rare, transient, and not serious.

Table 141. Hypoglycemia

Category	Placebo n (%)	Perampanel n (%)				Total
		<4 mg	4 mg	>4-8 mg	>8-12mg	
Epilepsy Phase 3 DB Pool*	431	179	169	422	246	1016
Glucose <3.0 mmol/L [^]	2 (0.5)	0	1 (0.6)	10 (2.4)	6 (2.5)	17 (1.7)
Shift from normal to low	9 (2.1)	5 (2.8)	4 (2.4)	10 (2.4)	7 (2.8)	26 (2.6)
Epilepsy Phase 2 DB Pool	68	12	101		38	151
Glucose <3.0 mmol/L [^]	2 (3.1)	0	1 (1.1)	0	0	1 (0.7)
Shift from normal to low	3 (4.4)	0	4 (4.0)	0	1 (2.6)	5 (3.3)
Nonepilepsy DB Pool	1047	877	771	279	0	1927
Glucose <3.0 mmol/L [^]	14 (1.6)	12 (1.6)	7 (1.1)	1 (0.5)	0	20 (1.3)
Shift from normal to low	22 (2.1)	16 (1.8)	5 (0.6)	3 (1.1)	0	24 (1.2)

Source: ISS Table 20.11-5.5, 20.11-2.6, 20.11-51.5, 20.11-53.5, 20.11-61.6, 20.11-61.5, 20.11-105.6, 20.11-112.6

*Randomized treatment groups: 2 mg, 4 mg, 8 mg, and 12 mg

[^]Subjects with normal values at baseline

7.4.2.4 Urinalysis

In response to the Division's information request, the Sponsor submitted analyses for the urine parameters assessed in the epilepsy Phase 3 DB pool including mean changes from baseline for pH and specific gravity and shift results to abnormal for urine parameters. In the epilepsy Phase 3 DB pool, shifts from normal at baseline to abnormal for the urine parameters were infrequent and occurred in similar frequencies between the perampanel and placebo groups (Safety Information Amendment 7/27/12 Table 23.11-20 and 8/3/12 Table 23.11-22). Although the shift from normal to high for urine protein was slightly higher for perampanel subjects (8.4%) than placebo (7.2%), there was no dose response observed (Safety Information Amendment 8/3/12, Table 23.11-22). The mean changes from baseline to final for pH and specific gravity were similar for perampanel and placebo subjects (Safety Information Amendment 7/27/12, Table 23.11-19).

7.4.3 Vital Signs

Comprehensive analyses of perampanel's effects on weight along with other metabolic parameters are presented in Section 7.3.4.3 of this review. Of note, the following analyses for blood pressure provided by the Sponsor in the ISS used large categories for blood pressure changes (SBP changes of 20 mmHg), precluding the recognition of more subtle or smaller differences in SBP. Additional, more granular analyses of blood pressure were requested by the Division and are also presented in Section 7.3.4.3.

The following table summarizes the clinically notable values and changes relative to baseline in vital sign parameters for the epilepsy DB pools. Clinically notably high or low values for BP and HR occurred in a small percentage of subjects. In the epilepsy Phase 3 pool, similar percentages of perampanel and placebo subjects had clinically notable values and changes relative to baseline in SBP, DBP, and HR. In the epilepsy

Phase 2 pool, conflicting results were reported with higher percentages of perampanel subjects than placebo with both increases and decreases in BP and HR.

Table 142. Clinically notable values in vital sign parameters (and changes relative to baseline), Epilepsy DB Pools

	Epilepsy Phase 3 DB Pool		Epilepsy Phase 2 DB Pool	
	Placebo	Perampanel	Placebo	Perampanel
# Subjects	n=438	n=1034	n=68	n=151
SBP <90 mmHg	3 (0.7)	9 (0.9)	0	3 (2.0)
SBP >180 mmHg	0	0	0	0
SBP increase ≥20	80 (18.3)	194 (18.8)	7 (10.3)	24 (15.9)
SBP increase ≥40	5 (1.1)	7 (0.7)	0	4 (2.6)
SBP decrease ≥20	77 (17.6)	164 (15.9)	8 (11.8)	26 (17.2)
SBP decrease ≥40	4 (0.9)	13 (1.3)	0	3 (2.0)
DBP <50 mmHg	5 (1.1)	12 (1.2)	1 (1.5)	0
DBP >105 mmHg	4 (0.9)	5 (0.5)	0	0
DBP increase ≥10	179 (40.9)	416 (40.2)	29 (42.6)	54 (35.8)
DBP increase ≥20	42 (9.6)	103 (10.0)	4 (5.9)	12 (7.9)
DBP decrease ≥10	177 (40.4)	389 (37.6)	23 (33.8)	65 (43.0)
DBP decrease ≥20	40 (9.1)	81 (7.8)	3 (4.4)	15 (9.9)
HR <50 bpm	1 (0.2)	1 (0.1)	0	1 (0.7)
HR >120 bpm	2 (0.5)	0	1 (1.5)	0
HR increase ≥15	111 (25.3)	227 (22.0)	11 (16.2)	33 (21.9)
HR increase ≥30	12 (2.7)	29 (2.8)	2 (2.9)	3 (2.0)
HR decrease ≥15	75 (17.1)	140 (13.5)	12 (17.6)	14 (9.3)
HR decrease ≥30	6 (1.4)	7 (0.7)	1 (1.5)	0

Source: ISS Tables 191, 192, 20.12-23, 20.12-27

There were no SAEs related to vital signs (Table 20.7-1). Vital sign-related TEAEs that led to discontinuation were tachycardia (one subject in the 2 mg/d group), palpitations (one subject in the placebo group), weight decreased (one subject in the placebo group), hypotension (one subject in the 8 mg/d group) (Table 20.8-1).

The nonepilepsy DB pool, similar percentages of perampanel and placebo subjects had clinically notable values and changes relative to baseline in SBP, DBP, and HR (ISS Tables 199, 20.12-56).

The following table summarizes the mean change from baseline to the end of treatment for the vital sign parameters. The mean values for systolic blood pressure, diastolic blood pressure, and pulse rate were within the normal range at baseline and the end of treatment in all groups. Almost all of the mean changes were small and clinically insignificant except for some dose groups in epilepsy Phase 2 DB pool with larger increases in HR and BP.

Comment: In the epilepsy Phase 2 DB pool, all of the 12 subjects in the <4mg dose group were in Study 203. According to Table 14.3.5.1.2 of the Clinical Study Report,

the baseline values for SBP and DBP were lower than values measured in the screening period (by 9 mmHg). Therefore, if the mean change from screening were calculated, the changes would be <0 mmHg for both SBP and DBP. As for HR, the perampanel subjects had a mean increase of 7.7 bpm. However, the placebo group also had a mean increase in HR of 3.3 bpm.

All of the 38 subjects in the >8-12 mg dose group were in Study 208. According to Table 14.3.3.1 of the Clinical Study Report, the baseline values for SBP and HR were lower than the values measured in the screening period (by 2 mmHg and 1 bpm, respectively). Therefore, if the mean change from screening were calculated, the changes would be only 0.8 mmHg and 1.0 bpm, respectively (instead of 2.8 mmHg and 2.0 bpm).

Table 143. Mean Change from Baseline to End of Treatment for Vital Signs

Category	Placebo n (%)	Perampanel n (%)				
		<4 mg	4 mg	>4-8 mg	>8-12mg	Total
Epilepsy Phase 3 DB Pool*	n=438	n=180	n=171	n=430	n=253	n=1034
SBP (mmHg)	-0.1	0.8	-0.1	0.7	-0.3	0.3
DBP (mmHg)	-0.1	0.8	-0.8	0.9	0.4	0.5
HR (bpm)	0.7	0.5	0.3	-0.4	-0.3	-0.1
Epilepsy Phase 2 DB Pool	n=68	n=12	n=101		n=38	n=151
SBP (mmHg)	-1.7	5.8	-1.6		2.8	0.1
DBP (mmHg)	-0.0	3.3	-0.7		0.2	-0.2
HR (bpm)	-0.1	7.7	-0.1		2.0	1.0
Parkinson's DB Pool	n=838	n=713	n=743	n=54		n=1510
SBP (mmHg)	-1.0	1.5	-0.2	-3.4		0.5
DBP (mmHg)	-0.6	1.2	-0.7	-1.3		0.2
HR (bpm)	0.2	-0.1	0.1	2.1		0.1
Neuropathic Pain DB Pool	n=118	n=70	n=68	n=227		n=365
SBP (mmHg)	0.2	1.1	-0.1	0.3		0.4
DBP (mmHg)	0.4	0.8	-1.1	0.3		0.1
HR (bpm)	0.4	-1.7	-0.7	-0.6		-0.8
Nonepilepsy DB Pool	n=1069	n=902	n=811	n=281		n=1994
SBP (mmHg)	-0.8	1.3	-0.2	-0.4		0.5
DBP (mmHg)	-0.4	1.0	-0.8	-0.0		0.1
HR (bpm)	0.6	0.2	0.1	-0.1		0.1

Source: ISS Tables 20.12-1, 20.12-25, 20.12-54, 20.12-59, 20.12-64

*Randomized dose groups 2 mg, 4 mg, 8 mg, 12 mg

Orthostatic Changes

Vital signs (VS) were measured with subjects in both supine and standing positions in the epilepsy Phase 2 studies and nonepilepsy studies. The following table summarizes the mean changes from baseline to end of treatment for orthostatic vital signs. The mean changes were similar in the placebo group and the total perampanel group.

Table 144. Mean Changes from Baseline to End of Treatment for Orthostatic VS

Parameter	Epilepsy Phase 2 DB Pool				Nonepilepsy DB Pool			
	Placebo		Perampanel		Placebo		Perampanel	
	n	mean Δ	n	mean Δ	n	mean Δ	n	mean Δ
SBP (mmHg)	68	-2.0	150	-0.5	1067	-0.4	1992	-0.7
DBP (mmHg)	68	-1.6	150	-0.4	1067	0.1	1992	-0.3
HR (bpm)	68	0.1	150	-0.7	1067	0.1	1992	0

Source: ISS Tables 20.12-27, 20.12-28

The following table summarizes the abnormal vital sign changes resulting from supine to standing position change. It is difficult to interpret these results which report higher incidences in the perampanel group than placebo of both SBP increases and decreases. Therefore, the Division requested the Sponsor to report vital sign changes resulting from supine to standing position change that occurred concurrently.

Table 145. Abnormal Vital Sign Changes Resulting from Supine to Standing Position Change

	Epilepsy Phase 2 DB Pool		Nonepilepsy DB Pool	
	Placebo	Perampanel	Placebo	Perampanel
# Subjects	n=68	n=150	n=1069	n=1994
SBP				
Increase ≥ 20	6 (8.8)	30 (20.0)	79 (7.4)	180 (9.0)
Increase ≥ 40	1 (1.5)	1 (0.7)	3 (0.3)	3 (0.2)
Decrease ≥ 20	1 (1.5)	17 (11.3)	229 (21.4)	506 (25.4)
Decrease ≥ 40	1 (1.5)	1 (0.7)	39 (3.6)	76 (3.8)
DBP				
Increase ≥ 10	33 (48.5)	77 (51.3)	361 (33.8)	649 (32.5)
Increase ≥ 20	8 (11.8)	18 (12.0)	57 (5.3)	108 (5.4)
Decrease ≥ 10	10 (14.7)	30 (20.0)	407 (38.1)	753 (37.8)
Decrease ≥ 20	1 (1.5)	3 (2.0)	67 (6.3)	138 (6.9)
Heart Rate				
Increase ≥ 15	20 (29.4)	47 (31.3)	209 (19.6)	402 (20.2)
Increase ≥ 30	3 (4.4)	6 (4.0)	17 (1.6)	28 (1.4)
Decrease ≥ 15	1 (1.5)	8 (5.3)	21 (2.0)	60 (3.0)
Decrease ≥ 30	1 (1.5)	0	1 (0.1)	4 (0.2)

Source: ISS Tables 20.12-27, 20.12-28

In response to the Division's information request dated April 20, 2012, the Sponsor submitted tables with concurrent orthostatic values (concurrent SBP decreases and HR increases). In the epilepsy Phase 2 DB pool and nonepilepsy DB pool, the incidences of concurrent orthostatic vital sign measurements were similar in the placebo and perampanel groups.

Table 146. Concurrent Orthostatic SBP Decrement and Pulse Increment

	Epilepsy Phase 2 DB Pool		Nonepilepsy DB Pool	
	Placebo	Perampanel	Placebo	Perampanel
# Subjects	n=68	n=150	n=1069	n=1994
SBP decrement ≥20 mmHg and HR increase				
HR increase ≥15	0	2 (1.3)	54 (5.1)	101 (5.1)
HR increase ≥30	0	0	5 (0.5)	6 (0.3)
SBP decrement ≥40 mmHg and HR increase				
HR increase ≥15	0	0	11 (1.0)	19 (1.0)
HR increase ≥30	0	0	2 (0.2)	2 (0.1)

Source: Safety information amendment (April 20, 2012) Tables 23.12-2, 23.12-5

*number of administrations (single-dose) or subjects (multiple-dose) with normal baseline

No TEAEs related to orthostatic changes were reported in any epilepsy study. In nonepilepsy DB studies, a similar percentage of perampanel subjects (1.6%) reported orthostatic hypotension TEAEs compared with placebo subjects (1.5%). There was one orthostatic hypotension SAE in the total perampanel group (subject 301-0157-0006 who after 82 days of 2 mg perampanel exposure experienced a mild orthostatic hypotension event that resolved the next day and was continued on perampanel for another 4 months without any recurrences of the event). A lower percentage of perampanel subjects (0.1%) discontinued due to orthostatic hypotension than placebo (0.2%).

Phase 1 Studies

In the single-dose studies, perampanel subjects had a lower incidence of concurrent orthostatic vital sign measurements than placebo (4.5% vs 10.3% for SBP≥20 and HR≥15, 1.5% vs 10.3% for SBP≥20 and HR≥30). In the multiple-dose studies, perampanel subjects had a lower (or similar) incidence of concurrent orthostatic vital sign measurements than placebo for all of the categories (11.1% vs 20.8%, 3.2% vs 4.2%, 2.0% vs 4.2%, and 0.4% vs 0, respectively for the 4 categories in the table above). (Safety Information Amendment April 20, 2012, Tables 22.6-7-1, 22.6-8-1).

In the single-dose studies, 1 orthostatic hypotension TEAE occurred in the perampanel group (vs 0 placebo). In the multiple-dose studies, a similar percentage of perampanel subjects (2.9%) reported orthostatic hypotension TEAEs compared with placebo subjects (2.6%). There were no SAEs or discontinuations due to orthostatic hypotension.

In Study 001, two potentially clinically significant AEs were reported following administration of 2 mg perampanel, while there were no clinically significant adverse events following administration at the 0.2, 0.5 or 1 mg dose levels. It is difficult to make any definite conclusions regarding the causal role of perampanel in these two cases of hypotension. Although the timing of the events corresponds to perampanel exposure, the events could have also been a result of vasovagal episodes. Furthermore, it is reassuring that the subjects made a rapid and full recovery without sequelae or the need for any treatment.

Subject 27 reported dizziness when standing up at 4 hours for measurement of standing blood pressure. He was immediately laid flat. His BP was recorded as 85/28 mmHg and pulse was 66 bpm. He did not lose consciousness and made quite a rapid recovery without any sequelae.

Subject 31 became pale, bradycardic (sinus bradycardia, with 1st degree atrioventricular block, pulse 35 bpm) and hypotensive (BP 86/31 mmHg) at 30 minutes post-dose. His conscious level decreased but he did not lose consciousness. Within a few minutes after he was laid in the head down position, his heart rate and BP increased, with his conscious level returning to normal. At 1 hour post-dose, his heart rate would decrease when he sat up, and blood pressure remained low (89/44 mmHg). The vital signs gradually improved with complete resolution by 4 hours post-dose.

7.4.4 Electrocardiograms (ECGs)

The ECG data for perampanel come from the thorough QT trial, Study 013, and from ECGs that were performed during the epilepsy, nonepilepsy, and Phase 1 trials. Based on review of the thorough QT study and on data from the clinical studies as discussed below, there is no evidence of QT prolongation with perampanel.

The Sponsor's NDA submission included results from a formal QT study that examined the effect of perampanel on cardiac repolarization. The FDA Interdisciplinary Review Team (IRT) for QT studies reviewed Study 013 in a review dated December 6, 2011. The IRT reported the following:

- No significant QTc prolongation effect of perampanel (6 mg and 12 mg) was detected in this TQT study.
- The largest upper bounds of the 2-sided 90% CI for the mean differences between perampanel (6mg and 12 mg) and placebo were below 10 ms, the threshold for regulatory concern.
- The largest lower bound of the 2-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms indicating that assay sensitivity was established.
- The 'supratherapeutic' dose (12 mg) produces mean C_{max} values less than twice the mean C_{max} for the therapeutic dose (6 mg). The highest expected clinical exposure is considered to occur after multiple daily doses of 12 mg/day (without concomitant administration of CYP3A4 inducers). At these concentrations, there are no detectable prolongations of the QT-interval.
- As perampanel is primarily cleared by the CYP3A4 pathway, there is potential for hepatic dysfunction or concomitant use of CYP3A4 inhibitors to increase perampanel exposure. It is predicted that concentrations achieved from a 12-mg once daily dose in healthy subjects will, on average, exceed those from use of 4 mg once daily in almost all individuals. Of note, the dosing of 12 mg once daily at steady state for healthy individuals would not cover the predicted exposures for subjects with mild or moderate hepatic impairment receiving ≥ 6 mg/day.

The IRT recommended the following labeling to summarize the results of the formal QT study:

Cardiac Electrophysiology

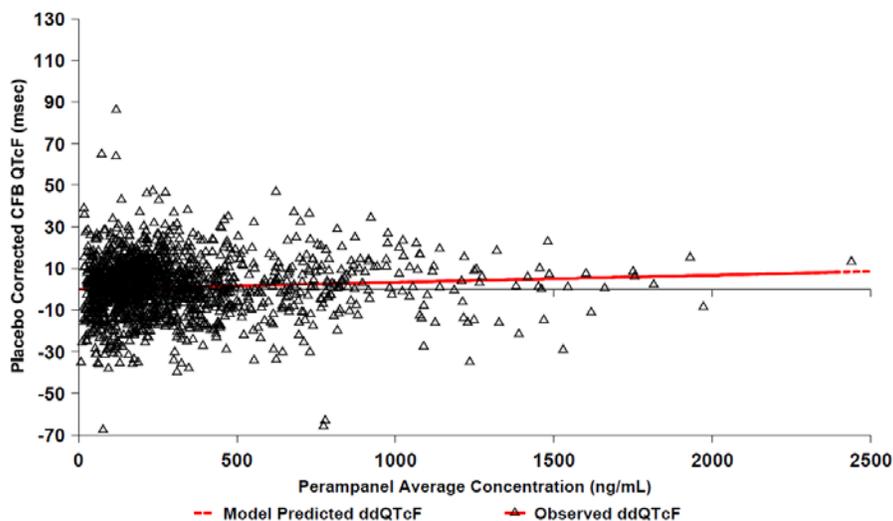
The effect of perampanel 6 and 12 mg following multiple doses on QTc interval was evaluated in a randomized, placebo- and active-controlled (moxifloxacin 400 mg) three-arm parallel group thorough QT study in 196 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on Fridericia's correction method (QTcF) was below 10 ms, the threshold for regulatory concern. The steady state exposures observed with 12 mg dose in this study will not cover the exposures expected in patients with hepatic impairment taking doses over 6 mg/day.

Comment: The FDA requested (in the Refuse to File letter dated July 21, 2011) that the Sponsor provide the rationale for not performing the TQT study at doses higher than 12 mg/day (as requested during the End of Phase 2 meeting on December 5, 2007). In the ISS (Section 9.3.2.1.2), the Sponsor stated that the rationale for not performing the perampanel TQT study at doses higher than 12 mg/day is "based on considerations of safety and tolerability due to drug-related adverse effects, with 12 mg/day considered at or near the maximum tolerated multiple dose regimen or perampanel in healthy subjects." However, acknowledging that the TQT study could not incorporate a suprathreshold dose, the Sponsor stated that the Phase 3 studies of perampanel were designed to include expanded ECG safety evaluations to "bridge" the concentration-QT response determined in healthy subjects with patients. The Sponsor submitted a Cardiac Safety Report in the 120-day Safety Update that concluded that perampanel did not cause QT prolongation. A cardiology consult was requested from the IRT-QT team in the Division of Cardiology and Renal Products to further evaluate the Sponsor's conclusions in the Cardiac Safety Report. The review by Dr. Fiszman dated July 27, 2012 agreed with the Sponsor and concluded that it was unlikely that changes from baseline of QTc reported in study 228 were a QT signal for perampanel.

Epilepsy DB Studies

The Sponsor reported that the relationship between perampanel plasma concentrations and QT interval duration was evaluated based on the epilepsy Phase 3 double-blind pool. The following figure shows that plasma concentrations of perampanel achieved in clinical studies were not associated with an increase in the QT interval duration.

Figure 8. Scatterplot of the Change from baseline in QTcF vs. Perampanel Plasma Concentration (Studies 304, 305, 306)



Source: Summary of Clinical Pharmacology Studies Figure 2.7.2-15

The following table summarizes the QTcF outliers from the analysis of ECG data from the epilepsy Phase 2/3 DB studies. In the epilepsy studies, no subject had a maximum QTcF value > 500 msec. Furthermore, the percentages of subjects with QTcF values > 450 msec or an increase of 30-60 msec were similar (or less) with perampanel than placebo. The percentages of subjects with QTcF increases from baseline of >60 msec were low and were comparable with placebo and perampanel.

Table 147. QTcF outliers, Epilepsy DB Pools

Outlier criteria	Epilepsy Phase 3 DB		Epilepsy Phase 2 DB	
	Placebo	Perampanel	Placebo	Perampanel
# Subjects	n=428	n=1009	n=68	n=151
QTcF>450ms	2 (0.5)	8 (0.8)	3 (4.4)	4 (2.6)
QTcF>500ms	0	0	0	0
QTcF increase 30-60 ms	14 (3.3)	37 (3.7)	14 (20.6)	16 (10.6)
QTcF increase >60ms	2 (0.5)	2 (0.2)	1 (1.5)	1 (0.7)

Source: ISS Tables 204, 205

In the nonepilepsy DB studies, ECGs were not performed in all of the studies in subjects with Parkinson’s disease, neuropathic pain, MS, or migraine. A maximum QTcF value > 500 msec occurred in two (0.2%) placebo and one (0.1%) perampanel subject. The percentages of subjects with QTcF values > 450 msec were similar in the placebo and total perampanel groups (5.2% and 4.5%, respectively). The percentages of subjects with QTcF increases from baseline of 30-60 msec and >60 msec were similar in the two groups (9.9% and 10.3%, 0.5% and 0.5%, respectively) (ISS Table 209).

In the Phase 1 studies, ECGs were not performed in all of the studies. In the studies with ECG data, no subject had a maximum QTcF value >500 msec. In the single-dose studies, a maximum QTcF value >450 msec occurred in fewer perampanel subjects (2.4%) than placebo (3.4%), and no subjects had an increase in QTcF value >60 msec. In the multiple-dose studies, one perampanel subject (0.9%) had a maximum QTcF value >450 msec and QTcF increase >60 msec (vs 0 placebo). Perampanel subjects (4.4%) had fewer QTcF increases of 30-60 msec than placebo (7.7%) in the multiple-dose studies. Conversely, in the single-dose studies, placebo subjects (4.5%) had fewer QTcF increases of 30-60 msec than perampanel subjects (8.4%) (ISS Tables 22.7-5, 22.7-6).

The following table summarizes the mean change from baseline results for the ECG data from the epilepsy Phase 2/3 DB studies. The mean changes tended to be small and of unknown clinical significance.

Table 148. Mean Change from Baseline Results for ECG Data, Epilepsy DB Pools

ECG Parameter	Epilepsy Phase 3 DB				Epilepsy Phase 2 DB			
	Placebo		Perampanel		Placebo		Perampanel	
	n	mean Δ	n	mean Δ	n	mean Δ	n	mean Δ
QT (ms)	428	-1.0	1009	0.6	68	2.0	151	0.7
QTcB (ms)	428	0.2	1009	0.4	68	4.9	151	1.2
QTcF (ms)	428	-0.2	1009	0.5	68	3.8	151	0.8
Heart rate (bpm)	431	0.7	1016	-0.1	62	0.5	139	-0.3
PR duration (ms)	428	0.5	1009	-0.4	68	2.0	150	-0.5
QRS duration	428	-0.2	1009	0.3	68	-0.3	151	-1.2
RR duration	431	-9.1	1016	0.6	68	-10.6	151	-4.8

Source: ISS Tables 20.13-1, 20.13-21

The following table summarizes the percentages of subjects who shifted from normal to abnormal in ECG interpretation and who developed treatment-emergent ECG abnormalities. In general, the incidences of shifts and ECG TEAEs were similar (or less) in the perampanel group than in the placebo group, except for the TEAE of sinus bradycardia (that occurred more in perampanel vs placebo in the Phase 3 pool and to a greater extent in the Phase 2 pool). Cardiovascular adverse events are discussed in more detail in Section 7.3.5.3. In the nonepilepsy DB pool, the incidences of shifts and ECG TEAEs were similar in the placebo and perampanel groups: abnormal ECG 2.1% vs 2.6%, sinus bradycardia 41.7% vs 42.6%, sinus tachycardia 1.9% (n=2) vs 4.0% (n=4), first degree AVB 10.6% vs 11.8%, intraventricular block 5.3% vs 5.6%, and ischemia/infarction 12.6% vs 11.6% (ISS Tables 20.13-42, 20.13-44).

Table 149. Shifts in ECG Interpretation and Treatment-Emergent ECG Abnormalities, Epilepsy DB Pools

Parameter	Epilepsy Phase 3 DB				Epilepsy Phase 2 DB			
	Placebo		Perampanel		Placebo		Perampanel	
	n	# (%)	n	# (%)	n	# (%)	n	# (%)
Shift to abnormal ECG*	432	65 (15)	1019	122 (12)	67	3 (4.5)	148	6 (4.1)
Treatment-emergent ECG abnormalities								
Sinus bradycardia	431	114 (26.5)	1018	286 (28.1)	62	24 (38.7)	139	70 (50.4)
Sinus tachycardia	431	16 (3.7)	1018	16 (1.6)	62	1 (1.6)	139	1 (0.7)
First degree AVB	429	23 (5.4)	1014	39 (3.8)	68	6 (8.8)	150	15 (10.0)
Intraventricular block	429	3 (0.7)	1014	10 (1.0)	68	3 (4.4)	151	4 (2.6)
Ischemia/infarction	432	2 (0.5)	1019	11 (1.1)	68	2 (2.9)	151	5 (3.3)

Source: ISS Tables 20.13-2, 20.13-20, 20.13-22, 20.13-24

*Shifts from normal at baseline to abnormal in ECG interpretation

In the Phase 1 studies, the Sponsor reported that all of the placebo and perampanel subjects had interpretations of “no clinically significant abnormalities” both at baseline and at end of study. Sinus tachycardia was detected in 3.4% of the ECGs in the perampanel group (vs 0 placebo) in the multiple-dose studies and was not detected on any of the ECGs in the single-dose studies. In the single-dose studies, sinus bradycardia was detected in slightly more ECGs in the perampanel group than placebo (87.5% vs 71.9%) whereas, in the multiple-dose studies, the converse was true (74.4% vs 80.8%, respectively). First degree atrioventricular block was detected in slightly more ECGs in the perampanel group than placebo in both the single-dose (9.9% vs 9.0%) and multiple-dose studies (10.3% vs 7.7%). Intraventricular block was detected rarely but only in ECGs in the perampanel group (1.0% of single-dose ECGs and 3.4% of multiple-dose ECGs).

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

Generally, there was a dose response observed for safety issues, with increasing dose associated with an increase in adverse events. These are noted in appropriate sections within Section 7. Dose response can be difficult to interpret in the controlled trials given that subjects were titrated to the target dose during the titration periods (of varying

lengths) and any AE occurring during titration may have occurred at a dose lower than the subjects' final target dose. Furthermore, within pooled groups, differences in the safety profile among the dose groups may reflect differences in the demographics of the studies that the dose groups represent (discussed further in Section 7.2.1).

The reader is referred to the Pharmacometric review for further details regarding the population PK/PD analysis based on pooled data from the double-blind, Phase 3 epilepsy studies that examined the relationship between plasma concentrations of perampanel and the occurrence of TEAEs.

Titration Intervals

The randomized, double-blind, placebo-controlled Study 218 in subjects with neuropathic pain investigated different titration intervals for perampanel. The study contained 2 cohorts (Cohort 1 with a placebo arm and a perampanel arm and Cohort 2 with a placebo arm and 2 perampanel arms). Up-titration in the perampanel arm in Cohort 1 occurred at 3-week intervals. Up-titration in the perampanel arms in Cohort 2 occurred at 1-week or 2-week intervals. Subjects assigned to each of the perampanel arms were started at 2 mg/day, and titrated according to the assigned schedule to their target dose or maximum tolerated dose (4 mg, 6 mg, or 8 mg perampanel). The 1-week titration perampanel group had the highest incidence of the neuro-related TEAEs dizziness, fall, gait disturbance, vision blurred, fatigue, dysarthria, balance disorder, headache, and confusional state (see Table below). Furthermore, study drug-related TEAEs and withdrawals due to TEAEs were most common in the 1-week titration perampanel group. The safety profile in the 2-week and 3-week titration groups was similar. Therefore, for subgroups at higher risk for these neurologic-related AEs, a slower titration interval should be recommended.

Table 150. Neuro-Related TEAEs Occurring in the 1-week Titration Group Greater than 2-week or 3-week Titration Groups, Neuropathy Study 218

Preferred Terms	Cohort 1		Cohort 2		
	Placebo n=26	3-wk Titration n=53	Placebo n=22	1-wk Titration n=22	2-wk Titration n=23
Dizziness	8 (30.8%)	22 (41.5%)	1 (4.5%)	12 (54.5%)	8 (34.8%)
Gait disturbance	0	2 (3.8%)	0	7 (31.8%)	2 (8.7%)
Dysarthria	0	2 (3.8%)	0	4 (18.2%)	1 (4.3%)
Confusional state	0	0	0	3 (13.6%)	0
Fatigue	1 (3.8%)	1 (1.9%)	1 (4.5%)	3 (13.6%)	2 (8.7%)
Headache	2 (7.7%)	4 (7.5%)	1 (4.5%)	3 (13.6%)	1 (4.3%)
Vision blurred	0	0	0	2 (9.1%)	1 (4.3%)
Fall	0	3 (5.7%)	0	2 (9.1%)	1 (4.3%)
Balance disorder	1 (3.8%)	2 (3.8%)	0	2 (9.1%)	2 (8.7%)

Source: Clinical Study Report 218 Table 41

Of note, somnolence was the only neuro-related TEAE reported less frequently in the 1-week titration group (9.1%) than the 2-wk or 3-wk titration groups (21.7% and 17.0%, respectively).

7.5.2 Time Dependency for Adverse Events

The distribution of TEAEs by time of onset is noted in appropriate sections within Section 7. The Sponsor provided Kaplan-Meier estimated rates of the time to first occurrence of the 21 ADRs identified from the epilepsy studies for the epilepsy all treated pool (120-day Safety Update Table 20.10-27). For at least half of the subjects who experienced these ADRs, the first occurrence was within the first 6 weeks of treatment (dizziness, fatigue, gait disturbance, increased appetite, somnolence, vertigo, vision blurred), the first 10 to 14 weeks of treatment (anger, ataxia, balance disorder, confusional state, decreased appetite, dysarthria, fall, irritability, nausea), the first 18 to 20 weeks of treatment (aggression, diplopia, weight increased), or after 6 months or more of treatment (anxiety, back pain). Subjects continued to have first occurrences of all ADRs during perampanel treatment.

The following table summarizes the duration of the ADRs identified from the epilepsy studies (in descending order of median duration). Although this table likely also includes events that led to discontinuation of perampanel (not specified by the Sponsor), these discontinuation events comprised a minority of the total event counts.

Table 151. Duration of Adverse Drug Reaction TEAEs for Perampanel Subjects, Epilepsy Studies

ADR TEAEs	# events*	Median duration (days)	Mean duration (days)
Aggression	72	5.0	29.8
Nausea	140	5.0	30.6
Diplopia	70	5.0	38.7
Back pain	69	8.0	23.8
Vertigo	135	8.0	35.5
Gait disturbance	95	12.0	39.5
Dizziness	1158	12.0	43.2
Vision blurred	44	12.5	50.3
Confusional state	21	13.0	30.9
Anxiety	55	16.0	45.2
Fatigue	169	18.0	46.7
Ataxia	105	20.0	42.2
Somnolence	366	21.0	58.5
Dysarthria	56	21.5	43.9
Balance disorder	89	23.0	56.3
Decreased appetite	40	29.5	72.0
Anger	27	30.0	50.1
Irritability	114	43.0	82.1
Increased appetite	15	54.0	125.5
Weight increased	68	89.0	127.8

Source: 120-day Safety Update, Table 20.10-28

*Resolved TEAEs with complete onset and end dates

7.5.3 Drug-Demographic Interactions

The effects of age, sex, or race on perampanel PK in subjects with partial-onset seizures were not evaluated in prospective clinical studies. Drug-demographic interactions were evaluated in population PK analyses of healthy subjects and patients.

Pediatric Subjects

Perampanel has not been studied in patients <12 years old. A total of 104 pediatric subjects (12 to ≤16 years-old) were exposed to perampanel in the epilepsy clinical development program. Specific information regarding the safety profile of adolescents is further discussed in appropriate sections within Section 7, particularly with respect to hostility and aggression.

Comment: I believe that this NDA did not provide enough information regarding the safety profile of perampanel in adolescent subjects. The Sponsor has recently initiated Study 235 which is a randomized, double-blind, placebo-controlled study of the effects of adjunctive therapy with perampanel specifically on the cognition, growth, safety, tolerability, and PK in adolescents (from 12 to <18 years of age). As of October 1, 2011, 39 subjects have been enrolled with an enrollment goal of 132 subjects. Only information regarding deaths and SAEs from this study was included in the ISS and the

120-day Safety Update. Five SAEs have already been reported from Study 235 (increased aggressive behavior, status epilepticus, fracture of right metacarpal in perampanel subjects along with 2 blinded SAEs of increased seizures and gastroduodenitis). I recommend waiting until the results of Study 235 before granting the indication of perampanel for adolescent pediatric subjects (12-16 years old).

Geriatric Subjects

The Sponsor reported no significant effect of age on perampanel clearance based on a population pharmacokinetic analysis of patients with partial-onset seizures ranging in age from 12 to 74 years. Two Phase 1 studies conducted in elderly healthy subjects (age range 65-79 years) reported that perampanel was safe and well tolerated in this age cohort. However, both studies enrolled only a few subjects (32 subjects total) who were only administered single doses of perampanel. The epilepsy Phase 2/3 DB studies included only 31 elderly subjects while the nonepilepsy studies included 1209 elderly subjects. (b) (4)

Comment: The number of elderly patients included in this NDA appears small. Even though there was a large elderly population in the nonepilepsy studies, these subjects were given lower doses for the nonepilepsy indications. Furthermore, in the epilepsy studies, elderly subjects had lower duration of exposure at higher doses. The safety profile of elderly subjects was different from adult subjects. For example, elderly subjects in the epilepsy Phase 3 DB pool had a much higher rate of discontinuation in the perampanel group (28.6%, 8/28) than placebo (0%, 0/8) with most discontinuing due to AEs (4) and subject choice (3), while the overall incidences of discontinuations were 14.6% vs 11.3%, respectively (ISS Tables 12 and 20.1-1.1). Specific information regarding the safety profile of elderly subjects, particularly with respect to neurologic TEAEs, is further discussed in appropriate sections within Section 7. Elderly subjects were at higher risk for these neurologic AEs (particularly dizziness/coordination, somnolence/ fatigue, and falls/injuries). Therefore, closer monitoring and a longer titration interval should be recommended for elderly subjects.

Sex

In a population pharmacokinetic analysis of patients with partial-onset seizures receiving perampanel up to 12 mg/day in placebo-controlled clinical trials, perampanel clearance in females (0.605 L/h) was 17% lower than in males (0.730 L/h) (both with a median fat body mass of 17.1 kg and not taking any AEDs that affect perampanel clearance). In the population PK analysis of data from 19 Phase 1 studies in healthy subjects, no effect of sex on perampanel clearance was found. The reader is referred to the Clinical Pharmacology review for further details regarding these analyses. 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

In a population pharmacokinetic analysis of patients with partial-onset seizures receiving perampanel up to 12 mg/day in placebo-controlled trials, the Sponsor reported that no significant effect of race on perampanel clearance was found. The reader is referred to the Clinical Pharmacology review for further details regarding these analyses. In the epilepsy Phase 3 DB pool and nonepilepsy DB pool, the subjects were predominantly white (75% and 92%, respectively). There were few Asians (7% and 1%) and blacks (4% and 6%) particularly in the highest dose groups (12 mg and >4-8 mg, respectively). Therefore, with the small sample sizes in these other racial groups, it is difficult to make any conclusions regarding racial differences in the safety profile of perampanel.

7.5.4 Drug-Disease Interactions

The reader is referred to the Clinical Pharmacology review for further details regarding the clinical pharmacology studies described briefly below.

Hepatic Impairment

The pharmacokinetics of perampanel following a single 1 mg dose were evaluated in 12 subjects with mild and moderate hepatic impairment (Child-Pugh A and B, respectively) compared with 12 healthy, demographically matched subjects. The mean apparent clearance of unbound FYCOMPA in mildly impaired subjects was 188 mL/min vs 338 mL/min in matched controls, and in moderately impaired subjects was 120 mL/min vs 392 mL/min in matched controls. The $t_{1/2}$ was longer in mildly impaired (306 h vs 125 h) and moderately impaired (295 h vs 139 h) subjects compared to matched healthy subjects. Based on this longer half-life, the Sponsor has recommended that during dose titration, dose increases should occur no more frequently than every 2 weeks for patients with mild or moderate hepatic impairment. Furthermore, the Sponsor has recommended that dosing not exceed (b) (4) in this population. There are no data on the use of perampanel in patients with severe hepatic impairment and, therefore, perampanel is not recommended for use in these patients.

Renal Impairment

A prospective clinical study examining the effect of renal impairment on perampanel PK has not been conducted. Perampanel is eliminated almost exclusively by metabolism followed by rapid excretion of metabolites with only trace amounts of perampanel metabolites are observed in plasma. The Sponsor reported that the population PK analysis for data from the controlled Phase 3 studies showed that clearance of perampanel was not significantly affected by baseline creatinine clearance.

7.5.5 Drug-Drug Interactions

The reader is referred to the Clinical Pharmacology review for further details regarding the clinical pharmacology studies described briefly below. Drug-drug interactions were evaluated in individual in vitro studies, studies in healthy volunteers and in a population PK analysis based on the pool of the double-blind, Phase 3 studies.

CYP3A4 Inducers

Treatment with carbamazepine (300 mg BID) increased the clearance of perampanel 3-fold and decreased C_{max} and AUC values by 26% and 67%, respectively. In agreement with this finding, the population PK analysis for data from the controlled Phase 3 studies showed that clearance of perampanel was significantly increased in the presence of the co-administered carbamazepine (approximately 3-fold), oxcarbazepine (approximately 2-fold), and phenytoin (approximately 2-fold). Phenobarbital and primidone showed no significant effect on perampanel clearance. Coadministration of perampanel with topiramate also slightly increased perampanel clearance by 22.8%. None of the other concomitantly administered AEDs had an effect on perampanel clearance.

Furthermore, in this population PK analysis, perampanel had a statistically significant effect on the clearance of carbamazepine, clobazam, lamotrigine, and valproic acid (magnitude of this effect was <10% for each drug with 12 mg dose of perampanel). Perampanel co-administration resulted in a 26% decrease in oxcarbazepine clearance. Perampanel did not significantly affect the clearance of clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate, or zonisamide.

Ketoconazole

Administration with perampanel caused a small increase (15%) in perampanel half-life with a corresponding increase in total exposure (20% increase in AUC), without affecting C_{max} .

Oral contraceptives (OC)

The PK of estradiol and levonorgestrol were not altered by 4 mg of perampanel in a multiple-dose study. Steady-state concentrations of perampanel following multiple doses of 12 mg perampanel induced a decrease of C_{max} and AUC of levonorgestrel by approximately 40% (along with a decrease of C_{max} of ethinylestradiol by 18%).

Midazolam

The AUC values of midazolam were not altered by the administration of 6 mg of perampanel for 20 days. The C_{max} values for midazolam decreased by 15%.

Levodopa

In a multiple-dose study, the PK of levodopa was not altered by 4 mg of perampanel.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

In the preclinical studies, the Sponsor reported that there was no evidence of carcinogenicity in mice and rats. The reader is referred to the Pharmacology, Toxicology review by Dr. Christopher Toscano for further details regarding the limitations of these preclinical studies.

Evaluation of deaths, serious AE, discontinuations due to AE and common AE under the MedDRA SOC Neoplasms benign, malignant and unspecified (including cysts and polyps) in the perampanel clinical program did not suggest an increased risk of malignancy in subjects taking perampanel.

In the epilepsy Phase 2/3 DB studies, none of the perampanel subjects developed malignant neoplasms (only 1 benign lung neoplasm and 1 lipoma). In the epilepsy all treated pool, the top 6 preferred terms in the Neoplasms SOC were benign conditions (3 lipoma, 3 uterine leiomyoma, 2 skin papilloma, 1 acrochordon, 1 benign breast neoplasm, 1 benign lung neoplasm). Additionally, there were rare cases of breast cancer (1), breast cancer in situ (1), breast cancer metastatic (1), breast cancer recurrent (1), colon cancer (1), colon neoplasm/hepatic neoplasm (1), prostate cancer (1), thyroid cancer (1), and thyroid neoplasm (1). There was also one case of malignant melanoma in the epilepsy all treated pool. The following table summarizes the SAEs in the Neoplasm SOC.

Table 152. Neoplasm SAEs, Epilepsy Studies

Subject #	Age, Sex, Race	Study: Treatment, Dose	Adverse event (Preferred Term)	Study day	Prior history?
0057-0064	49, M, W	DB 206: placebo OLE 207: Pera 6 mg	Malignant melanoma	OLE 1701	New diagnosis
2806-5004	45, F, W	DB 305: placebo OLE 307: Pera 12 mg	Breast cancer metastatic	OLE 252	New diagnosis by biopsy
0003-0163	52, F, W	DB 206: Pera 1 mg OLE 207: Pera 12 mg	Breast cancer in situ	OLE 895	New diagnosis mammogram, biopsy
3012-1007	58, F, W	DB 208: Pera 6 mg OLE 207: Pera 8 mg	Breast cancer recurrent	OLE~180	History of breast cancer
2803-5002	72, M, W	DB 305: Pera 8 mg OLE 307: Pera 12 mg	Colon cancer	OLE 582	New diagnosis colonoscopy
4501-5006	53, F, W	DB 305: Pera 12 mg OLE 307: Pera 8 mg	Colon neoplasm/ Hepatic neoplasm	OLE 381	New diagnosis CT scan
3022-1052	55, W, M	DB 208: Pera 12 mg OLE 207: Pera 12 mg	Prostate cancer	OLE 870	New diagnosis PSA, biopsy
1305-5003	28, F, W	DB 305: placebo OLE 307: Pera 12 mg	Thyroid cancer	OLE 519	New diagnosis
3001-6005	47, F, W	DB 306: Pera 8 mg	Benign lung neoplasm	DB 12	New diagnosis chest xray
1203-6013	48, M, W	DB 306: Pera 2 mg OLE 307: Pera 12 mg	Glioma	OLE 172	History of astrocytoma glioma
2455-6002	43, F, W	DB 306: placebo OLE 307: Pera 4 mg	Uterine leiomyoma	OLE 80	New diagnosis

Source: Created by the reviewer using subject narratives and the epilepsy ADSL and ADAE datasets.

In the nonepilepsy DB studies, the only neoplasm that occurred in 2 or more subjects and greater than placebo was basal cell carcinoma. In the nonepilepsy OLE studies, the following additional neoplasms were reported in perampanel subjects:

- Lung: metastatic bronchial carcinoma (1), lung neoplasm (1), lung neoplasm malignant (2)
- Endocrine: breast cancer (1), thyroid neoplasm (1)
- GI: colon cancer (1), rectal cancer (1), pancreatic cancer (1), gastric neoplasm (1)
- GU: endometrial cancer (1), uterine cancer (1), prostate cancer (1)
- Other: squamous cell carcinomas (4), adenocarcinoma (1), chondrosarcoma (1)
- Skin: basal cell carcinomas (10), lentigo maligna stage unspecified (1)
 - malignant melanoma (2), both subjects newly diagnosed (Day 33 and Day 96)
 - malignant melanoma in situ (2), one subject with history of melanoma and one subject newly diagnosed on Day 69
 - melanoma recurrent (1) in a subject with history of melanoma

Comment: The higher number of neoplasms in the nonepilepsy studies is expected with this older population (mean age 61.8 years). The number and types of neoplasms are similar to what would be expected for this patient population (older, white, male subjects). Even the 4 cases of lung neoplasms (0.15%) in the nonepilepsy population is consistent with the background rate (0.19%).¹⁶ Therefore, the assessment of the causal relationship between perampanel exposure and neoplasms is difficult. Interestingly, there is one case of malignant melanoma in the epilepsy population and 5 cases in the nonepilepsy population. The cases in the nonepilepsy population were in subjects with either a prior history (n=2) or diagnosed within 3 months of initiation of perampanel (n=3) (likely too soon for carcinogenicity to be due to perampanel exposure). However, the one case in epilepsy population was in a young subject without a prior history of melanoma and after 4.7 years of perampanel exposure. According to the National Cancer Institute, Surveillance Epidemiology and End Results (SEER), the incidence of melanoma of the skin in this cohort (white, male, 45-49 years) is low (27.9 per 100,000 subjects).¹⁷ In the epilepsy population, the incidence rate of melanoma is 60.6 per 100,000 subjects (1/1651) which is twice the SEER rate. However, with only one case in the epilepsy population, it is difficult to distinguish these results from chance alone.

7.6.2 Human Reproduction and Pregnancy Data

The Sponsor proposes that perampanel be classified as Pregnancy Class C, noting that reproductive toxicity studies demonstrate adverse effects on fetal development but that there are no data from adequate and well controlled trials in humans that allow an evaluation of the effects of perampanel on reproduction and fetal development. The Sponsor recommends that perampanel “should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.” Furthermore, for nursing mothers, the Sponsor recommends that (b) (4)

In the preclinical studies, the Sponsor reported that perampanel did not cause fetal malformations in rats or rabbits, although an increased number of stillbirths was observed (at the mid and high doses) along with suppression of body weight gains and delay of morphologic differentiation (at the high doses). Furthermore, in rats, perampanel crossed the placenta and was secreted into milk. The reader is referred to the Pharmacology, Toxicology review by Dr. Christopher Toscano for further details regarding the preclinical studies.

16 National Cancer Institute, Surveillance Epidemiology and End Results, Fast Stats by Cancer Site: SEER incidence 2000-2009, Lung and Bronchus, Age-specific rate table, white, both sexes, age range 55-69. <http://seer.cancer.gov/faststats/selections.php?series=cancer> (Accessed August 9, 2012).

17 National Cancer Institute, Surveillance Epidemiology and End Results, Fast Stats by Cancer Site: SEER incidence 2000-2009, Melanoma of the Skin, Age-specific rate table, white, male, age range 45-49. <http://seer.cancer.gov/faststats/selections.php?series=cancer> (Accessed July 23, 2012).

There was minimal data on the use of perampanel in pregnant women as the protocols for the epilepsy 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). Women using hormonal contraceptives also used an additional approved method of contraception.

As of the cutoff date for the 120-day Safety Update, there were a total of 16 pregnancies (perampanel-exposed, treatment-emergent pregnancies) in 14 subjects in the entire safety database:

- Epilepsy studies: 15 pregnancies in 13 subjects
 - 13 pregnancies in OLE Study 307, 1 in DB Study 304, 1 in OLE Study 207
- Nonepilepsy studies: 1 pregnancy
- Phase 1 studies: 0 pregnancies

The 16 pregnancies resulted in the following outcomes:

- 8 (50%) induced abortions
- 4 (25%) spontaneous abortions – described in more detail in the following Table
- 2 (12.5%) healthy births - described in more detail in the following Table
- 1 (6.3%) neonatal death – described in more detail in the following Table
- 1 ongoing (subject 306-3956-6001)

Comment: There were discrepancies between the number of pregnancies that the Sponsor reported in Section 15 of the 120-day Safety Update (Table 20.35) and my independent review of the epilepsy ADAE dataset and pregnancy narratives. In response to our information request, the Sponsor explained the discrepancies and resubmitted Table 20.35 with a comprehensive list of all of the subjects who experienced pregnancy during any of the epilepsy, nonepilepsy, and Phase 1 studies with the outcome of the pregnancy listed for each pregnancy. The Sponsor confirmed that my totals for the number of pregnancies were correct and that pregnancies were “inadvertently missed in the manual tabulation provided in the original table.” The Sponsor stated that no further information was available in the Pharmacovigilance database as of June 13, 2012 for the neonatal death and stated that the second pregnancy for subject 306-3956-6001 did not have a reported outcome.

Furthermore, when queried regarding any further information regarding any congenital malformations in the 2 healthy births, the Sponsor replied with the following: “Pregnancy outcome forms were received from the investigator sites for the two births reported in Subject 3019-1008 (Study 207) and Subject 3002-6004 (Study 306/307). The pregnancy outcome form requires the investigator to report any congenital outcomes observed. There were no congenital abnormalities noted by the investigator on the pregnancy outcome forms for these two births.”

Table 153. Descriptions of Select Pregnancy Exposures to Perampanel

Subject #	Age, Race	Study: Treatment, Dose	Adverse event (Preferred Term)	Study day	Phase of Study
2760-6003	20, A	DB 306: Pera 8 mg OLE 307: Pera 12 mg	Neonatal death	OLE 197	Maintenance
<p>Perampanel discontinued after positive pregnancy test on OLE Day 197 (last menstrual period was 54 days prior). Outcome: delivery of male neonate (39 weeks gestation) who died within 6 hours of birth. Cause of death listed as neonatal aspiration of fluid during birth. Autopsy was performed but the results were not available. Concomitant medications included clobazam, domperidone, and carbamazepine.</p>					
1012-4006	29, W	DB 304: Pera 8 mg OLE 307: Pera 12 mg	Abortion spontaneous, incomplete	OLE 391	Maintenance
<p>Perampanel discontinued after positive pregnancy test. Outcome: incomplete spontaneous abortion 48 days after last menstrual period Concomitant medications included carbamazepine and valproic acid. Subject underwent a dilatation and curettage procedure and perampanel was restarted.</p>					
5151-4001	34, W	DB 304: 8 mg	Abortion spontaneous	DB ~130	Maintenance
<p>Perampanel discontinued 2 days prior to positive pregnancy test. Outcome: spontaneous abortion at "38 days gestation" Concomitant medications included oxcarbazepine and lamotrigine. Subject underwent a dilatation and curettage procedure and was discontinued from the study.</p>					
3003-6001	15, W	DB 306: placebo OLE 307: Pera 12 mg	Abortion spontaneous	OLE 651	Maintenance
<p>Perampanel discontinued after positive pregnancy test. Outcome: spontaneous abortion 20 days after positive pregnancy test Concomitant medications included lamotrigine. Earlier in the study, the subject had a prior pregnancy and underwent an induced abortion on Day 419.</p>					
3956-6001	34, A	DB 306: Pera 4 mg OLE 307: Pera 10 mg	Abortion spontaneous	OLE 207	Maintenance
<p>Perampanel was continued despite positive pregnancy test. Outcome: spontaneous abortion "3 weeks into the pregnancy" (10 days after positive pregnancy test) Concomitant medications included phenobarbital and valproic acid. Perampanel was continued and on OLE Day 420, the subject had another positive pregnancy test (December 27, 2011). As of the narrative report, no additional information was available.</p>					
3019-1018	26, W	DB 208: Pera 2 -12 mg OLE 207: Pera 6 mg	Pregnancy	OLE ~189	Maintenance
<p>Perampanel discontinued after positive pregnancy test (last menstrual period was 39 days prior). Outcome: delivery of healthy female baby (~38 weeks gestation) with Apgar of 8-9 after 5 minutes Concomitant medications included oxcarbazepine and valproic acid.</p>					

3002-6004	18, W	DB 306: Pera 4 mg OLE 307: Pera 10 mg	Pregnancy	OLE ~790	Maintenance
Perampanel discontinued after positive pregnancy test (last menstrual period was 38 days prior). Outcome: delivery of healthy baby at 38 weeks gestation with Apgar of 7 after 5 minutes Concomitant medications included lamotrigine and diazepam.					

Source: Created by the reviewer using subject narratives provided by the Sponsor.

Most of these women were taking concomitant Pregnancy Class D medications, such as carbamazepine, valproic acid, and diazepam. However, there were 2 deliveries of full-term, healthy infants born to mothers exposed to the Pregnancy Class D medications, valproic acid and diazepam. Furthermore, there were 2 spontaneous abortions (50% of the spontaneous abortions) in subjects only on Pregnancy Class C concomitant medications (oxcarbazepine and lamotrigine). However, with such a small number of pregnancies, the assessment of the causal relationship between perampanel exposure and spontaneous abortions is difficult.

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: skull malformation and atrial septal defect. These TEAEs occurred in an adolescent and an adult subject, respectively, and not due to perampanel exposure during pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

In the preclinical studies, reduction of growth progression was observed in rats. A dose range-finding study was completed in dogs. However, the Sponsor reported in the ISS that the definitive toxicity study in juvenile dogs was completed after the cutoff date for the NDA submission (further updates were not provided in the 120-day Safety Update). The reader is referred to the Pharmacology, Toxicology review by Dr. Christopher Toscano for further details regarding the preclinical studies.

Information regarding the effect of perampanel on growth and development parameters in pediatric subjects was not included in the NDA submission. These areas are still under ongoing evaluation in the ongoing epilepsy Studies 307 and 235. The Sponsor stated that the results will be summarized in the final CSRs for those studies (which have not yet been submitted as of August 8, 2012).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The effects of overdose with perampanel will be discussed in this section. The reader is referred to the Controlled Substance Staff review by Dr. Alicja Lerner for further details regarding drug abuse potential and withdrawal, to the Pharmacology/Toxicology review by Dr. Christopher Toscano for details regarding the preclinical studies, and to Dr. Martin Rusinowitz's review of efficacy for details regarding rebound epilepsy.

Overdose

In the epilepsy Phase 3 studies, the following sources of information provided information regarding an overdose: (1) monitoring of medication dispensed and medication returned during the study, (2) expedited reporting of serious and nonserious AEs to the sponsor (CIOMS forms), (3) investigator-reported AEs that coded to MedDRA preferred terms for overdose, and (4) AEs that the investigator indicated were associated with overdose by checking a box on the AE page of the case report form.

The Sponsor reported no fatal overdose cases. The adverse event most frequently associated with overdose was dizziness, which was reported as an overdose-associated TEAE in a total of eight (0.8%) of the 1038 subjects who received perampanel in the epilepsy Phase 3 DB pool. Other overdose-associated TEAEs that were reported for more than one subject were nausea (n=3), somnolence (n=2), vomiting (n=2), and accidental overdose (n=2) (CSR Study 304, Table 12.6; CSR Study 305, Table 12.6; CSR Study 306, Table 12.6). In the Phase 3 OLE study, the event most frequency associated with overdose was dizziness (2.2% of 1186 subjects) (CSR Study 307, Table 14.3.2.2.8).

The following table summarizes the perampanel overdoses that were reported by the investigators in the epilepsy studies.

Table 154. Perampanel Overdoses, Epilepsy Studies

Subject #	Perampanel dose	TEAEs	Outcome	Discontinued?
306-2453-6007	~264 mg instead of 8 mg (suicide attempt)	agitated, aggressive (awake and alert)	SAE, Recovered	Yes
306-1806-6003	48 mg instead of 12 mg (intentional overdose)	unsteady gait, blurred vision, weakness	SAE, Recovered	Interrupted but later restarted
305-5167-5002	36 mg instead of 12 mg (accidental overdose)	ataxia, slurred speech, "drunk like", confused	SAE, Recovered	Interrupted but later restarted
305-2402-5010	14 mg instead of 2 mg	nausea and vomiting	Recovered	Interrupted but later restarted
306-1505-6001	"additional amt" (dose not known) instead of 12 mg	dizziness, fatigue, nausea, memory impairment	Recovered	Dose was reduced
305-5181-5003	16 mg instead of 8 mg	hypoesthesia, coordination abnormal, dizziness	Recovered	No
305-2806-5011	14 mg instead of 6 mg	dizziness, somnolence	Recovered	No
304-5148-4001	14 mg instead of 2 mg	nausea	Recovered	No
306-1202-6007	12 mg instead of 2 mg	dizziness, headache	Recovered	No
305-3905-5002	16 mg instead of 8 mg	none		No
304-5118-4012	14 mg instead of 4 mg	none		No
305-4202-5006	14 mg instead of 2 mg	none		No
305-2309-5001	12 mg instead of 8 mg	none		No
305-5201-5008	12 mg instead of 8 mg	none		No
305-2803-5002	8 mg instead of 6 mg	none		No

Source: ISS and 120-day Safety Update Section 16.2

7.7 Additional Submissions / Safety Issues

The Division made several request for information and additional analyses after the NDA resubmission on December 22, 2011. The 120-Day Safety Update Report was submitted on April 20, 2012. Review of the responses to the FDA requests for information has been incorporated throughout this review up to August 8, 2012.

8 Postmarket Experience

During the course of the FDA's review of the perampanel NDA, the European Medicines Agency's Committee for Medicinal Products for Human Use adopted a positive opinion on May 24, 2012, recommending the granting of marketing authorization for perampanel, Fycompa, for the adjunctive treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. The European Commission has issued marketing authorization for the use of Fycompa in late July of 2012. Postmarketing data from Europe was not yet available for FDA review as of August 8, 2012.

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 in the e-room.

9.3 Advisory Committee Meeting

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

Appendix 1: Description of Perampanel Studies

Table 155. Descriptions of Perampanel Epilepsy Studies

Study ID	No. of Centers Location(s)	Study Dates Enrollment: Total/goal	Design	Study & Control Drugs: Dose, Route, Regimen ^a	No. Subjects by Arm Treated ^b / Completed	Duration of Treatment	No. M/F ^b Mean Age ^b (Range)
EPILEPSY: DOUBLE-BLIND, PHASE 3 STUDIES							
E2007-G000-304	77 Argentina, Canada, Chile, Mexico, US	Apr 2008 to Nov 2010 390/375	Randomized, DB, placebo-controlled	Perampanel 8 mg Perampanel 12 mg Placebo	133/114 134/100 121/106	19 weeks	188/200 36.0 (12-77)
E2007-G000-305	138 Australia, EU, India, Israel, Russian Federation, South Africa, US	May 2008 to Jan 2011 389/375	Randomized, DB, placebo-controlled	Perampanel 8 mg Perampanel 12 mg Placebo	129/108 121/93 136/120	19 weeks	186/200 35.5 (12-76)
E2007-G000-306	116 Asia, Australia, Europe, Russia	Aug 2008 to Jul 2010 712/680	Randomized, DB, placebo-controlled	Perampanel 2 mg Perampanel 4 mg Perampanel 8 mg Placebo	180/154 172/158 169/145 185/166	19 weeks	345/361 33.8 (12-72)
EPILEPSY: DOUBLE-BLIND, PHASE 2 STUDIES							
E2007-E049-203	1 Germany	Feb 2003 to Aug 2003 18/18	Randomized, DB, placebo-controlled	Perampanel 1 mg Perampanel 2 mg Placebo	6/6 6/6 6/6	28 days	11/7 32.2 to 39.2 ^c (20-52)
E2007-A001-206	43 Australia, Europe, US	Mar 2005 to Feb 2007 153/144	Randomized, DB, placebo-controlled	Perampanel BID dosing (total dose 4 mg or MTD) Perampanel QD dosing (total dose 4 mg or MTD) Placebo	51/47 51/45 51/46	14 weeks	67/85 40.2 (18-72)
E2007-G000-208	17 Australia, Belgium, Estonia, Finland, France, Latvia, Lithuania, Netherlands	Mar 2007 to Jan 2008 48/48	Randomized, DB, placebo-controlled	Perampanel 12 mg or MTD Placebo	38/34 10/8	16 weeks	23/25 41.7 (19-63)
E2007-G000-235 ^d	Up to 35 planned North America, EU, RoW	Ongoing 23/132	Randomized, DB, placebo-controlled with OLE	Perampanel 2 to 12 mg Placebo	Not applicable	52 weeks	Not applicable
EPILEPSY: OPEN-LABEL, PHASE 2 STUDY							
E2007-J081-231	9 Japan	Mar 2009 to Nov 2009 30/30	OL exploratory	Perampanel 12 mg or MTD	30/23	10 weeks	16/14 35.4 (20-62)
EPILEPSY: OPEN-LABEL EXTENSION STUDIES							
E2007-G000-307	283 Argentina, Asia, Australia, Canada, Chile, EU, India, Israel, Mexico, Russian Federation, South Africa, US	Ongoing 1218 ^e /1430	OLE of Studies 304, 305, and 306	Perampanel 12 mg or MTD	1186/0 ^e (849 ongoing)	Approximately 5 years or until the product becomes available commercially	598/588 ^e 34.3 (12-76)
E2007-A001-207	48 Australia, Belgium, Czech Republic, Estonia, Finland, France, Germany, Latvia, Lithuania, The Netherlands, Spain, Sweden, UK, US	Ongoing 192 ^f /138	OLE of Studies 206 and 208	Perampanel 12 mg or MTD	138/1 ^e (53 ongoing)	436 weeks	58/80 ^e 40.7 (18-68)
E2007-J081-233	9 Japan	Ongoing 30 ^g /21	OLE of Study 231	Perampanel 2 to 12 mg	21/0 ^e (17 ongoing)	112 weeks	11/10 ^e 36.5 (20-62)

Source: ISS Table 1

Table 156. Descriptions of Perampanel Nonpilepsy Studies

Study ID	No. of Centers Location(s)	Study Dates Enrollment: Total/goal	Design	Study & Control Drugs: Dose, Route, Regimen ^a	No. Subjects by Arm Treated ^b / Completed	Duration of Treatment	No. M/F ^b Mean Age ^b (Range)
PARKINSON'S DISEASE: DOUBLE-BLIND STUDIES							
E2007-E044-301	114 Austria, Belgium, Czech Republic, Estonia, France, Germany, Hungary, Israel, Italy, Lithuania, Poland, Portugal, Serbia, South Africa, Spain, Sweden, UK	Jan 2006 to Aug 2007 764/702	Randomized, DB, placebo-controlled	Perampanel 2 mg Perampanel 4 mg Placebo	256/186 253/175 255/197	30 weeks	460/303 64.1 (36-86)
E2007-A001-302	128 Argentina, Australia, Brazil, Canada, Chile, New Zealand, US	Aug 2006 to Jan 2008 752/720	Randomized, DB, placebo-controlled	Perampanel 2 mg Perampanel 4 mg Placebo	251/198 250/182 251/187	20 weeks	492/259 62.6 (37-88)
E2007-G000-309 ^f	96 Argentina, Chile, Czech Republic, Estonia, France, Hungary, India, Israel, Italy, Korea, Latvia, Lithuania, Poland, Russia, Serbia, Singapore, South Africa, Spain, Taiwan, Ukraine	Dec 2006 to Jun 2008 723/702	Randomized, DB, placebo- and active-controlled	Perampanel 4 mg Entacapone 200 mg Placebo	242/154 234/155 247/171	18 weeks	433/290 63.4 (33-85)
E2007-A001-226 ^d	1 US	Oct 2007 to Dec 2007 1/16	Randomized, DB, placebo-controlled	Perampanel 4 mg	1/1	28 days	1/0 75
E2007-E049-202	1 Germany	Apr 2003 to Nov 2003 19/18	Randomized, DB, placebo-controlled	Perampanel 1 mg Perampanel 2 mg Placebo	6/6 7/6 6/6	28 days	14/5 56.7 to 65.5 ^e (41-72)
E2007-E044-204	38 Czech Republic, France, Germany, Italy, Serbia Montenegro, Spain	May 2004 to Feb 2005 263/225	Randomized, DB, placebo-controlled, dose-ranging	Perampanel 0.5 mg Perampanel 1 mg Perampanel 2 mg Placebo	68/59 65/56 64/56 66/55	12 weeks	147/116 61.5 to 63.4 ^e (33 to 77)
E2007-A001-214 ^f	12 US	Sep 2005 to Sep 2006 75/60	Randomized, DB, placebo-controlled, two-cohort	Cohort 1: Perampanel 6 mg Placebo Cohort 2: Perampanel 8 mg Placebo	20/16 8/8 35/21 12/11	10 weeks	16/12 67.6 and 68.5 ^e (51-80) 33/14 67.5 and 68.5 ^e (46-85)
PARKINSON'S DISEASE: OPEN-LABEL EXTENSION STUDIES							
E2007-E044-205 ^f	28 Czech Republic, France, Germany, Italy, Serbia Montenegro	Nov 2004 to Jun 2008 185/225	OLE of Study 204	Perampanel (prior DB placebo) Perampanel (prior DB perampanel)	49/0 136/0	48 months	105/77 62.6 (33-76)
E2007-G000-318 ^f	64 Argentina, Chile, Czech Republic, Estonia, France, Hungary, India, Israel, Italy, Korea, Latvia, Lithuania, Poland, Serbia, Singapore, South Africa, Spain, Taiwan, Ukraine	Aug 2007 to Jun 2008 328/726	OLE of Study 309	Perampanel (prior DB placebo) Perampanel (prior DB perampanel) Perampanel (prior DB entacapone)	121/0 96/0 108/0	56 weeks	205/120 63.8 (34-85)
E2007-A001-220 ^f	9 US	Feb 2007 to May 2008 25/60	OLE of Study 214	Perampanel	25/0	Open-ended	18/7 69.0 (53-85)

Source: ISS Table 1

Descriptions of Perampanel Nonpilepsy Studies – continued

Study ID	No. of Centers Location(s)	Study Dates Enrollment: Total/goal	Design	Study & Control Drugs: Dose, Route, Regimen ^a	No. Subjects by Arm Treated ^b / Completed	Duration of Treatment	No. M/F ^b Mean Age ^b (Range)
PARKINSON'S DISEASE: OPEN-LABEL EXTENSION STUDIES							
E2007-E044-205 ^f	28 Czech Republic, France, Germany, Italy, Serbia Montenegro	Nov 2004 to Jun 2008 185/225	OLE of Study 204	Perampanel (prior DB placebo) Perampanel (prior DB perampanel)	49/0 136/0	48 months	105/77 62.6 (33-76)
E2007-G000-318 ^f	64 Argentina, Chile, Czech Republic, Estonia, France, Hungary, India, Israel, Italy, Korea, Latvia, Lithuania, Poland, Serbia, Singapore, South Africa, Spain, Taiwan, Ukraine	Aug 2007 to Jun 2008 328/726	OLE of Study 309	Perampanel (prior DB placebo) Perampanel (prior DB perampanel) Perampanel (prior DB entacapone)	121/0 96/0 108/0	56 weeks	205/120 63.8 (34-85)
E2007-A001-220 ^f	9 US	Feb 2007 to May 2008 25/60	OLE of Study 214	Perampanel	25/0	Open-ended	18/7 69.0 (53-85)
E2007-G000-303 ^f	200 Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Czech Republic, Estonia, France, Germany, Hungary, Israel, Italy, Lithuania, New Zealand, Poland, Portugal, Serbia, South Africa, Spain, Sweden, UK, US	Oct 2006 to Jul 2008 997/1400	OLE of Studies 301 and 302	Perampanel (prior DB placebo) Perampanel (prior DB perampanel)	333/0 664/2	108 weeks	644/353 63.4 (37-89)
NEUROPATHIC PAIN: DOUBLE-BLIND STUDIES							
E2007-A001-218	50 Canada, US	Jan 2008 to Dec 2008 146/135	Randomized, DB, placebo-controlled	Cohort 1: Perampanel MTD (3-week titration) Placebo Cohort 2: Perampanel MTD (1-week titration) Perampanel MTD (2-week titration) Placebo	53/21 26/15 22/8 23/9 22/18	15 weeks	Cohorts 1 & 2 71/75 71.6 (26-94)
E2007-G000-227	61 Australia, Canada, Germany, Hungary, Lithuania, UK, US	Jun 2007 to Jul 2008 355/350	Randomized, DB, placebo-controlled	Perampanel 2 mg Perampanel 4 mg Perampanel 6 mg Perampanel 8 mg Placebo	71/56 68/57 67/49 68/37 71/63	15 weeks	194/151 61.8 (27-90)
NEUROPATHIC PAIN: OPEN-LABEL STUDY							
E2007-G000-228	56 Australia, Canada, Germany, Hungary, Lithuania, UK, US	Jan 2008 to Nov 2009 262/333	OLE of Studies 218 and 227	Perampanel (prior DB placebo) Perampanel (prior DB perampanel)	84/42 178/112	1 year	104/74 62.4 (28-91)
MULTIPLE SCLEROSIS: DOUBLE-BLIND STUDY							
E2007-E049-201	1 Germany	Feb 2003 to Oct 2003 27/27	Randomized, DB, placebo-controlled	Perampanel 1 mg Perampanel 2 mg Perampanel 3 mg Placebo	6/6 6/6 6/6 9/9	28 days	13/14 39.0 to 46.8 ^c (26-59)
MIGRAINE HEADACHE: DOUBLE-BLIND STUDY							
E2007-A001-210	24 US	Nov 2004 to Jun 2006 206/180	Randomized, DB, placebo-controlled	Perampanel 2 mg Placebo	102/80 104/92	14 weeks	27/179 41.4 (18-65)

Source: ISS Table 1

Table 157. Descriptions of Perampanel Phase 1 Studies

Study ID	No. of Centers Location(s)	Study Dates Enrollment: Total/goal	Design	Study & Control Drugs: Dose, Route, Regimen ^a	No. Subjects by Arm Treated ^b / Completed	Duration of Treatment	No. M/F ^b Mean Age ^b (Range)
HEALTHY SUBJECTS: BIOAVAILABILITY STUDIES							
E2007-E044-017	1 UK	Nov 2009 to Dec 2009 10/10	OL	Perampanel 8 mg p.o. ¹⁴ C-perampanel microdose (10 µg i.v.)	10/10	Single dose	10/0 35.5 (22-53)
E2007-E044-003	1 UK	Dec 2001 to Mar 2002 24/24	Randomized, OL crossover	Perampanel 1 mg (fasted) Perampanel 1 mg (fed)	24/24	Single dose	12/12 25.3 (19-41)
HEALTHY SUBJECTS: BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES							
E2007-A001-008	1 US	Nov 2003 to Jul 2004 34/34	Randomized, OL crossover	Perampanel 2 mg (reference formulation) Perampanel 2 mg (test formulation)	34/30	Single dose	23/11 29.7 (18-45)
E2007-E044-016	1 Belgium	Oct 2006 to Jan 2007 24/24	Randomized, OL crossover	Perampanel 4 mg (two tablets) Perampanel 4 mg (one tablet)	24/24	Single dose	12/12 38.6 (20-55)
E2007-E044-037	1 UK	Jun 2010 to Sep 2010 28/28	Randomized, OL crossover	Perampanel 12 mg (six tablets of reference formulation) Perampanel 12 mg (one tablet of test formulation)	28/22	Single dose	21/7 40.8 (21-54)
E2007-A001-040	1 US	Dec 2010 to Mar 2011 54/54	Randomized, OL crossover	Perampanel 12 mg (six tablets of reference formulation) Perampanel 12 mg (one tablet of test formulation)	54/47	Single dose	32/22 28.8 (18-54)
E2007-A001-039	1 US	Dec 2010 to Mar 2011 54/54	Randomized, OL crossover	Perampanel 6 mg (three tablets of reference formulation) Perampanel 6 mg (one tablet of test formulation)	54/50	Single dose	34/20 28.0 (18-55)
HEALTHY SUBJECTS: PHARMACOKINETICS AND INITIAL TOLERABILITY STUDIES							
E2007-E044-001	1 UK	May 2001 to Oct 2001 55/not stated	Randomized, DB, placebo-controlled, sequential ascending-dose	Perampanel 0.2 mg Perampanel 0.5 mg Perampanel 1 mg Perampanel 2 mg Perampanel 4 mg Perampanel 6 mg Perampanel 8 mg Placebo	6/6 6/6 6/6 6/6 6/6 6/6 6/6 13/13	Single dose	55/0 27.4 (18-45)
E2007-E044-002	1 UK	Nov 2001 to Jul 2002 32/32	Randomized, DB, placebo-controlled	Perampanel 1 mg Perampanel 2 mg Perampanel 4 mg Perampanel 6 mg Placebo	6/6 6/6 6/6 6/4 8/8	14 days	32/0 26.7 (19-45)
E2007-J081-010	1 Japan	Apr 2005 to Oct 2005 56/56	Randomized, DB, placebo-controlled	Perampanel 0.25 mg Perampanel 0.5 mg Perampanel 1 mg Perampanel 2 mg Perampanel 4 mg Perampanel 6 mg Perampanel 8 mg Placebo	6/6 6/6 6/6 6/6 6/6 6/6 6/6 14/14	Single dose	56/0 26.2 (20-43)

Source: ISS Table 1

Descriptions of Perampanel Phase 1 Studies - continued

Study ID	No. of Centers Location(s)	Study Dates Enrollment: Total/goal	Design	Study & Control Drugs: Dose, Route, Regimen ^a	No. Subjects by Arm Treated ^b / Completed	Duration of Treatment	No. M/F ^b Mean Age ^b (Range)
HEALTHY SUBJECTS: INTRINSIC FACTOR PHARMACOKINETICS STUDIES							
E2007-E044-015	1 Germany	Oct 2006 to May 2007 24/24	OL	Perampanel 1 mg	24/24	Single dose	18/6 48.0 to 52.2 ^c (33-69)
E2007-E044-004	2 UK	May 2002 to Dec 2002 24/24	Randomized, DB, placebo-controlled, ascending-dose	Perampanel 1 mg Perampanel 2 mg Placebo	8/8 8/8 8/8	Single dose	12/12 70.0 (65-76)
E2007-E044-007	1 The Netherlands	Jan 2004 to Feb 2004 8/8	OL	¹⁴ C-perampanel 2 mg	8/8	Single dose	4/4 70.6 (65-79)
E2007-J081-026	1 Japan	Nov 2007 to Mar 2008 24/24	Randomized, DB, placebo-controlled	Step 1 Perampanel 2 mg Placebo Step 2 Perampanel 4 mg Placebo	9/9 3/3 9/9 3/3	14 days 28 days	24/0 Step 1 26.5 (23-37) Step 2 27.5 (21-40)
HEALTHY SUBJECTS: EXTRINSIC FACTOR PHARMACOKINETICS STUDIES							
E2007-E044-005	1 UK	Apr 2002 to Jun 2002 26/26	Randomized, OL crossover	Perampanel 1 mg Ketoconazole 400 mg	26/26	Single dose (perampanel)	26/0 24.3 (20-32)
E2007-E044-006	1 UK	Apr 2003 to Sep 2003 20/16	OL	Perampanel 2 mg Carbamazepine 600 mg	20/14	Single dose (perampanel)	20/0 27.5 (18-51)
E2007-A001-014	1 US	Dec 2006 to Mar 2007 35/35	OL	Perampanel 6 mg Midazolam 4 mg	35/30	21 days (perampanel)	25/10 34.0 (20-55)
E2007-E044-019	1 UK	Jun 2006 to Apr 2007 Initial regimen 14/24 Revised regimen 24/24	OL crossover	Initial regimen Perampanel 4 mg/d Microgynon 30 ED OC placebo Revised regimen Perampanel 2 mg/d for 7 days, 4 mg/d for 21 days Microgynon 30 ED OC placebo	14/0 24/20	28 days (perampanel) 28 days (perampanel)	0/14 26.6 (20-36) 0/24 27.4 (19-40)
E2007-E044-025	1 UK	Sep 2007 to Jan 2008 60/60	OL	Perampanel 4 mg Levodopa 100 mg	60/59	19 days (perampanel)	43/17 30.4 (19-54)
E2007-E044-029	1 UK	Feb 2010 to Oct 2010 Part A: 28/24 Part B: 24/24	OL	Part A Perampanel 12 mg/d Single doses of Microgynon-30 Part B Single doses of perampanel 6 mg Microgynon-30 for 21 days	28/20 24/24	35 days Single dose	0/28 30.6 (21-43) 0/24 27.4 (20-42)
E2007-E044-030	1 UK	May 2010 to Nov 2010 Part A: 35/36 Part B: 24/24	Randomized, DB, placebo-controlled	Part A Perampanel 4 mg Perampanel 8 mg Perampanel 12 mg Alcohol Placebo Part B Perampanel 12 mg/d Alcohol Placebo	35/35 24/24	Single dose 34 days (perampanel)	22/13 29.7 (18-49) 18/6 27.0 (20-47)

Source: ISS Table 1

Descriptions of Perampanel Phase 1 Studies - continued

Study ID	No. of Centers Location(s)	Study Dates Enrollment: Total/goal	Design	Study & Control Drugs: Dose, Route, Regimen ^a	No. Subjects by Arm Treated ^b / Completed	Duration of Treatment	No. M/F ^b Mean Age ^b (Range)
HEALTHY SUBJECTS: PHARMACOKINETICS AND PHARMACODYNAMICS/PHARMACOKINETICS STUDIES							
E2007-E044-009	1 UK	Apr 2006 to Jul 2006 Single-dose phase 32/31 Repeated-dose phase 20/20	Randomized, DB, placebo-controlled	Single-dose phase Perampanel 6 mg (fed) Perampanel 6 mg (fasted) Placebo Diazepam 5 mg (fasted) Repeated-dose phase Perampanel 10 mg (AM) Perampanel 10 mg (PM) Placebo (AM and PM)	8/8 8/8 8/8 7/7 8/8 8/7 4/4	Single dose 21 days	26/5 24.1 to 30.1 ^c (20-45) 10/10 23.6 to 27.5 ^c (18-55)
E2007-A001-013	1 US	Sep 2007 to Mar 2008 257/264	Randomized, DB, placebo- and active-controlled	Perampanel 6-12 mg/d Moxifloxacin 400 mg Placebo	107/83 75/70 75/75	16 days	129/128 28.4 to 29.0 ^c (18-55)
E2007-E044-020	1 UK	May 2007 to Mar 2008 36/36	Randomized, DB, placebo- and active-controlled	Perampanel 6 mg/d Ciprofloxacin 1000 mg/d Placebo	12/11 12/11 12/11	10 days	30/6 31.5 to 35.7 ^c (19-54)
E2007-A001-023	1 Canada	May 2007 to Jul 2008 56/48	Randomized, DB, fixed-order, single ascending-dose, within-subject, staggered-group	Perampanel 8 mg Perampanel 12 mg Perampanel 16 mg Perampanel 20 mg Perampanel 24 mg Perampanel 28 mg Perampanel 32 mg Perampanel 36 mg Placebo	8/4 6/6 8/8 8/8 8/8 8/7 7/7 8/8 31/25	Single dose	38/18 33.1 (21-50)
E2007-A001-024	1 Canada	Aug 2009 to Jan 2010 40/40	Randomized, DB, placebo- and active-controlled	Perampanel 8 mg Perampanel 24 mg Perampanel 36 mg Alprazolam 1.5 mg Alprazolam 3 mg Ketamine 100 mg Placebo	40/33	Single dose	31/9 34.1 (19-54)
HEALTHY SUBJECTS: RELATIVE BIOAVAILABILITY OF SUSPENSION							
E2007-E044-028	1 UK	Oct 2009 to Jan 2010 16/12	OL crossover	Perampanel 4 mg oral suspension Perampanel 4 mg tablet	16/15	Single dose	9/7 38.4 (20-53)

BID = twice daily, DB = double-blind, EU = European Union, F = female, M = male, MTD = maximum tolerated dose, OL = open-label, OLE = open-label extension, PLA = placebo, QD = once daily, RoW = rest of world, UK = United Kingdom, US = United States

a: All study and control drugs were tablets taken orally once daily, unless otherwise indicated.

b: Based on the Safety Analysis Sets as defined in the clinical study reports for the studies in epilepsy, Parkinson's disease, neuropathic pain, multiple sclerosis, and migraine headache; based on subjects included in the evaluation of safety for the studies in healthy subjects.

c: Mean age for all subjects was not presented in the clinical study report. Results shown are the range of means, which were calculated separately for each treatment group.

d: This is a recently initiated, ongoing study. As of 01 Jul 2011, 23 subjects had been enrolled. No clinical study report is included in this submission. The only information about this study included in this submission is identification of any deaths or serious adverse events that had occurred as of 01 Jul 2011.

e: Number with available data as of the cutoff date for this submission.

f: The study was terminated early because the sponsor decided to no longer pursue the development of perampanel for the treatment of Parkinson's disease.

Source: ISS Table 1

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CLINICAL REVIEW

Application Type NDA
Application Number(s) 202834
Priority or Standard Standard

Submit Date(s) December 22, 2011
Received Date(s) December 22, 2011
PDUFA Goal Date October 22, 2012
Division / Office DNP/OND1

Reviewer Name(s) Martin S. Rusinowitz, MD
Review Completion Date August 20, 2012

Established Name Perampanel
(Proposed) Trade Name Fycompa
Therapeutic Class Anticonvulsant
Applicant Eisai, Inc.

Formulation(s) Immediate release, film coated
tablets
Dosing Regimen Once daily
Indication(s) Adjunctive treatment of partial
onset seizures
Intended Population(s) 12 years of age and older

Template Version: [March 6, 2009](#)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Perampanel is safe and effective at doses of 4mg to 8mg daily. It is recommended for approval on the basis of this medical review.

1.2 Risk Benefit Assessment

Efficacy is established based on three adequate and well controlled Phase 3 studies. The evidence for efficacy for perampanel in all three Phase 3 studies was based on reduction in seizure frequency, specifically, the percent change in seizure frequency from baseline of all partial-onset seizures per 28 days, during the double-blind phase in the ITT double-blind population. Study 304 establishes that perampanel is superior to placebo at doses of 8mg and 12mg, Study 305 demonstrates superiority at doses of 8mg and 12mg and Study 306 shows superiority at doses of 4mg and 8mg, but not 2mg.

Safety will be reviewed separately by Dr. Mary Doi. No serious, life threatening, risks have been reported for perampanel. There have been no serious skin reactions, aplastic anemia or Hy's Law cases reported. There appears to be a signal for anger and aggression, particularly in adolescents. Other potential safety signals, including fractures, cholelithiasis, weight gain, and mildly elevated liver enzymes are being further evaluated. Most of these adverse events appear to be more prevalent in the highest dose evaluated (12mg).

The potential benefit of an additional effective anticonvulsant medication clearly outweighs the adverse event profile of perampanel.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

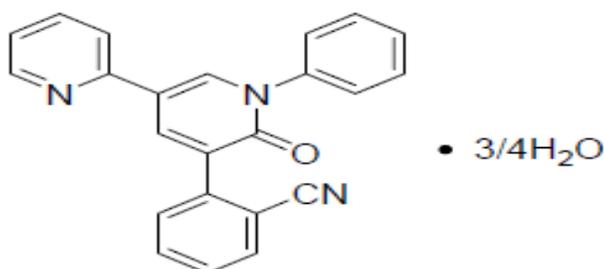
None

2 Introduction and Regulatory Background

2.1 Product Information

Perampanel, a new molecular entity, is an orally active, noncompetitive and highly selective α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist. AMPA receptors play a key role in mediating cortical glutamatergic transmission. AMPA antagonists might potentially reduce excessive excitatory activity and excitotoxicity, and thus exhibit anticonvulsant and potentially anti-epileptogenic effects. Perampanel has shown anticonvulsant activity in seizure models in rodents. In a rat model of partial seizures, oral perampanel elevated the “after discharge threshold” at a dose of 10 mg/kg, and reduced seizure severity at 5 mg/kg and 10 mg/kg, while a significant effect on “after discharge duration” was observed at 10 mg/kg. The results in these animal models suggest that perampanel might be effective in the treatment of partial-onset seizures, with or without secondary generalization.

2.1.1 Molecular Formula



Molecular Formula, C₂₃H₁₅N₃O • 3/4H₂O

Chemical name: 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3yl)benzotrile hydrate (4:3) (IUPA)

International Non-proprietary Name (INN): Perampanel

The proprietary name for perampanel is Fycompa™. Its proposed indication is for the treatment of partial-onset seizures in patients with epilepsy aged 12 years and older.

Perampanel film-coated tablets used in the clinical trials contained 2-, 4-, 6-, 8-, 10-, and 12-mg of perampanel and were round, biconvex, and engraved. In these clinical trials, treatment with perampanel was initiated with a dose of 2 mg/day. This was increased based on clinical response and tolerability by 2 mg/day increments to a dose of 4 mg to 12 mg/day. There was an interval of at least one week between increasing the dose. The maximum dose of perampanel was 12 mg/day. Because of the side-effect of somnolence, dosing is recommended at bedtime, with or without food.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 Anticonvulsants in common clinical use for the treatment of partial epilepsy

Phenobarbital
Primidone
Phenytoin
Carbamazepine
Valproic Acid
Gabapentin
Lamotrigine
Topiramate
Tiagabine
Levetiracetam
Oxcarbazepine
Pregablin
Lacosamide
Ezogabine

2.3 Availability of Proposed Active Ingredient in the United States

The active moiety (perampanel) is an NCE (new chemical entity) and not currently marketed.

2.4 Important Safety Issues with Consideration to Related Drugs

Perampanel has a relatively low systemic clearance, in part due to its relatively high plasma protein binding. The average $t_{1/2}$ is 105 hours. Perampanel is primarily eliminated by oxidative metabolism followed by glucuronidation with relatively rapid fecal and urinary excretion of perampanel metabolites. There are no active metabolites.

Clearance of perampanel was significantly increased in the presence of the co-administered CYP3A4 inducers carbamazepine, oxcarbazepine and phenytoin, resulting in lower exposure of perampanel. Phenobarbital and primidone, showed no significant effect on perampanel clearance. In addition, the co-administered AEDs clobazam, clonazepam, lamotrigine, levetiracetam, topiramate, valproic acid, and zonisamide also had no clinically relevant effect on perampanel clearance or the resulting serum concentration. In a population PK analysis of patients with partial-onset seizures receiving perampanel up to 12 mg/day, perampanel did not significantly affect the clearance of clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate, or zonisamide. Perampanel had a significant effect on the clearance of carbamazepine, clobazam, lamotrigine, and valproic acid, but the magnitude of these effects was less than 10% for each drug at the highest perampanel dose evaluated (12 mg/day). Perampanel co-administration resulted in a 26% decrease in oxcarbazepine clearance.

For more detailed discussion refer to section 6.1.7.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Formal discussions regarding the development program and New Drug Application submission for perampanel were held with the FDA on December 5, 2007 at the End of Phase 2 meeting. The issues agreed upon at that meeting included the following:

- **The design, duration, study population and endpoints for the Phase 3 studies were acceptable to support the proposed indication for perampanel.**
- **Phase 3 Study 306, together with the Phase 2 studies 206 and 208, were sufficient to establish the minimal effective dose of perampanel, provided that Study 306 was sufficiently powered.**
- **Registration of the 8 mg daily dose of perampanel as an effective dose was acceptable provided that efficacy was demonstrated for this dose in at least two of the three Phase 3 studies, and the tolerability profile for this dose was established in relation to lower and higher perampanel doses.**
- **The primary efficacy endpoint would be the percent change in seizure frequency per 28 days in the Double-blind Phase (Titration Period + Maintenance Period).**
- **The Intent-to-treat (ITT) Analysis Set would exclude subjects with less than 2 weeks of post-baseline seizure data.**

The sponsor subsequently sent the protocols and Statistical Analysis Plan (SAP) to the FDA with a revised primary analysis for the controlled Phase 3 studies. The sponsor proposed the same primary endpoint (percent change in seizure frequency) and ITT analysis set (subjects with at least 2 weeks of post-baseline seizure data) as discussed at the End of Phase 2 meeting, but the analysis proposed would use data collected over the defined Maintenance Period (using a last observation carried forward [LOCF] approach for missing data) instead of the entire Double-blind Phase. This analysis also excluded data during the Titration Period for subjects who completed at least 8 weeks of the Maintenance Period.

On September 13, 2010, in response to the submitted SAP for the controlled Phase 3 studies, DNP reiterated that the ITT population used for primary efficacy analysis should include all subjects who were randomized, took at least one dose of study medication, and had at least one baseline and post-baseline assessment (the Full ITT approach). Based on this, a protocol amendment to Study 305 was made prior to study completion to redefine the primary efficacy analysis. The other Phase 3 Studies 304 and 306 had already been completed before the amendment was made to Study 305. The changes implemented by the protocol amendment to Study 305 were incorporated into the final analyses for Studies 306 and 304 as well.

2.6 Other Relevant Background Information

On July 21, 2011, a Refuse to File letter was sent to Eisai indicating their application was not sufficiently complete to permit a substantive review. In particular, there were inadequate pharmacology/toxicology data regarding fetal observations in pivotal embryo-fetal development studies as well as numerous unsigned and undated pathology reports along with missing pages in the oral toxicity study in rats.

Additionally, there were many inadequacies with regard to clinical safety. Many datasets for the studies performed for non-epilepsy indications were not submitted and the format and organization of the submission did not provide comprehensive hyperlinks. A number of narratives for some serious adverse events (AEs) and dropouts due to AEs were missing. There were inadequacies in the analysis and presentation of the integrated safety data along with problems in the data presented for the analyses of demographic characteristics. There were also a number of impediments to filing with regard to chemistry, manufacturing and controls as well as biopharmaceutics and controlled substance data.

On September 26, 2011, a meeting was held with DNP to discuss the Refuse to File correspondence. Based on the discussion points at this meeting, Eisai submitted a resubmission of their NDA on December 22, 2011. After completing a filing review of this NDA resubmission, DNP communicated with Eisai indicating that their application was sufficiently complete to permit a substantive review.

In accordance with 21 CFR 314.101(a), the application was considered filed 60 days after the date it was received. The review classification for this application was Standard and the user fee goal date is October 22, 2012.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, eCTD format was followed and fully functional. There were numerous errors and inconsistencies with regard to the coding of adverse events and safety reporting. These will be detailed separately by Dr. Mary Doi in her safety review.

3.2 Compliance with Good Clinical Practices

A DSI consultation was submitted on March 27, 2012 requesting clinical inspections of four sites, two for Study 304 and two for Study 305.

Study 304: In this study the treatment effect was significant in US sites but not in Central and South America. Site # 5128, in Jacksonville, Florida was selected because of its large sample size, a high number of protocol violations and a large treatment effect. Site # 1701, in Santiago, Chile was chosen because of a large sample size and a high number of adverse events.

Study 305: Site # 4501, in Goteorg, Sweden was selected because of its large sample size and large treatment effect. Site # 1303, in Leuven, Belgium, was chosen because of a large sample size, large treatment effect and high number of discontinuations.

DSI Inspection Results are pending.

3.3 Financial Disclosures

The Director of Finance and Accounting at Esiai, Michael R. Melfi, has certified that there have been no financial arrangements with the listed clinical investigators whereby the value of compensation to the investigators listed could be affected by the outcome of the study as defined in 21 CFR 54.2(a). He has also certified that each listed clinical investigator has been required to disclose to the sponsor whether the investigator has a propriety interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) and none were disclosed. There was further certification that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

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4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The complete review is not submitted at the time of this writing, but Dr. Lyndmila Soldatova, from CMC, continues to evaluate the possibility of (b) (4) contamination. She is also evaluating solubility data from perampanel physician sample blister packs.

4.2 Clinical Microbiology

None

4.3 Preclinical Pharmacology/Toxicology

The complete review is not submitted at the time of this writing, but Dr. Christopher Toscano has found prolonged covalent binding of either the parent compound, or a metabolite, after 2 years in the aorta and 45 weeks in the eye in animal studies. Although this is of unknown relevance, this may bear some relationship to the safety finding of increased bone fractures.

Although there were animal findings of ataxia and sedation, most of these appeared to reverse over time. Genotoxicology and carcinogenicity studies are apparently negative while there is some evidence of phototoxicity.

There may be some evidence increased seizure activity at higher dosages, perhaps an induction effect.

4.4 Clinical Pharmacology

The complete review is not submitted at the time of this writing, but Drs. Xinning Yang and Joo-Yeon Lee are evaluating the many unidentified metabolites found in clinical pharmacology studies. They are also looking in to changes needed in the starting and maximum dosages in patients with hepatic impairment. There is evidence to suggest that 6mg of perampanel may be the maximum safe dose in such patients.

4.4.1 Mechanism of Action

See section 4.4

4.4.2 Pharmacodynamics

See section 4.4

4.4.3 Pharmacokinetics

See section 4.4

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 9

The following tables of all studies/clinical trials are provided by the sponsor.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	E2007-E044-017	5.3.1.1.1	<ul style="list-style-type: none"> To evaluate the absolute oral bioavailability of perampanel following concomitant administration of an intravenous (IV) microdose of ¹⁴C-perampanel solution and a single oral dose of perampanel. To investigate the metabolite profile of perampanel in plasma, urine, and feces and characterize metabolites where appropriate. 	Open-label	<ul style="list-style-type: none"> Oral: 4 mg tablets, 8 mg dose IV: perampanel 10 µg labeled with approx. 200pCi of radioactivity (¹⁴C) in a solution of not more than 10mL. 	N=10	Healthy subjects	Single dose	Complete; Final CSR
BA	E2007-E044-003	5.3.1.1.2	To evaluate the pharmacokinetics and pharmacological effects of single oral doses of E2007 in the fed, as compared to the fasted state, in healthy adult male and female volunteers.	Open-label	E2007: 1 mg tablet, oral	N=24	Healthy subjects	Single dose	Complete; Final CSR
BE	E2007-A001-008	5.3.1.2.1	To evaluate the bioequivalence of a new formulation of E2007 (test formulation) compared to a reference formulation, after a single oral dose in healthy subjects.	Open-label	E2007: 2 mg tablets, oral	N=34	Healthy subjects	Single dose	Complete; Final CSR
BE	E2007-E044-016	5.3.1.2.2	To demonstrate dose strength equivalence between two 2 mg E2007 tablets and a single 4 mg tablet.	Open-label	E2007: 2 mg and 4 mg tablets, oral	N=24	Health subjects	Single dose	Complete; Final CSR

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Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	E2007-E044-037	5.3.1.2.3	To demonstrate bioequivalence between 6 x 2-mg tablets of perampanel and a single 12-mg tablet of perampanel.	Open-label	Perampanel: 2 mg and 12 mg tablets, oral	N=28	Healthy subjects	Single Dose	Complete; Final CSR
BE	E2007-A001-040	5.3.1.2.4	To demonstrate bioequivalence between 6 x 2-mg tablets of perampanel and a single 12-mg tablet of perampanel.	Open-label	Perampanel: 2 mg and 12 mg tablets, oral	N=54	Healthy subjects	Single Dose	Complete; Final CSR
BE	E2007-A001-039	5.3.1.2.5	To demonstrate bioequivalence between 3 x 2-mg tablets of perampanel and a single 6-mg tablet of perampanel.	Open-label	Perampanel: 2 mg and 6 mg tablets, oral	N=54	Healthy subjects	Single Dose	Complete; Final CSR
Method Val	EIS-R791R2	5.3.1.4.1	Validation Report for Method BTM-1076-R0	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	EIS-R791A1	5.3.1.4.2	Validation Report Addendum 1 for Method BTM-1076-R0	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	EIS-R791R1A2	5.3.1.4.3	Validation Report Addendum 2 for Method BTM-1076-R0	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	EIS-R1458	5.3.1.4.4	Interference Evaluation of 19 AEDs on E2007 with Method BTM-1076-R0	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	BTM-1076-R0	5.3.1.4.5	Determination of E2007 in Human Plasma by LC/MS/MS	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	SH09-E01-TR352	5.3.1.4.6	Partial Validation Report for Method SHAM-1076-R0	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	SH09-E01-TR352A1	5.3.1.4.7	Addendum 1 for Partial Validation Report for Method SHAM-1076-R0	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	SH09-E01-TR352A2	5.3.1.4.8	Addendum 2 for Partial Validation Report for Method SHAM-1076-R0	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	SHAM-1076-R0	5.3.1.4.9	Determination of E2007 in Human Plasma (Sodium Heparin) by LC/MS/MS	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	GB04062V	5.3.1.4.10	Method Validation for the Determination of E2007 in Human Plasma	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	GB09008V	5.3.1.4.11	Additional Validation of a Bioanalytical Method for the Determination of E2007 in Human Plasma	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	105-001	5.3.1.4.12	Validation Report for the Determination of E2007 in Human Plasma by HPLC with Fluorescence Detection	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	891-001b	5.3.1.4.13	Bioanalytical Report for the Comparison of a Validated E2007 HPLC-FLD Method to a Validated E2007 LC-MS/MS Method	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	ME0714-001	5.3.1.4.14	Sample Analysis Report for the Determination of E2007 in Human Plasma by HPLC-Fluorescence (ME0714/001, E2007-E044-005)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	ME0751-002	5.3.1.4.15	Sample Analysis Report for the Determination of E2007 in Human Plasma by HPLC-Fluorescence (ME0751/002, E2007-E044-006)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report

Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Method	ME0743-002	5.3.1.4.16	Sample Analysis Report for the Determination of E2007 in Human Plasma by HPLC-Fluorescence (ME0743/002, E2007-E049-202)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	ME0743-003	5.3.1.4.17	Sample Analysis Report for the Determination of E2007 in Human Plasma by HPLC-Fluorescence (ME047/003, E2007-E049-203)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	105-001v3	5.3.1.4.18	Method Report for the Determination of E2007 in Human Plasma by HPLC-Fluorescence	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	238-001	5.3.1.4.19	Validation Report for the Determination of E2007 in Human Plasma by LC-MS/MS	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	0003-036b	5.3.1.4.20	Sample Analysis Report for the Determination of E2007 in Human Plasma by LC-MS/MS (0003/036b, E2007-E044-025)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	238v1	5.3.1.4.21	Method Report for the Determination of E2007 in Human Plasma by LC-MS/MS (Method No 238 Version 1)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	238v2	5.3.1.4.22	Method Report for the Determination of E2007 in Human Plasma by LC-MS/MS (Method No 238 Version 2)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report

Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Method	238v3	5.3.1.4.23	Method Report for the Determination of E2007 in Human Plasma by LC-MS/MS (Method No 238 Version 3)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	238v5	5.3.1.4.24	Method Report for the Determination of E2007 in Human Plasma by LC-MS/MS (Method No 238 Version 5)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	238v6	5.3.1.4.25	Method Report for the Determination of E2007 in Human Plasma by LC-MS/MS (Method No 238 Version 6)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	238v7	5.3.1.4.26	Method Report for the Determination of E2007 in Human Plasma by LC-MS/MS (Method No 238 Version 7)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	228-001	5.3.1.4.27	Validation Report for the Determination of Unbound E2007 in Human Plasma by LC-MS/MS (228/001)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	228-001v1	5.3.1.4.28	Method Report for the Determination of Unbound E2007 in Human Plasma by LC-MS/MS (228/001)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	100-001	5.3.1.4.29	Validation Report for the Determination of E2007 in Human Urine by LC-MS/MS (101/001)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report

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Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Method Val	101-001M0	5.3.1.4.30	Partial Validation Method for the Determination of E2007 in Human Urine by LC-MS/MS (101/001)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	45-0401	5.3.1.4.31	Determination of E2007 in Human Plasma by LC/MS/MS	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	45-0401A1	5.3.1.4.32	Determination of E2007 in Human Plasma by LC/MS/MS Addendum 1	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	45-0401A2	5.3.1.4.33	Determination of E2007 in Human Plasma by LC/MS/MS Addendum 2	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	45-0603	5.3.1.4.34	Partial Validation Report: Determination of E2007 in Human Plasma by LC/MS/MS	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	45-0603A.d1	5.3.1.4.35	Determination of E2007 in Human Plasma by LC/MS/MS Addendum 1	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	45-0603A.d2	5.3.1.4.36	Determination of E2007 in Human Plasma by LC/MS/MS Addendum 2	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	45-0603A.m1	5.3.1.4.37	Determination of E2007 in Human Plasma by LC/MS/MS Amendment 1	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	W-20010551	5.3.1.4.38	Assay Validation for the Quantitative Analysis of Unchanged Drug (E2007) in Human Plasma (E2007-Va02-P)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report

Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Method Val	W-20020096	5.3.1.4.39	Assay Validation for the Quantitative Analysis of Unchanged Drug (E2007) in Human Plasma – The stability of E2007 in frozen human plasma	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	W-20010818	5.3.1.4.40	The Stability of Standard Solutions of the Unchanged Drug (E2007) and the Internal Standard (b) (4)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	W-20011197	5.3.1.4.41	Assay Validation of the Quantitative Analysis of Unchanged Drug (E2007) in Human Urine (E2007-Va03-U)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	QBR101588-2	5.3.1.4.42	Validation of an LC-MS/MS Method for the Measurement of Free and Total E2007 and Metabolites M1, M2, M3, M4, M5 and M7 in Human Plasma	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	QBR104264-3	5.3.1.4.43	Determination of ethinylestradiol, levonorgestrel and perampanel (E2007) in Human Plasma Samples by LC-MS/MS from Clinical Study E2007-E044-029	N/A	N/A	N/A	N/A	N/A	Complete; Final Report

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Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Method	24-010	5.3.1.4.44	Analysis of Biological Samples Derived from Humans Administered a Single Intravenous Dose of 10 µg/200 nCi C14-Perampanel, for C14-content, by Accelerator Mass Spectrometry (Eisai Study E2007-E044-017)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method	B00021	5.3.1.4.45	Quantitative determination of E2007 in rat, dog, human plasma and 1/15 mol/L phosphate buffer (pH 7.4) containing 50 mmol/L NaCl by HPLC with FL detection	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Report	QBR103785-1	5.3.1.4.46	Determination of E2007 in human plasma samples by LC-MS/MS from clinical study E2007-E044-028	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Report	QBR105673-1	5.3.1.4.47	Determination of E2007 (Perampanel) in human plasma samples by LC-MS/MS from clinical study E2007-E044-037	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Report	QBR106309-1	5.3.1.4.48	Determination of E2007 (Perampanel) in human plasma samples by LC-MS/MS from clinical study E2007-E044-030	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Report	45-0706	5.3.1.4.49	Determination of E2007 in Human Plasma by LC-MS/MS Supporting E2007-A001-023	N/A	N/A	N/A	N/A	N/A	Complete; Final Report

Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Report	45-0707	5.3.1.4.50	Determination of E2007 in Human Plasma by LC-MS/MS Supporting E2007-A001-024	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Report	GB05026D	5.3.1.4.51	Determination of E2007 in human plasma from the clinical study entitled Phase I Ascending Single Dose Study of E2007 in Healthy Japanese Male Volunteers (E2007-J081-010)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Report	GB07052D	5.3.1.4.52	Determination of E2007 in human plasma from the clinical study entitled Phase I Ascending Repeated-Dose Study of E2007 in Healthy Japanese Male Volunteers (E2007-J081-026)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Report	GB09022D	5.3.1.4.53	Determination of E2007 concentration in human plasma from the clinical study entitled "A Phase II, Ascending High-dose, Add-on Study of E2007 in Patients with Refractory Partial Seizures Uncontrolled with other AEDs (E2007-J081-231)	N/A	N/A	N/A	N/A	N/A	Complete; Final Report

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Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Report	EIS-R1102	5.3.1.4.54	LC/MS/MS Analysis for the Determination of the Concomitant AEDs of E2007 in Human Plasma: A Phase II, Ascending High-dose, Add-on Study of E2007 in Patients with Refractory Partial Seizures Uncontrolled with Other AEDs	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Method Val	NB10155E	5.3.1.4.55	Cross validation of the bioanalytical methods for the determination of E2007 in human plasma across various bioanalytical laboratories	N/A	N/A	N/A	N/A	N/A	Complete; Final Report
Protein Binding	B00033	5.3.2.1.1	Protein binding of E2007 in rat, dog and human plasma.	Equilibrium dialysis	20 ng/mL 200 ng/mL 2000 ng/mL	N=3 per species	N/A	N/A	Complete; Final Report
Protein Binding	AE-4737-G	5.3.2.1.2	Protein binding of ¹⁴ C-E2007 to human serum protein in vitro	Equilibrium dialysis	20 ng/mL 200 ng/mL 2000 ng/mL	N=3 per species	N/A	N/A	Complete; Final Report
Hepatic Metabolism	B07001	5.3.2.2.1	Effect of Ketoconazole and CYP3A4 Antibody on the Formation of E2007 Metabolites in Human Liver Microsomes	N/A	1000 ng/mL	N/A	N/A	N/A	Complete; Final Report
Hepatic inhibition	B00030	5.3.2.2.2	Kinetic and Inhibition Studies using Human Liver Microsomes with E2007	N/A	0 to 30 µmol/L	N/A	N/A	N/A	Complete; Final Report
Hepatic inhibition	AE-4739-G	5.3.2.2.3	Inhibitory Study of E2007 for CYP Isoforms Using Human Liver Microsomes	N/A	0 to 30 µmol/L	N/A	N/A	N/A	Complete; Final Report

Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Enzyme induction	GE-0045	5.3.2.2.4	Enzyme Induction Study of E2007 in Primary Cultured Human Hepatocytes	N/A	0 to 30 µmol/L	N/A	N/A	N/A	Complete; Final Report
Metabolites analysis	B05007	5.3.2.2.5	Structural Analysis of E2007 Metabolites Produced by Human Liver Microsomes	N/A	60 µg/mL	N/A	N/A	N/A	Complete; Final Report
Enzyme inhibition	XT095036	5.3.2.2.6	In Vitro Evaluation of E2007 as a Direct Inhibitor of UGT Enzymes in Human Liver Microsomes	N/A	0 to 30 µmol/L	N/A	N/A	N/A	Complete; Final Report
Enzyme induction	Xr093050	5.3.2.2.7	In Vitro Evaluation of E2007 as an Inducer of Cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT) Expression in Cultured Human Hepatocytes	N/A	0 to 30 µmol/L	N/A	N/A	N/A	Complete; Final Report
Metabolism	B04006	5.3.2.2.8	Estimation of Human CYP Isoforms Response for E2007 Metabolism	N/A	10 ng/mL 30 ng/mL 100 ng/mL	N/A	N/A	N/A	Complete; Final Report
Metabolism	B06012	5.3.2.2.9	Assessment of E2007 Metabolism by Recombinant Human CYP3A5	N/A	10 ng/mL 30 ng/mL 100 ng/mL	N/A	N/A	N/A	Complete; Final Report
Metabolites	B08002	5.3.2.2.10	Comparison of E2007 Metabolites in Rat, Monkey and Human in vitro	N/A	10 µg/mL	N/A	N/A	N/A	Complete; Final Report
Metabolites	B03033	5.3.2.2.11	Comparison of Metabolite Pattern of E2007 after Incubation with Rat, Monkey, Mouse and Human Cryopreserved Hepatocytes	N/A	16.6 µg/mL	N/A	N/A	N/A	Complete; Final Report

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Metabolites	C07139	5.3.2.3.1	Isolation and Identification of E2007 Metabolites in Human Urine	N/A	Human urine samples from E2007-A001-014 6 mg q.d. for 20 days	N/A	N/A	N/A	Complete; Final Report
Metabolic Profile	L07002	5.3.2.3.2	Metabolic Profile of E2007 in Plasma, Urine or Bile after Oral Administration of E2007 to Rat, Monkey and Human	N/A	Rat: 10 mg/kg Monkey: 1 mg/kg Human urine samples from E2007-A001-014 6 mg q.d. for 20 days	N/A	N/A	N/A	Complete; Final Report
Cellular Transport	GE-0258-G	5.3.2.3.3	Cellular Transport Study of e2007 Using MDR1 Expressing Cell	N/A	0 to 30 µmol/L	N/A	N/A	N/A	Complete; Final Report
Transport Study	GE-0404-G	5.3.2.3.4	Transport Study of E2007 using OATP1B1 and OATP1B3 Expressing Oocytes	N/A	0 to 30 µmol/L	N/A	N/A	N/A	Complete; Final Report
Transport Study	B06015	5.3.2.3.5	Characterization of E2007 Transport via Human Organic Anion and Organic Cation Transporters	N/A	0 to 30 µmol/L	N/A	N/A	N/A	Complete; Final Report
Transport Study	DM/PKT2011-002	5.3.2.3.6	Transport of E2007 across Human Breast Cancer Resistance Protein (BCRP)-Expressed Cell Monolayer and the Inhibition Potency of E2007 on BCRP	N/A	0 to 100 µmol/L	N/A	N/A	N/A	Complete; Final Report
Concentration Ratio	B06013	5.3.2.3.7	Blood to Plasma Concentration Ratio of 14C-E2007 in Rat, Dog Monkey and Human	N/A	20 ng/mL 200 ng/mL 2000 ng/mL	N/A	N/A	N/A	Complete; Final Report

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PK	E2007-E044-001	5.3.3.1.1	To evaluate preliminary safety and tolerability of E2007 in healthy male volunteers.	Randomized, double-blind, placebo-controlled	E2007: 0.1 mg, 1mg and 5 mg tablets, doses up to 8 mg, oral	N=55	Healthy subjects	Single dose	Complete; Final CSR
PK	E2007-E044-002	5.3.3.1.2	To evaluate the safety, tolerability, PK and PD of multiple oral doses of E2007 as compared to placebo in healthy adult male subjects.	Randomized, double-blind, placebo-controlled	E2007: 1 mg and 5 mg tablets, doses up to 6 mg, oral	N=32	Healthy subjects	14 Days	Complete; Final CSR
PK	E2007-J081-010	5.3.3.1.3	To evaluate safety, tolerability and PK of a single dose of E2007 when given orally at dose levels of 0.25, 0.5, 1, 2, 4, 6 and 8 mg to healthy Japanese male subjects.	Randomized, double-blind, placebo-controlled	E2007: 0.25 mg, 0.5 mg, 1 mg and 2 mg tablets, doses up to 8 mg, oral	N=56	Healthy Japanese subjects	Single dose	
PK	E2007-E049-203	5.3.3.2.1	<ul style="list-style-type: none"> To assess the tolerability and safety of E2007 in patients with refractory partial or generalized seizures. To assess the PK of E2007 in epileptic patients receiving at least one concomitant anti-epileptic drug. 	Randomized, double-blind, placebo-controlled	E2007: 1 mg and 2 mg tablets, doses up to 2 mg, oral	N=18	Subjects with epilepsy (simple or complex partial or PGTC)	28 Days	Complete; Final CSR
PK	E2007-E044-015	5.3.3.3.1	To determine the effect of impaired hepatic function on the pharmacokinetics of E2007.	Open-label	E2007: 1 mg tablet, 1 mg dose, oral	N=24	Hepatically impaired subjects	Single dose	Complete; Final CSR

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PK	E2007-E044-004	5.3.3.3.2	To evaluate the safety and tolerability of E2007 after single oral administration to generally healthy, elderly, male and female volunteers.	Randomized, double-blind placebo-controlled	E2007: 1 mg tablets, doses up to 2 mg, oral	N=25	Healthy elderly subjects	Single dose	Complete; Final CSR
PK	E2007-E044-007	5.3.3.3.3	To gain information on the absorption, metabolism and elimination of ¹⁴ C-E2007 after a single-radiolabelled dose in healthy elderly volunteers.	Open-label	E2007: 2 mg tablet, 2 mg dose, oral	N=16	Healthy elderly subjects	Single dose	Complete; Final CSR
PK	E2007-J081-026	5.3.3.3.4	To evaluate the safety, tolerability and PK of E2007 when administered orally at dosages of 2 and 4 mg once daily to Japanese healthy adult male volunteers.	Randomized, placebo-controlled	E2007: 2 mg and 4 mg tablets, doses of 2 mg and 4 mg, oral	N=24	Healthy Japanese subjects	Part 1: 14 days Part 2: 28 days	Complete; Final CSR
PK	E2007-E044-005	5.3.3.4.1	To assess the effect of repeated oral doses of ketoconazole on the PK of single oral doses of E2007 in healthy men.	Randomized, open-label crossover	E2007: 1 mg tablet, dose of 1 mg, oral Ketoconazole: 400mg tablet, 400mg dose, oral	N=26	Healthy subjects	E2007: single dose Ketoconazole :10 Days	Complete; Final CSR
PK	E2007-E044-006	5.3.3.4.2	To compare the pharmacokinetics of a single dose of E2007 before and during treatment with carbamazepine.	Open-label	E2007: 1 mg tablet, 2 mg dose, oral CBZ: 100mg and 200mg tablets, doses up to 300 mg, oral	N=20	Healthy subjects	E2007: two single doses CBZ: 31 days	Complete; Final CSR

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PK	E2007-A001-014	5.3.3.4.3	To determine the effect of E2007 on the pharmacokinetics of the CYP3A4/5 substrate midazolam.	Open-label	E2007: 2mg tablet, doses up to 6 mg, oral Midazolam: Syrup, 4mg dose (2mL of 2mg syrup), oral	N=35	Healthy subjects	Period 1: midazolam single dose Period 2: E2007 20 days Period 3: E2007 and midazolam single dose	Complete; Final CSR
PK	E2007-E044-019	5.3.3.4.4	To determine the effect of E2007 on the pharmacokinetics of components of the combined ethinylestradiol and levonorgestrel oral contraceptive (OC) pill.	Open-label	E2007: 2 mg tablet, doses up to 4 mg, oral OC: Microgynon® 30 ED memopack/ blister pack 21 active 7 placebo, oral	N=24	Healthy subjects	Period 1: OC 21 days Period 2: OC and E2007 2mg 7 days Period 3: OC and E2007 4mg 21 days	Complete; Final CSR
PK	E2007-E044-025	5.3.3.4.5	To determine the effect of steady-state E2007 on the pharmacokinetics of current Parkinson's disease therapy levodopa in healthy volunteers.	Open-label	E2007: 4 mg tablet, 4mg dose, oral Sinemet®: 110 tablets (containing 10.8mg carbidopa, 100 mg levodopa), oral	N=60	Healthy subjects	Period 1: levodopa single dose Period 2: E2007 alone 19 days Period 3: levodopa singled dose with E2007 steady state	Complete; Final CSR

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PK	E2007-E044-029	5.3.3.4.6	<p>Part A: To investigate the effect of steady state perampanel on the pharmacokinetics (PK) of a single-dose oral contraceptive (OC) containing ethinylestradiol (EE) and levonorgestrel (LN) (Microgynon® 30)</p> <p>Part B: To investigate the effect of repeated dosing of an OC containing EE and LN (Microgynon® 30) on the PK of a single dose of perampanel.</p>	Open-label	<p>E2007: 2 mg tablets, doses up to 12 mg, oral</p> <p>Microgynon® 30: (30µg EE and 150 µg LN), oral</p>	<p>Part A: N=28</p> <p>Part B: N=24</p>	Healthy subjects	<p>Part A: 72 days</p> <p>Part B: 61 days</p>	Complete; Final CSR
PK	E2007-E044-030	5.3.3.4.7	<p>Part A: To determine the effects upon psychomotor function of a single dose of perampanel when administered alone and in combination with a single dose of alcohol</p> <p>Part B:</p> <ul style="list-style-type: none"> To determine the psychomotor function and the cognitive effects of steady-state perampanel when administered alone and in combination with a single dose of alcohol. To determine the effect on driving performance of a single dose of 	<p>Part A: Open-label</p> <p>Part B: randomized, placebo-controlled</p>	<p>Perampanel: 2 mg tablet, doses up to 12 mg, oral;</p> <p>Alcohol: (Smirnoff 40% Black Label Vodka) to 80-100mg/100mL B.A.L given with equal volume carbonated, caffeine-free and sugar-free beverage, oral</p>	<p>Part A: N=35</p> <p>Part B: N=24</p>	Healthy subjects	<p>Part A: 51 days</p> <p>Part B: 83 days</p>	Complete; Final CSR

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			perampanel when administered alone and at steady-state, and in combination with a single dose of alcohol.						
Pooled Pop PK	CPMS-E2007-2011-002	5.3.3.5.1	<ul style="list-style-type: none"> To characterize the PK profile of perampanel in subjects from Phase 1 studies Investigate dependence of perampanel PK on dose and time Identify covariates that explain between subject variability Quantify magnitude of unexplained variability 	N/A	N/A	N=606	N/A	N/A	Complete; Final Report
Pooled Pop PK and PKPD	EMFFR2008/06/00	5.3.3.5.2	To describe the pharmacokinetics of perampanel, the exposure-response relationship between the exposure of perampanel and efficacy in adult patients with epilepsy, and to describe the relationship between perampanel exposure and selected adverse events.	N/A	N/A	<p>206: 143 for PK; 141 for PKPD; 148 for PKPD QT; 143 for PKPD AE.</p> <p>208: 33 for PK; 42 for PKPD; 42 for PKPD QT; 43 for PKPD AE</p>	N/A	N/A	Complete; Final Report

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Pooled Pop PK and PKPD	CPMS-E2007-2011-003	5.3.3.5.3	To describe the PK of perampanel as adjunctive therapy in subjects with refractory partial seizures and to describe the exposure-response relationship between the exposure of perampanel, efficacy, selected adverse events, withdrawal questionnaires and to assess potential interactions with concomitant AEDs.	N/A	N/A	N=770 for PK N=1109 for PKPD	N/A	N/A	Complete; Final Report
Pooled Pop PK and PKPD	CPMS-E2007-2011-004	5.3.3.5.4	To describe the PK of perampanel as adjunctive therapy in adolescent subjects with refractory partial seizures and to describe the exposure-response relationship between the exposure of perampanel, efficacy, selected adverse events, withdrawal questionnaires and to assess potential interactions with concomitant AEDs.	N/A	N/A	N=74 for PK N=105 for PKPD	N/A	N/A	Complete; Final Report

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PD	E2007-E044-009	5.3.4.1.1	To identify an E2007 dosing regimen suitable to achieve supratherapeutic plasma concentrations in healthy young volunteers.	Part 1: randomized, active- and placebo-controlled Part 2: randomized, double-blind, placebo-controlled	E2007: 2 mg tablets, doses up to 10 mg, oral Diazepam: 5 mg tablets, 5 mg dose, oral	Part 1: N=32 Part 2: N=20	Healthy Subjects	Part 1: single dose Part 2: 21 days	Complete; Final CSR
PD	E2007-A001-013	5.3.4.1.2	To quantify the effect of perampanel on the QT interval duration in healthy subjects.	Double-blind, active- and placebo-controlled	Perampanel: 2 mg tablets, doses up to 12 mg, oral Moxifloxacin: 400 mg over-encapsulated, oral	N=261	Healthy Subjects	16 Days	Complete; Final CSR
PD	E2007-E044-020	5.3.4.1.3	To investigate the potential of perampanel to induce skin phototoxicity to ultraviolet and visible light in healthy volunteers.	Randomized, placebo- and active-controlled	Perampanel: 2 mg tablets, doses up to 6 mg, oral Ciprofloxacin: 500 mg tablet	N=36	Healthy subjects	Perampanel: 10 days Ciprofloxacin 10 days	Complete; Final CSR
PD	E2007-A001-023	5.3.4.1.4	To determine the safety and tolerability of single oral escalating doses of perampanel for the purposes of identifying the maximum tolerated dose (MTD) in healthy adult, recreational polydrug users.	Randomized, Double-blind, placebo-controlled	Perampanel 2 mg tablets, 8mg, 12mg, 16mg, 20mg, 24 mg, 28 mg, 32mg, 36mg doses, oral	N=56	Healthy recreational drug users	Single dose	Complete; Final CSR

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PD	E2007-A001-024	5.3.4.1.5	To evaluate the abuse potential of single doses of perampanel compared to alprazolam, oral ketamine, and placebo in healthy recreational polydrug users.	Randomized, double-blind, placebo- and active-controlled	Perampanel: 2 mg tablets, doses of 8 mg, 24 mg and 36 mg, oral Alprazolam: 0.5 mg and 1.0 mg overencapsulated tablets, oral Ketamine: 100 mg solution, oral	N=40	Healthy recreational 1 drug users	Single dose	Complete; Final CSR
Phase 2 Safety Efficacy	E2007-A001-206	5.3.4.2.1	To determine the maximal tolerated dose (MTD) of E2007 given BID or QD in subjects with refractory partial-onset seizures (including secondarily generalized seizures)	Randomized, double-blind, placebo-controlled	Perampanel: 0.5 mg, 1 mg and 2 mg tablets, doses up to 4 mg, oral	N=153	Subjects with refractory partial-onset seizures	14 weeks	Complete; Final CSR
Phase 2 Safety Efficacy	E2007-G000-208	5.3.4.2.2	To determine the safety and tolerability of doses up to a maximum of 12 mg per day of E2007 (perampanel) in patients with refractory partial seizures who were taking inducing and noninducing anti-epileptic drugs (AEDs).	Randomized, double-blind, placebo-controlled	Perampanel: 2 mg tablets, doses up to 12 mg, oral	N=48	Subjects with refractory partial-onset seizures	16 weeks	Complete; Final CSR
Phase 3 Efficacy	E2007-G000-304	5.3.5.1.1	To evaluate the efficacy of two doses of perampanel (8 and 12 mg) given as adjunctive therapy in subjects with refractory partial seizures.	Randomized, double-blind, placebo-controlled	Perampanel: 2 mg tablets, doses of 8mg and 12 mg, oral	N=390	Subjects with refractory partial-onset seizures	19 weeks	Complete; Final CSR

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Phase 3 Efficacy	E2007-G000-305	5.3.5.1.2	To evaluate the efficacy of two doses of perampanel (8 and 12 mg) given as adjunctive therapy in subjects with refractory partial seizures.	Randomized, double-blind, placebo-controlled	Perampanel: 2 mg tablets, doses of 8 mg and 12 mg, oral	N=389	Subjects with refractory partial-onset seizures	19 weeks	Complete; Final CSR
Phase 3 Efficacy	E2007-G000-306	5.3.5.1.3	To evaluate the efficacy of three doses of perampanel (2, 4, and 8 mg) given as adjunctive therapy in subjects with refractory partial seizures.	Randomized, double-blind, placebo-controlled	Perampanel: 2 mg tablets, doses of 2mg, 4mg and 8 mg, oral	N=712	Subjects with refractory partial-onset seizures	19 weeks	Complete; Final CSR
Phase 2 Safety	E2007-E044-205	5.3.5.2.1	To evaluate the long-term safety and tolerability of perampanel in subjects with Parkinson's disease (PD) with "wearing-off" motor fluctuations and on-period dyskinesias.	Open-label	Perampanel: 1 mg and 2 mg tablets, doses up to 4 mg, oral	N=185	Subjects with idiopathic PD	48 months	Complete; Final Synoptic CSR
Phase 3 Safety	E2007-G000-318	5.3.5.2.2	To evaluate the long-term safety and tolerability of perampanel in subjects with Parkinson's disease (PD) who experienced end-of-dose "wearing-off" motor fluctuations.	Open-label	Perampanel: 2mg tablets, doses up to 4 mg, oral	N=328	Subjects with idiopathic PD	56 weeks	Complete; Final Synoptic CSR
Phase 2 Safety	E2007-A001-220	5.3.3.2.3	To evaluate the long-term safety and tolerability of perampanel in subjects with Parkinson's disease (PD) who experienced end-of-dose "wearing-off" motor fluctuations.	Open-label	Perampanel: 2 mg tablets, doses up to 8 mg, oral	N=26	Subjects with idiopathic PD	54 weeks	Complete; Final Synoptic CSR

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Phase 2 Safety	E2007-G000-228	5.3.5.2.4	To evaluate long-term (1-year) safety while administering perampanel to patients with PDN or PHN.	Open-label	Perampanel: 2 mg tablets, doses up to 12 mg, oral	N=262	Subjects with PDN or PHN	1 year	Complete; Final CSR
Phase 2 Safety	E2007-J081-231	5.3.5.2.5	To explore the safety and tolerability of E2007 up to 12 mg coadministered with other AEDs	Open-label	Perampanel: 2 mg tablets, doses up to 12 mg, oral	N=32	Subjects with refractory partial-onset seizures	10 weeks	Complete; Final CSR
Phase 3 Safety	E2007-G000-303	5.3.5.2.6	To evaluate the long-term safety and tolerability of perampanel as an adjunctive therapy in levodopa treated Parkinson's disease (PD) subjects with motor fluctuation.	Open-label	Perampanel: 2 mg tablets, doses up to 4 mg	N=1005	Subjects with idiopathic PD	108 weeks	Complete; Final Synoptic CSR
ISS	N/A	5.3.5.3.1	Integrated Summary of Safety	N/A	N/A	N/A	N/A	N/A	Final Report
ISE	N/A	5.3.5.3.2	Integrated Summary of Efficacy	N/A	N/A	N/A	N/A	N/A	Final Report
Assessment of Abuse Potential	N/A	5.3.5.3.3	Abuse Potential Evaluation Report	N/A	N/A	N/A	N/A	N/A	Final Report
Phase 2 Safety	E2007-A001-207	5.3.5.4.1	To evaluate the safety and tolerability of perampanel given as adjunctive, long-term treatment in subjects with refractory partial seizures with or without secondary generalization.	Open-label	Perampanel: 2 mg tablets, doses up to 12 mg, oral	N=138	Subjects with refractory partial-onset seizures	436 weeks	Ongoing; Interim Synoptic CSR

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Phase 3 Safety	E2007-G000-307	5.3.5.4.2	To evaluate the safety and efficacy of perampanel (up to 12 mg/day) given as adjunctive treatment in subjects with refractory partial seizures.	Open-label	Perampanel: 2 mg tablets, doses up to 12 mg, oral	N=1218	Subjects with refractory partial-onset seizures	TBD	Ongoing; Interim Synoptic CSR
BA	E2007-E044-028	5.3.5.4.3	To compare relative bioavailability between a 4 mg dose of an oral suspension of perampanel and a 4 mg tablet of perampanel.	Open-label	Perampanel: 2 mg tablet, dose of 4 mg, oral 0.5 mg/mL suspension, 4 mg dose in 8 mL suspension, oral	N=16	Healthy subjects	Single-dose	Complete; Final Report
Imaging	E2007-A001-226	5.3.5.4.4	To assess the displacement of striatal [¹²⁵ I]-IBZM binding by carbidopa/levodopa in Hoehn and Yahr II-IV Parkinson's disease (PD) subjects.	Double-blind, placebo-controlled	Perampanel: 2 mg tablet, doses up to 4 mg, oral	N=1	Subjects with idiopathic PD	28 days	Complete; Final Synoptic CSR

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Phase 2 PK and Safety	E2007-E049-202	5.3.5.4.5	To assess the tolerability and safety of E2007 when given to Parkinson's disease patients receiving a stable dose of levodopa and other antiparkinsonian medications.	Randomized, double-blind, placebo-controlled	Perampanel: 1 mg tablet, doses up to 2 mg, oral	N=19	Subjects with idiopathic PD	28 days	Complete; Final CSR
Phase 2 Safety and Efficacy	E2007-E044-204	5.3.5.4.6	To compare the efficacy of 3 different doses of E2007 with placebo (in addition to stable antiparkinsonian treatment) on the duration of "off time" during the waking day in Parkinson's disease patients with "wearing-off" motor fluctuations and "on" period dyskinesias	Randomized, double-blind, placebo-controlled	Perampanel: 0.5 mg tablet, doses up to 2 mg, oral	N=263	Subjects with idiopathic PD	12 weeks	Complete; Final CSR
Phase 2 MTD	E2007-A001-214	5.3.5.4.7	To determine the tolerability of doses up to a maximum of 8 mg per day of perampanel among subjects with Parkinson's disease who experienced end-of-dose "wearing-off" motor fluctuations.	Randomized, double-blind, placebo-controlled	Perampanel: 1 mg and 2 mg tablets, doses up to 8 mg, oral	N=75	Subjects with idiopathic PD	10 weeks	Complete; Final CSR
Phase 3 Efficacy	E2007-E044-301	5.3.5.4.8	To compare the efficacy of 2 mg perampanel, 4 mg perampanel and placebo on motor function in subjects with Parkinson's disease (PD) who were on optimized and stabilized therapy and experiencing end-of-dose "wearing off"	Randomized, double-blind, placebo-controlled	Perampanel: 1 mg and 2 mg tablets, doses up to 4 mg, oral	N=764	Subjects with idiopathic PD	30 weeks	Complete; Final CSR

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Phase 3 Efficacy	E2007-A001-302	5.3.5.4.9	motor fluctuations. To compare the efficacy of 2 mg and 4 mg of perampanel and placebo on duration of daily "OFF" state in subjects with Parkinson's disease (PD) who experienced end-of-dose "wearing off" motor fluctuations.	Randomized, double-blind, placebo-controlled	Perampanel: 1 mg and 2 mg tablets, doses up to 4 mg, oral	N=752	Subjects with idiopathic PD	20 weeks	Complete; Final Abbreviated CSR
Phase 3 Efficacy	E2007-G000-309	5.3.5.4.10	To compare the efficacy and safety of 1 dose strength (4 mg) of perampanel with that of placebo on motor function in subjects with Parkinson's disease (PD) who were on optimized and stabilized therapy and experienced end-of-dose "wearing off" motor fluctuation.	Randomized, double-blind, placebo- and active-controlled	Perampanel: 2 mg tablets, doses up to 4 mg, oral Entacapone: 200 mg capsules, oral	N=723	Subjects with idiopathic PD	18 weeks	Complete; Final Abbreviated CSR
Phase 2 Safety and Efficacy	E2007-A001-210	5.3.5.4.11	To evaluate the efficacy and safety of E2007 (perampanel) in reducing migraine headaches based on the change in the frequency of migraine periods per 28 days during the treatment phase compared to the baseline phase.	Randomized, double-blind, placebo-controlled	Perampanel: 0.5 mg and 1.0 mg tablets, doses up to 2 mg, oral	N=206	Subjects with history of migraine	14 weeks	Complete; Final CSR
Phase 2 Safety and Efficacy	E2007-A001-218	5.3.5.4.12	To evaluate perampanel for evidence of efficacy with respect to pain reduction in subjects with PHN.	Randomized, double-blind, placebo-controlled	Perampanel: 2 mg tablets, doses up to 8 mg, oral	N=146	Subjects with PHN	15 weeks	Complete; Final CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 2 Safety and Efficacy	E2007-G000-227	5.3.5.4.13	To provide evidence of the effectiveness of perampanel for treating the pain associated with PDN.	Randomized, double-blind, placebo-controlled	Perampanel: 2 mg tablets, doses up to 8 mg, oral	N=355	Subjects with Type I or II diabetes with PDN	15 weeks	Complete; Final CSR.
Phase 2 Safety	E2007-E049-201	5.3.5.4.14	To assess the tolerability, safety and PK of E2007 in patients with multiple sclerosis.	Randomized, double-blind, placebo-controlled	Perampanel: 1 mg tablets, doses up to 3 mg, oral	N=27	Subjects with multiple sclerosis	28 days	Complete; Final CSR.
Phase 2 Safety	E2007-J081-233	5.3.5.4.15	To evaluate the safety and tolerability of E2007 (perampanel) given as adjunctive therapy in subjects with refractory partial seizures.	Open-label	Perampanel: 2 mg tablets, doses up to 12 mg, oral	N=21	Japanese subjects with refractory partial-onset seizures	112 weeks	Ongoing; Interim CSR.

AED=Antiepileptic drug; BA=Bioavailability; BE=Bioequivalence; CSR=Clinical Study Report; E2007=perampanel; IV=Intravenous; MTD=Maximum Tolerated Dose; PK=pharmacokinetic; PD=Pharmacodynamic or Parkinson's disease; PDN=Painful Diabetic Neuropathy; PHN=Post-herpetic Neuralgia; N/A = Not Applicable; Val=Validation

5.2 Review Strategy

The submission was in eCTD format which allowed review of the sponsor's narrative ISE and ISS and analysis using individual study and ISS datasets.

Safety will be reviewed separately by Dr. Mary Doi.

The primary demonstration of efficacy of perampanel therapy in the treatment of partial-onset seizures, with or without secondary generalization, was shown in three multicenter and multinational Phase 3 studies: E2007-G00-304 ("304"), E2007-G000-305 ("305") and E2007-G000-306 ("306"). These were supported by two Phase 2 studies, E2007-A001-206 ("206") and E2007-G000-208 ("208") and an open label extension (OLE) study, E2007-G000-307 ("307").

5.3 Discussion of Individual Studies/Clinical Trials

PHASE 3 STUDY 304

Title of Study: A double-blind, placebo-controlled, dose-escalation, parallel-group study to evaluate the efficacy and safety of perampanel given as adjunctive therapy in subjects with refractory partial seizures.

Study Centers: 77 centers in Argentina, Canada, Mexico and the United States.

Publication: None

Studied Period: April 30, 2008 to November 11, 2010

Objectives: The primary objective was to evaluate the efficacy of two doses of perampanel (8 and 12 mg) given as adjunctive therapy in subjects with refractory partial seizures. The secondary objective was to evaluate the safety and tolerability of perampanel in these subjects.

Methodology: This was a randomized, double-blind, placebo-controlled study consisting of three phases: Prerandomization, Double-blind, and Follow-up. During the 6-week Prerandomization Phase, subjects began recording seizures in a daily diary. Those who experienced the required minimum number of seizures despite receiving AEDs then entered the Double-blind Phase and were randomly assigned to one of three treatment groups (placebo or 8, 12 mg perampanel). The Double-blind Phase included a 6-week Titration Period followed by a 13-week Maintenance Period, during which the subjects continued to receive the doses they achieved at the end of the Titration Period. Subjects who either withdrew from the study prematurely or completed the Double-blind Phase but did not enter the optional open-label extension study returned for a final visit at the end of the 4-week Follow-up Phase.

Number of Subjects: Planned: 375 subjects. Randomized: 390 subjects. Completed: 320 subjects.

Diagnosis and Main Criteria for Inclusion: Male and female subjects 12 years of age or older were eligible for this study if they had a diagnosis of epilepsy with partial seizures, were taking stable doses of up to three marketed AEDs, and had uncontrolled partial seizures.

Test Product, Dose, and Mode of Administration: Perampanel was supplied as 2mg tablets and administered orally at bedtime.

Reference therapy, dose and mode of administration: The reference therapy was placebo administered orally as matching tablets at bedtime.

Duration of Treatment: The duration of double-blind treatment for each subject was 19 weeks (6-week Titration Period and 13-week Maintenance Period).

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was the percent change in seizure frequency per 28 days during treatment relative to baseline. The 50% responder rate was the key secondary efficacy endpoint. The other secondary endpoint was percent change in the frequency of complex partial plus secondarily generalized seizures. The primary endpoints, the secondary endpoints, and many of the exploratory endpoints were based on seizure counts from subject diaries. Other exploratory endpoints were based on the Global Impression of Change questionnaires and the Quality of Life in Epilepsy Questionnaire.

Safety: Safety assessments included prior and concomitant medication use, AEs, withdrawals due to AEs, clinical laboratory results, vital signs, ECGs, physical and neurologic examinations, and photosensitivity and withdrawal questionnaires.

Statistical Methods: The full ITT analysis set included all randomized subjects who received study drug and had any seizure frequency data from the Double-blind Phase. The ITT analysis set included all randomized subjects who received study drug and had at least 2 weeks of seizure frequency data from both the Prerandomization and Double-blind Phases. For the analysis of percent change in seizure frequency, both the baseline seizure frequencies per 28 days and the percent change per 28 days during treatment were rank transformed separately. An ANCOVA was then conducted on the rank-transformed percent change data, with treatment and pooled countries as factors and the ranked baseline seizure frequency per 28 days as a covariate. Log-transformation based ANCOVA was conducted to assess the robustness of the analysis method. A dose-response trend test on the percent change in seizure frequency was performed via a linear contrast using the ranked ANCOVA. Responder rates were analyzed using the Cochran-Mantel-Haenszel test adjusting for pooled countries. A closed, sequential testing procedure, was employed to control the family-wise type-I error rate for the analyses of the primary efficacy endpoint for different dose groups.

PHASE 3 STUDY 305

Title of the Study: A double-blind, placebo-controlled, dose-escalation, parallel-group study to evaluate the efficacy and safety of perampanel given as adjunctive therapy in subjects with refractory partial seizures.

Study Centers: 84 centers in Australia, Austria, Belgium, Finland, France, Germany, Greece, India, Israel, Italy, Netherlands, Russian Federation, South Africa, Sweden, United Kingdom, and the United States.

Publication: None

Study Period: May 20, 2008 to January 14, 2011

Objectives: The primary objective was to evaluate the efficacy of two doses of perampanel (8 and 12 mg) given as adjunctive therapy in subjects with refractory partial seizures. The secondary objective was to evaluate the safety and tolerability of perampanel in these subjects.

Methodology: This was a randomized, double-blind, placebo-controlled study consisting of three phases: Prerandomization, Double-blind, and Follow-up. During the 6-week Prerandomization Phase, subjects began recording seizures in a daily diary. Those who experienced the required minimum number of seizures despite receiving AEDs then entered the Double-blind Phase and were randomly assigned to one of three treatment groups (placebo or 8, 12 mg perampanel). The Double-blind Phase included a 6-week Titration Period followed by a 13-week Maintenance Period, during which the subjects continued to receive the doses they achieved at the end of the Titration Period. Subjects who either withdrew from the study prematurely or completed the Double-blind Phase but did not enter the optional open-label extension study returned for a final visit at the end of the 4-week Follow-up Phase.

Number of Subjects: Planned: 375 subjects. Randomized: 389 subjects. Completed: 321 subjects.

Diagnosis and main criteria for Inclusion: Male and female subjects 12 years of age or older were eligible for this study if they had a diagnosis of epilepsy with partial seizures, were taking stable doses of up to three marketed AEDs, and had uncontrolled partial seizures.

Test Product, Dose, and Mode of Administration: Perampanel was supplied as 2mg tablets and administered orally at bedtime.

Reference therapy, dose and mode of administration: The reference therapy was placebo administered orally as matching tablets at bedtime.

Duration of Treatment: The duration of double-blind treatment for each subject was 19 weeks (6-week Titration Period and 13-week Maintenance Period).

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was the percent change in seizure frequency per 28 days during treatment relative to baseline. The 50% responder rate was the key secondary efficacy endpoint. The other secondary endpoint was percent change in the frequency of complex partial plus secondarily generalized seizures. The primary endpoints, the secondary endpoints, and many of the exploratory endpoints were based on seizure counts from subject diaries. Other

exploratory endpoints were based on the Global Impression of Change questionnaires and the Quality of Life in Epilepsy Questionnaire.

Safety: Safety assessments included prior and concomitant medication use, adverse events (AEs), withdrawals due to AEs, clinical laboratory results, vital signs, ECGs, physical and neurologic examinations, and photosensitivity and withdrawal questionnaires.

Statistical Methods: The Full ITT Analysis Set included all randomized subjects who received study drug and had any seizure frequency data from the Double-blind Phase. The ITT analysis set with at least 14 days of seizure data during treatment included all randomized subjects who received study drug and had at least 2 weeks of seizure frequency data from both the Prerandomization and Double-blind Phases. For the analysis of percent change in seizure frequency, both the baseline seizure frequencies per 28 days and the percent change per 28 days during treatment were rank transformed separately. An ANCOVA was then conducted on the rank transformed percent change data, with treatment and pooled countries as factors and the ranked baseline seizure frequency per 28 days as a covariate. Log-transformation based ANCOVA was conducted to assess the robustness of the analysis method. A dose-response trend test on the percent change in seizure frequency was performed via a linear contrast using the ranked ANCOVA. Responder rates were analyzed using the Cochran-Mantel-Haenszel test adjusting for pooled countries. A closed, sequential testing procedure was employed to control the family-wise type-I error rate for the analyses of the primary efficacy endpoint for different dose groups.

PHASE 3 STUDY 306

Title of the Study: A double-blind, placebo-controlled, dose-escalation, parallel-group study to evaluate the efficacy and safety of perampanel given as adjunctive therapy in subjects with refractory partial seizures.

Study Centers: 116 centers in Asia, Australia, Europe, and Russia.

Publication: None

Study Period: August 4, 2008 to May 19, 2010

Objectives: The primary objective was to evaluate the efficacy of three doses of perampanel (2, 4, and 8 mg) given as adjunctive therapy in subjects with refractory partial seizures. The secondary objective was to evaluate the safety and tolerability of perampanel in these subjects.

Methodology: This was a randomized, double-blind, placebo-controlled study consisting of three phases: Prerandomization, Double-blind, and Follow-up. During the 6-week Prerandomization Phase, subjects began recording seizures in a daily diary. Those who experienced the required minimum number of seizures despite receiving AEDs then entered the Double-blind Phase and were randomly assigned to one of four treatment groups (placebo or 2, 4, 8 mg perampanel). The Double-blind Phase began with a 6-week Titration Period, during which the subjects had their doses increased to the randomized dose level. During the subsequent 13-week Maintenance Period, the subjects continued to receive the doses they achieved at the end of the Titration Period. Subjects who either withdrew from the study prematurely or completed the Double-blind Phase but did not enter the optional open-label extension study returned for a final visit at the end of the 4-week Follow-up Phase.

Number of Subjects: Planned: 680 subjects. Randomized: 712 subjects. Completed: 623 subjects.

Diagnosis and Main Criteria for Inclusion: Male and female subjects 12 years of age or older (18 years of age or older in some countries) were eligible for this study if they had a diagnosis of epilepsy with partial seizures, were taking stable doses of up to three marketed AEDs, and had uncontrolled partial seizures.

Test Product, Dose, and Mode of Administration: Perampanel was supplied as 2mg tablets and administered orally at bedtime.

Reference therapy, dose and mode of administration: The reference therapy was placebo administered orally as matching tablets at bedtime.

Duration of Treatment: The duration of double-blind treatment for each subject was 19 weeks (6-week Titration Period and 13-week Maintenance Period).

Criteria for Evaluation:

Efficacy: Efficacy assessments included seizure counts from subject diaries, Clinical and Patient Global Impression of Change questionnaires, and the Quality of Life in Epilepsy Questionnaire (QOLIE-31-P). The primary efficacy endpoint was the percent change in seizure frequency per 28 days in the Maintenance Period relative to the Prerandomization Phase. The responder rate was a secondary efficacy endpoint. Other secondary efficacy endpoints included the percent change in the frequency of complex partial seizures plus secondarily generalized seizures in the Maintenance Period relative to the Prerandomization Phase, and a dose-response analysis of the percent change in seizure frequency.

Safety: Safety assessments included prior and concomitant medication use, AEs, withdrawals due to AEs, clinical laboratory results, vital signs, ECGs,

physical and neurologic examinations, and photosensitivity and withdrawal questionnaires.

Statistical Methods: The primary efficacy analyses were based on the ITT Analysis Set (all randomized subjects who received study drug and had at least 2 weeks of seizure frequency data from the Prerandomization Phase and at least 2 weeks of seizure frequency data from the Double-blind Phase) using LOCF imputation. Sensitivity analyses were based on all randomized subjects with any seizure data during study treatment, on all subjects in the ITT Analysis Set who completed the study, and on the PP Analysis Set, which excluded subjects with major protocol deviations and low compliance. Percent changes in seizure frequencies were analyzed using an ANCOVA with treatment and pooled countries as factors, and seizure frequency in the Prerandomization Phase as a covariate. Responder rates were analyzed using the Cochran-Mantel-Haenszel test adjusting for pooled countries. The dose-response trend test on the percent change in seizure frequency was performed via a linear contrast using the ranked ANCOVA. A closed, sequential testing procedure was employed to control the family-wise type-I error rate for the analyses of the primary efficacy endpoints.

PHASE 2 STUDY 206

Title of Study: A Double-Blind, Placebo-Controlled, Dose -Escalation, Parallel-Group Study of E2007 Given as Adjunctive Therapy in Patients with Refractory Partial Seizures

Studied Period: March 8, 2005 to February 6, 2007

Objectives: The primary objective of this study was to determine the MTD of perampanel given BID or QD in subjects with refractory partial-onset seizures (including secondarily generalized seizures). The secondary objectives were to evaluate the safety, efficacy, concentration-efficacy relationship, and pharmacokinetics of perampanel and its effects on the Profile of Mood States (POMS) test.

Methodology: The trial was a double-blind, placebo-controlled, dose-escalation, parallel-group study with 3 arms: Drug-treated using BID dosing, drug-treated using QD dosing and placebo-treated. Within groups, subjects were stratified 1:1 according to their concomitant AEDs into one of 2 categories: (1) induced (treated with one or a maximum of 2 marketed and approved antiepileptic inducer medications such as carbamazepine, phenytoin, phenobarbital, or primidone) and (2) non-induced (treated with one or a maximum of 2 marketed and approved antiepileptic non-inducer medications such as topiramate, lamotrigine, gabapentin, tiagabine, zonisamide, valproate, oxcarbazepine, pregabalin, or

levetiracetam, and none of the drugs in the induced group). To be enrolled, a 4 week retrospective Baseline using the subject's seizure calendar was evaluated. The study consisted of the following phases:

1. Baseline Phase (4 weeks): Prospective ascertainment of seizure frequency based on the subject's seizure calendar.

2. Titration Phase (up to 8 weeks): Subjects were titrated from a starting dose of 1 mg/day (0.5 mg BID or 1 mg QD). The dose was increased every 2 weeks up to 4 mg/day or the MTD. Subjects suffering intolerable AEs were to have the dose reduced one step. Once reduced, the same dose was to be continued until the end of the Maintenance Phase. PK samples were obtained at each visit.

3. Maintenance Phase (4 weeks): The perampanel dose was given at the MTD that each subject maintained during the Titration Phase, and PK samples were obtained at each visit. At the last Maintenance Visit, all completing subjects (including the placebo group) were started on 1 mg/day of the study drug.

4. Transition Phase (2 weeks): Subjects were maintained on 1 mg/day of study drug. After 2 weeks, a final visit was conducted and subjects were withdrawn from study drug treatment. Subjects were to return for the Safety Visit 4 weeks later.

Number of Patients: 144 subjects were planned; 153 subjects were analyzed for safety; 152 subjects were analyzed for efficacy.

Diagnosis and Main Criteria for Inclusion: Male and nonpregnant females who had a diagnosis of refractory partial seizures, were treated with 1 or a maximum of 2 other AEDs, and met all other inclusion criteria and none of the exclusion criteria.

Test Product, Dose and Mode of Administration: Perampanel was formulated as 0.5 mg, 1 mg and 2 mg tablets for oral administration.

Duration of Treatment: 14 weeks (8-week Titration, 4-week Maintenance and 2-week Transition Phases)

Criteria for Evaluation: Efficacy was assessed by seizure counts (subject's diary), Clinical Global Impression of Change (CGI), Patient's Global Impression of Change (PGI) and the Seizure Severity Questionnaire.

Primary Endpoint: Determination of the MTD for each subject was a primary study endpoint. For the trial the MTD was defined as the maximum tolerated dose by the majority of the subjects up to a maximum of 4 mg per day.

Efficacy: The proportion of responders during the Maintenance Phase in the ITT Population constituted the primary endpoint analysis

Safety: Safety was evaluated using frequency and severity of AEs; physical, neurological and ophthalmological (at selected sites) examinations; 12-lead ECG; and laboratory assessments including hematology, clinical chemistry and urinalysis during the trial period.

Statistical Methods: Data analysis, tabulations of descriptive statistics and inferential statistics were performed using SAS. The following subject populations were defined for data analyses:

Safety Population: Subjects included in the safety analysis were those who were randomized and took at least one dose of double-blind study drug.

Intent-To-Treat Population: Subjects included in the ITT analysis were those who both were included in the Safety Population and had at least 2 weeks of Baseline, and had at least one week of Titration and/or Maintenance seizure frequency data.

Per Protocol/Fully Evaluable Population: Subjects included in the Per Protocol/Fully Evaluable analysis were those who were included in the ITT Population, did not have any major protocol deviations/violations and were at least 80% compliant with the study drug at Week 13 as well as during the entire Maintenance Phase.

Efficacy: The primary efficacy variable was the proportion of responders in the ITT-LOCF Population in the Maintenance Phase. A subject was a responder if they experienced a 50% or greater reduction in seizure frequency from the Baseline Phase. Seizure frequency was based on the number of seizures per 28 days, calculated as the number of seizures over the entire time interval divided by the number of days in the interval and multiplied by 28.

Statistical significance at $\alpha < 0.05$ (2-sided) in the ITT-LOCF Population was required to establish the efficacy of perampanel vs. placebo. Supportive analyses of the ITT-LOCF and FE Populations were conducted for secondary efficacy measures. Other secondary efficacy endpoints included assessments of the proportion of responders at other intervals and for subsets of the ITT Population, the percent change in seizure frequency from baseline, seizure freedom, seizure severity, and subjective assessments of the subjects' improvement during the study (CGIC and PGIC) and of their mood (POMS). Categorical variables (proportion of responders, percent reduction in seizure frequency, percent of subjects who achieve seizure-free status, no significant change in seizure frequency, significant increase in seizures, CGIC, PGIC, and the percentage of subjects needing back titration) were analyzed by using a CMH test stratified by center. Continuous variables (percent change in seizure frequency and the percent change in partial seizure frequency, the number of seizure-free days per 28 days, changes in the Seizure Severity Questionnaire) were analyzed by using ranked ANOVA with terms for treatment and center in the model.

PHASE 2 STUDY 208

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Explore the Safety and Tolerability of Doses of perampanel up to a Maximum of 12 mg in Patients with Refractory Partial Seizures.

Studied Period: March 13, 2007 to January 15, 2008

Objectives:

Primary:

The primary objective of this study was to determine the safety and tolerability of doses up to a maximum of 12 mg per day of perampanel in patients with refractory partial seizures who were taking inducing and noninducing AEDs.

Secondary:

- Investigate the efficacy of perampanel for the treatment of partial seizures
- Explore the relationship between perampanel plasma concentrations and safety and efficacy measurements.

Exploratory:

- Determine the proportion of responders at the MTD in the Maintenance Phase.

Methodology: This was a randomized, double-blind, placebo-controlled, parallel-group study. Subjects were initially stratified (inducers vs. non-inducers of the cytochrome P450 3A4 isoenzyme) according to their concomitant AEDs, with the aim to recruit approximately 24 subjects to each stratum. Following stratification, subjects were then randomized to 1 of 2 double-blind treatment groups in a 3:1 ratio (perampanel to placebo) such that, within each stratum, approximately 18 subjects were to receive perampanel and approximately 6 subjects were to receive placebo. All subjects were to receive treatment for a total of 16 weeks (Days 1 to 112). Induced subjects were to be treated with 2 to 3 (maximum) marketed and approved anti-epileptic inducer medications such as: carbamazepine, phenytoin, phenobarbital, or primidone. Non-induced subjects were to be treated with 2 to 3 marketed and approved anti-epileptic noninducer medications such as: topiramate, lamotrigine, gabapentin, tiagabine, zonisamide, valproate, oxcarbazepine, pregabalin, or levetiracetam, and none of the drugs in the inducer group. Subjects on multiple AEDs were to be considered as induced if at least 1 concomitant medication was an inducer. The study was to consist of the following phases:

- Baseline Phase (4 weeks, Days –28 to –1): prospective ascertainment of seizure frequency based on the subject's diary. To be enrolled into the study, a 4-week retrospective baseline using the subject's diary was to be evaluated.
- Titration Phase (12 weeks, Days 1 to 84): During the dose-titration period, study drug dosing in the perampanel group was to be started at 2 mg once daily

and titrated up to 12 mg. Titrations were to be made at 2-week intervals on the basis of individual tolerability and in 2-mg incremental steps. Subjects were to be instructed to take the study drug in the evening with food, except on Visit Days 1, 15, 29, 43, 57, 71, and 85. On only those days, subjects were to receive their study drug with food during their clinic visit. At each titration step, the investigator was to review all data available for each subject. The dose was only to be increased if, in the opinion of the investigator and with the agreement of the subject, the current dose had been adequately tolerated. Subjects who did not tolerate the study drug during the first 2 weeks of treatment were to be withdrawn and not replaced. Subjects who did not tolerate the study drug from the third to the twelfth week of treatment could have remained on the same dose or had their dose reduced to their previously tolerated dose (subjects receiving placebo were to have a sham down-titration). Only 1 dose reduction was to be allowed, and any subject requiring more than 1 dose reduction was to be withdrawn and was not to be replaced. Any subject judged to require dose reduction between visits was to return to the study center for an unscheduled visit. During this phase, a blood sample for plasma concentrations of concomitant AEDs was to be obtained at Visit 2 (Day 1).

- **Maintenance Phase (4 weeks, Days 85 to 112):** During the Maintenance Phase, the subject was to continue using the final dose reached during the Titration Phase. No further dose reductions were to be allowed, although the investigator retained the option to withdraw the subject at any time. At the end of the Maintenance Phase (Day 113), blood samples for plasma concentrations of perampanel and other concomitant AEDs were to be obtained for PK analysis. During this phase, blood samples for plasma concentrations of perampanel and concomitant AEDs were to be obtained at Visits 8, 9, or at a Premature Discontinuation Visit (if applicable).

- **Follow-up Phase (4 weeks, Day 113 to 141):** All subjects were to return for end-of-study assessments. Subjects were to return to the study center for monitoring during dose-titration steps (Days 15, 29, 43, 57, 71), at the end of the Titration Phase (Day 85), and at the end of the Maintenance Phase (Day 113). During the dose-titration steps, subjects were to be observed in the study center and discharged at the discretion of the investigator. An observation period of 2 hours after dosing was required. All subjects were to be contacted by telephone on the day following dose administration and again at the midpoint of the 4-week Maintenance Phase to determine if any adverse events had occurred following dosing at the new dose level.

Number of Subjects:

- 48 subjects were planned
- 55 subjects were screened and 48 subjects were enrolled and randomized
- 38 subjects were randomized to the perampanel group and 10 subjects were randomized to the placebo group

- 48 subjects were analyzed for safety (i.e., all randomized subjects)
- 47 subjects were analyzed for efficacy (1 subject, subject #1030 in the placebo group, was excluded from the ITT population due to an invalid baseline seizure diary)

Diagnosis and Main Criteria for Inclusion: Eligible subjects were male or female aged 18 to 70 years, inclusive, with the diagnosis of epilepsy with partial seizures with or without secondarily generalized seizures according with the International League Against Epilepsy's Classification of Epileptic Seizures (1981). Subjects had to have uncontrolled partial seizures despite having been treated with at least 3 different AEDs (given concurrently or sequentially) for at least 2 years, and they had to have an average of at least 3 partial seizures per month, with no 21-day seizure free period during the 2 months preceding randomization. Simple partial seizures without motor signs were not to be counted towards this inclusion criterion. Subjects were currently being treated with 2 to 3 (maximum) marketed and approved AEDs and were known to take their medications as directed. Use of a vagal nerve stimulator was not to be considered an AED by this criterion. Subjects were to have been on a stable dose of the same AEDs for 1 month prior to Visit 1.

Test Product, Dose and Mode of Administration: perampanel, 2 mg tablets, oral

Duration of Treatment: 16 weeks

Criteria for Evaluation:

Efficacy: Seizure counts (recorded in a diary); Clinical Global Impression of Change; and Patient Global Impression of Change.

Dose Tolerability and PK: Tolerability of dose (MTD) and AED plasma concentrations.

Safety: Physical and neurological examination; AEs; orthostatic vital signs; ECG; and laboratory assessments.

Statistical Methods:

Analysis populations were the Safety Population, the ITT Population, and the FE Population. The primary efficacy analysis was performed on the ITT Population.

Efficacy:

The primary efficacy endpoint was the proportion of responders in the active treatment group during the Maintenance Phase. A subject was said to have been a responder for a time period if she/he experienced a 50% or greater reduction in seizure frequency per 28 days from the Baseline Phase. Seizure frequency was based on the total number of seizures during that period (as recorded in the subject's diary), rescaled to a 28-day-frequency.

Secondary efficacy endpoints were:

- 1. Proportion of responders during the Maintenance Phase, Maintenance observed cases (OC), the Titration Phase, each dose phase (2-mg dose phase, 4-mg dose phase, ..., 12-mg dose phase), the Overall Treatment Phase (= 12-week Titration Phase plus 4-week Maintenance Phase), 6-week Maintenance (= last 2 weeks of the Titration Phase plus the Maintenance Phase), and the Follow-up Phase.**
- 2. Percentage change in seizure frequency per 28 days from the Baseline Phase to each of the same phases listed in item (1) above.**
- 3. Proportion of subjects experiencing 0 to 25%, > 25% to 50%, > 50% to 75%, > 75% to 100% reduction/increase and > 100% increase in seizure frequency per 28 days from the Baseline Phase to each of the same phases listed in item (1) above.**
- 4. Number of days without seizures per 28 days (during each of the same phases listed in item (1) above.**
- 5. Change from baseline in the Clinician's Global Impression of Change over the previous 4 weeks at the end of the Maintenance Phase.**
- 6. Change from baseline in the Patient's Global Impression of Change over the previous 4 weeks at the end of the Maintenance Phase.**

Exploratory efficacy endpoints were:

- 1. Proportion of responders at the Study MTD.**
- 2. Change from baseline in seizure frequency per 28 days at the Study MTD.**
- 3. Determination of the Response Ratio (RRatio).**

Safety:

The primary safety endpoint was the MTD for perampanel. Other safety parameters were AEs, physical and neurological examination findings, laboratory assessments, discontinuations due to study medication, orthostatic vital signs, and ECG findings.

PHASE 3 STUDY 307

***Title of the Study:* An Open-label Extension Phase of the Double-blind, Placebo-controlled, Dose-escalation, Parallel-group Studies to Evaluate the Efficacy and Safety of Perampanel Given as Adjunctive Therapy in Subjects with Refractory Partial Seizures**

Study Period: October 17, 2008 to December 1, 2010

Objectives: The primary objective was to evaluate the safety and tolerability of perampanel (up to 12 mg/day) given as adjunctive treatment in subjects with refractory partial seizures. The secondary objective was to evaluate the maintenance of effect of perampanel for the control of refractory partial seizures.

Methodology: This was an OLE study for subjects who completed one of the following DB, placebo-controlled Phase 3 studies: 304,305, or 306. This OLE study consisted of two phases: an Open-label Treatment Phase (comprised of a 16-week blinded Conversion Period and a 256-week Maintenance Period) and a Follow-up Phase (4 weeks). During the Conversion Period, subjects and investigators remained blinded to the treatment received in the previous DB study. To achieve this, all subjects continued to take six tablets of study medication (2-mg perampanel or matching placebo) or fewer as they were instructed during the core DB study. An InteractiveVoice Response System (IVRS) was used to provide dosing instructions to the site for each subject enrolled in the OLE study. Subjects who had been assigned to placebo in the core DB study were started on blinded treatment with perampanel 2 mg/day and were titrated to the MTD of perampanel, (up to 12 mg/day). Subjects assigned to a perampanel arm in the core DB study continued to receive perampanel on a blinded basis. The daily dose of perampanel was titrated upwards to 12 mg/day or the MTD for subjects who had achieved a daily perampanel dose less than 12 mg in the core DB study. No titration was necessary for subjects who had achieved a daily dose of perampanel 12 mg in the core DB study. If additional dose adjustment was necessary during the Conversion Period, the site contacted the IVRS for dosing instructions, which may have lengthened the duration of the Conversion Period by 2 or 3 weeks. At the end of the Conversion Period, sites registered each subject MTD dose with the IVRS, who then informed the site of the subject current dose. The open-label Maintenance Period began at completion of the blinded Conversion Period. Subjects remained on the dose achieved at the end of the Conversion Period unless dose titration for tolerability and/or efficacy reasons was necessary. During the open-label Maintenance Period, subjects were treated with the perampanel dose that provided the best combination of individual efficacy and tolerability. Subjects who either withdrew from the study prematurely or completed the Maintenance Phase returned for a final visit at the end of the 4-week open-label Follow-up Phase. Visit 8 of the core DB between 8 and 56 days of entry into the OLE study were restarted on perampanel at a dose of 2 mg/day (i.e., same as for subjects who had been assigned to placebo in the core DB study). Subjects entered the OLE study on the concomitant AED regimen they were on during the core DB study. The dose(s) of the concomitant AED(s) could have been adjusted.

Number of Subjects:

Planned: Up to 1430 subjects. Enrolled as of interim data cutoff date: 1218 subjects, including 124 adolescent subjects, defined as those aged 12 to 17 years at the time of providing informed consent/assent in the core DBstudy.

Diagnosis and Main Criteria for Inclusion: Male and female subjects were eligible for this OLE study if they completed the DB Phase (Visit 8) of Study 304, 305, or 306 and showed compliance with the inclusion and exclusion criteria for that study (other than criteria related to seizure frequency); provided informed consent for participation in the OLE study; were currently receiving treatment with a stable dose of one to a maximum of three marketed AEDs (on a stable dose of two or three marketed AEDs in Lithuania); and were considered reliable and able to record seizure data and report AE information (or have a caretaker able to perform these duties).

Test Product, Dose and Mode of Administration: Matching placebo 2-mg tablets, oral

Duration of Treatment: The planned total duration of treatment during the OLE study is up to 5 years or until the product becomes available commercially (except in the United Kingdom and India where the total duration is 272 weeks [16-week Conversion Period + 256-week Maintenance Period]).

Criteria for Evaluation:

Efficacy:

Efficacy assessments included seizure counts from subject diaries. The key efficacy endpoints included the percent change in seizure frequency (all seizures types) per 28 days during treatment relative to baseline as well as the proportion of subjects who experienced a 50% or greater reduction in seizure frequency during treatment per 28 days relative to baseline (responder).

Safety:

Safety assessments included examination of the incidence rates of AEs, SAEs, and withdrawals due to AEs; changes in vital signs and body weight; changes in laboratory test parameters; changes in withdrawal questionnaire responses, changes in quantitative ECG parameters and rates of abnormal overall ECG interpretations; and rates of concomitant medication use.

Statistical Methods: Efficacy analyses were based on the Full ITT Analysis Set, while safety analyses were based on the Safety Analysis Set. The Safety Analysis Set was defined as subjects who provided informed consent for the OLE study,

received at least one dose of perampanel in the OLE study, and had at least one post dose safety assessment in the OLE study (N = 1186 for overall population; N = 121 for adolescent population). Thirty-two subjects were enrolled and treated in the OLE study but were not included in the Safety Analysis Set as they did not have any post baseline safety data after the first OLE dose as of the interim cutoff date. The Full ITT Analysis Set was defined as subjects who provided informed consent for the OLE, received at least one dose of perampanel in the OLE study, and had valid seizure data during the perampanel treatment duration (DB and/or OLE studies) (N = 1207 for overall population; N = 122 for adolescents). As inclusion in the Full ITT Analysis Set for subjects treated in the OLE study was dependent on availability of seizure data during perampanel treatment in the DB and/or OLE studies, the number of subjects in this analysis set was higher than that in the Safety Analysis Set (which required availability of data in the OLE study) as of the interim cutoff date.

All data analyses were descriptive in nature, with summary statistics presented for continuous endpoints and frequency counts presented for categorical endpoints. Two general approaches were used to analyze efficacy data. The first examined seizure data by maximum perampanel dose received and used the Pre-perampanel Baseline for evaluating change. The second approach examined seizure data as a function of randomized treatment group in the core DB study and used the Pre-randomization Phase of the core DB study as the baseline for evaluating change

The Pre-perampanel Baseline was defined as follows unless otherwise specified:

(1) for subjects who had been assigned to placebo treatment in the core DB study, the Pre-perampanel Baseline was computed from all data during the core DB study, and

(2) for subjects who had been assigned to perampanel in the core DB study, the Pre-perampanel Baseline was computed from the Pre randomization Phase of the core DB study. For all efficacy analyses, the perampanel treatment duration consisted of (1) the DB (Titration + Maintenance Periods) plus the OLE (Conversion + Maintenance Periods) for subjects assigned to perampanel in the core DB study and who had a ≤ 14 -day gap in perampanel exposure between the DB and OLE studies; (2) the OLE Treatment Phase for subjects assigned to perampanel in the core DB study and who had a > 14 -day gap in perampanel exposure between the DB and OLE studies; or (3) the OLE Treatment Phase for subjects assigned to placebo in the core DB study. For analyses using the Pre-randomization Phase of the core DB study for determining baseline seizure frequency, efficacy data were summarized by randomized treatment group in the core DB study for the DB Titration Period, DB Maintenance Period, OLE Conversion Period, and by 13-week intervals during the OLE Maintenance Period.

Additional summaries of the efficacy endpoints were provided for subgroups defined by age (<18, 18-64, and ≥65 years), sex, race (White, Asian or Pacific Islander, and Other), and number of AEDs (one, two, three) at DB Baseline. Summaries of the key efficacy endpoints were also examined for the subgroup of adolescent subjects. Subgroup analyses were performed using both efficacy analysis approaches (i.e., using Pre-perampanel Baseline and Pre-randomization Phase Baseline). Safety data were summarized by maximum daily dose (defined as <4 mg/day, 4 mg/day, >4 to 8 g/day, and >8 or 12 mg/day) and included data from the entire perampanel treatment duration. The perampanel treatment duration for AE analyses was defined as all exposure to perampanel in the core DB study and current OLE study. The perampanel treatment duration for all other safety endpoints was similar to that specified for the efficacy analyses, except that for subjects assigned to perampanel treatment in the core DB study who had a > 14-day gap in exposure between the core and current OLE study, the treatment duration was defined as the either the DB or OLE treatment phase, whichever was longer. Safety endpoints were also summarized for the subgroup of adolescent subjects.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The indication proposed for perampanel in this application is for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

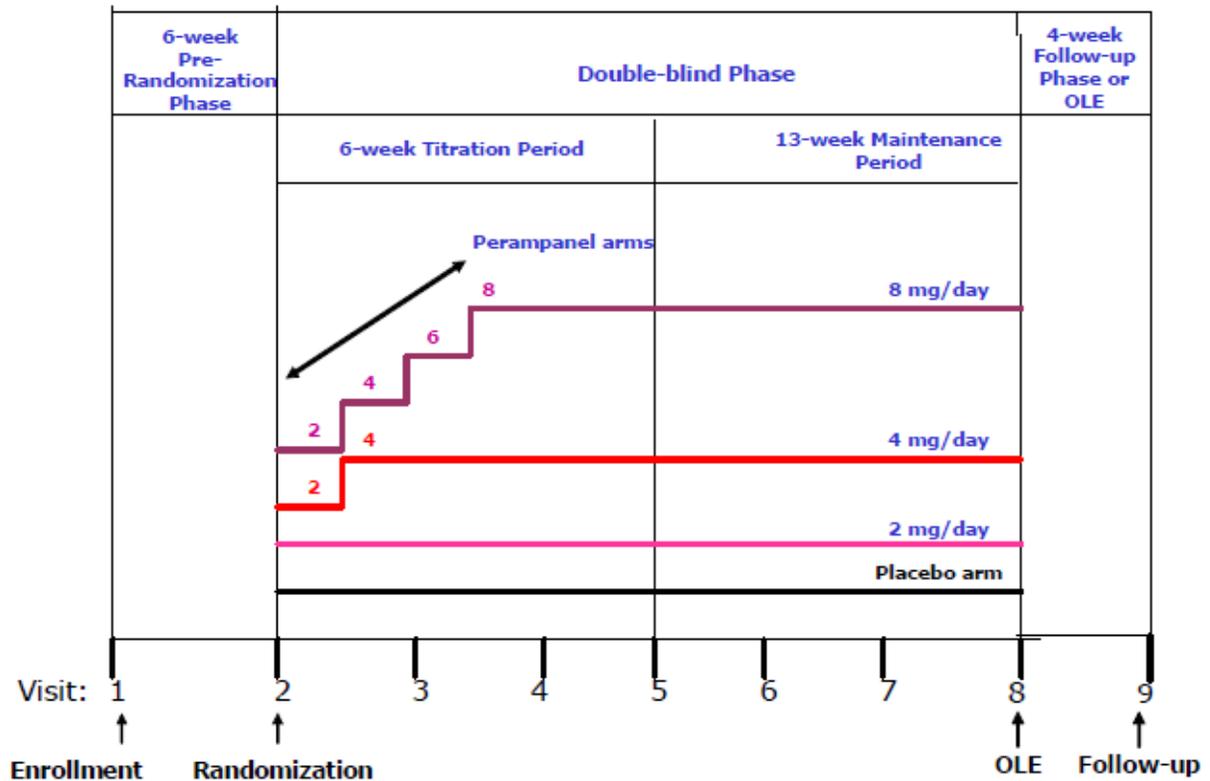
6.1.1 Methods

The three adequate and well-controlled Phase 3 studies of perampanel as adjunctive therapy for the treatment of partial-onset seizures, with or without secondarily generalized seizures, were similar in design. Studies 306, 305, and 304 were randomized, double-blind, placebo-controlled, parallel-group, multicenter investigations of the efficacy, safety, and tolerability of fixed doses of perampanel given as adjunctive therapy (one to three concomitant AEDs) in subjects aged 12 years and older (18 years for sites in some countries). The controlled Phase 3 studies differed in the fixed doses of perampanel evaluated.

In Study 306, perampanel doses of 2 mg, 4 mg, and 8 mg once daily were compared to placebo.

The study design for Study 306 is depicted in the figure below, supplied by the sponsor.

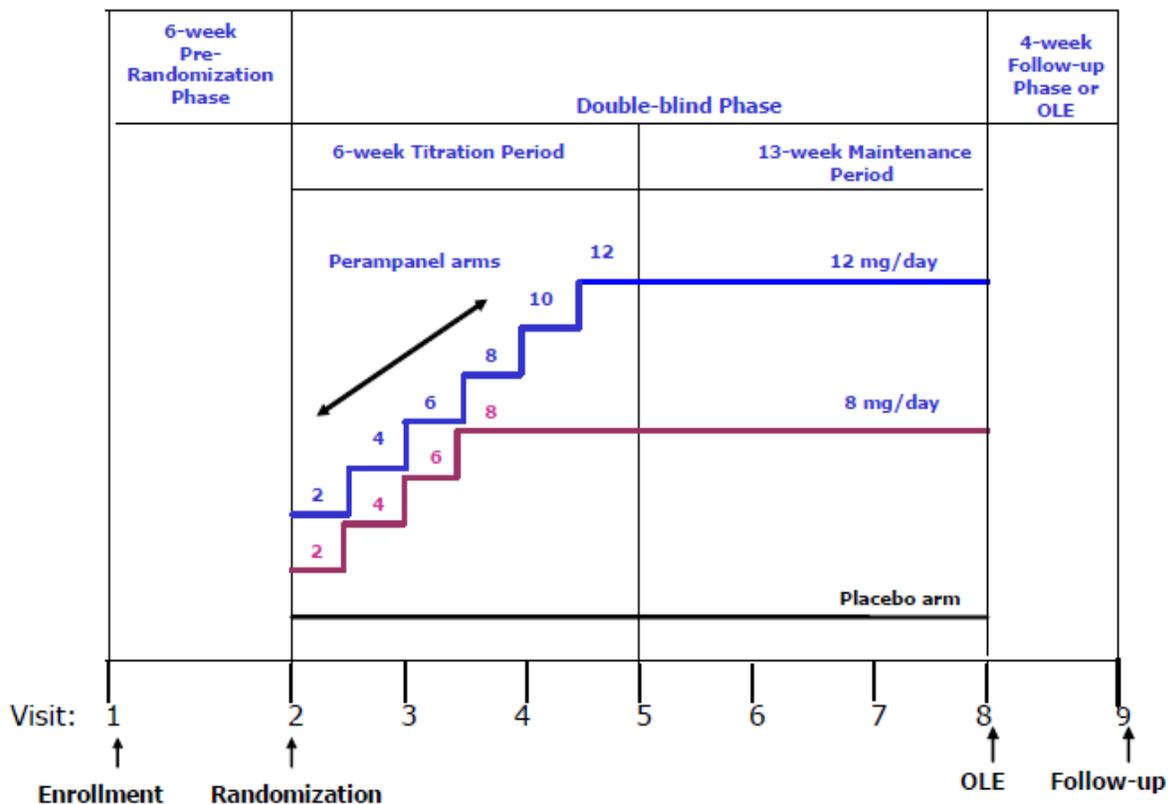
Figure 1 Study Design for Study 306



Studies 305 and 304 compared daily perampanel doses of 8 mg and 12 mg once daily to placebo. The doses evaluated in these studies were those expected to show efficacy based upon results of earlier Phase 2 studies.

The study design for Studies 305 and 304 are the same and are depicted in the figure below, supplied by the sponsor.

Figure 2 Study Design for Studies 305 and 304



Each of the Phase 3 studies consisted of three phases: Prerandomization Phase, including a Screening visit and a 6-week prospective Baseline Period; Double-blind Phase, consisting of a 6-week Titration Period and a 13-week Maintenance Period; and a Follow-up Phase of 4-weeks duration for subjects who withdrew prematurely or did not elect to enter the OLE study.

During the 6-week *Prerandomization Phase*, subjects who had provided written informed consent and who met study eligibility criteria at Visit 1 were required to record information about the number and type of seizures experienced in a daily diary. To be eligible to continue in the study, subjects must have experienced five or more partial-onset seizures (including at least two partial-onset seizures per each 3-week period) during this 6-week study phase and must not have had a 25-day period without seizures. Concomitant AED therapy must have remained unchanged during this study phase.

The *Double-blind Phase* was 19 weeks in duration and included Titration and Maintenance Periods. Subjects who met seizure frequency and type criteria during the Prerandomization Phase were randomly assigned with equal probability to receive study medication (placebo or 2, 4, or 8 mg perampanel in Study 306; placebo or 8 or 12 mg perampanel in Studies 305 and 304), administered once daily at bedtime with food. During the 6-week Titration Period a subject's dosage was increased in 2-mg increments on a weekly basis until the target dose was achieved. During the 13-week Maintenance Period subjects continued treatment with the randomly-assigned study medication in a blinded fashion. Subjects continued to take their baseline AED medication regimen throughout the Double-blind Phase and no changes to the concomitant AEDs were permitted. Down-titration of study medication was permitted during the Double-blind Phase for subjects experiencing intolerable adverse events; more than one down-titration was discouraged and the dose was to be increased again as soon as tolerability improved. Subjects who could not tolerate study drug (2 mg perampanel or placebo) by the end of the Titration Period were withdrawn from the study. Subjects who completed the Double-blind Phase could enter the OLE Study 307 and receive treatment with open-label perampanel.

Subjects who did not elect to enroll in the OLE study or who withdrew prematurely during the Double-blind Phase entered the 4-week *Follow-up Phase*. Study medication was discontinued at the start of this phase (i.e., there was no downward titration of study drug). Although subjects did not receive study medication during the Follow-up Phase, subjects and study sites remained blinded to the identity of the study medication received during the Double-blind Phase.

6.1.2 Demographics

For all three studies, the overall proportion of males and females was approximately equivalent. Between 8.5% and 11.4% of each study population were less than 18 years of age. Only a small minority (1.4% to 3.1%) of subjects in each study were 65 years of age or older. The controlled Phase 3 studies differed in the geographic location of the study sites which resulted in differences seen in the racial distribution of subjects between these studies. In each study, however, the majority of subjects were White (≥65%).

The geographic distribution of sites randomizing subjects in Studies 306, 305, and 304 is shown in the sponsor's table below.

Table 10 The geographic distribution of sites randomizing subjects in Studies 306, 305, and 304

Geographic Region	Study E2007-G000-306	Study E2007-G000-305	Study E2007-G000-304
All Sites, N	712	389	390
North America, n (%)	0	91 (23.4)	228 (58.5)
United States, n (%)	0	91 (23.4)	203 (52.1)
Europe, n (%)	416 (58.4)	241 (62.0)	0
Asia Pacific, n (%)	241 (33.8)	38 (9.8)	0
Central/South America, n (%)	0	0	162 (41.5)
Rest of World, n (%)	55 (7.7)	19 (4.9)	0

Source: 306, Table 14.1.2.4; 305, Table 14.1.2.4; 304, Table 14.1.2.4.

N (n) = number of subjects.

Percentages are based on the total number of randomized subjects.

North America includes Canada and US.

Europe includes Austria, Belgium, Bulgaria, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Israel, Italy, Lithuania, Latvia, Netherlands, Poland, Portugal, Romania, Russian Federation, Serbia, Spain, Ukraine, and United Kingdom.

Asia Pacific includes China, Hong Kong, India, Korea, Malaysia, Philippines, Taiwan, and Thailand.

Central/South America includes Argentina, Chile, and Mexico.

Rest of World includes Australia and South Africa.

The important demographic characteristics for each of the 3 Phase 3 studies are summarized in the sponsor's table below.

Table 11 The important demographic characteristics for each of the 3 Phase 3 studies

	Placebo	Perampanel				Total	Overall Total
		2 mg	4 mg	8 mg	12 mg		
Study E2007-G000-306							
N	185	180	172	169		521	706
Sex, male, n (%)	95 (51.4)	85 (47.2)	88 (51.2)	77 (45.6)		250 (48.0)	345 (48.9)
Mean (SD) age ^a (years)	33.4 (12.55)	33.8 (13.62)	33.6 (12.19)	34.6 (12.77)		34.0 (12.87)	33.8 (12.78)
Age category ^a , n (%)							
< 18 years	14 (7.6)	21 (11.7)	13 (7.6)	12 (7.1)		46 (8.8)	60 (8.5)
18 – 64 years	169 (91.4)	156 (86.7)	158 (91.9)	153 (90.5)		467 (89.6)	636 (90.1)
65+ years	2 (1.1)	3 (1.7)	1 (<1)	4 (2.4)		8 (1.5)	10 (1.4)
Race, n (%)							
White	119 (64.3)	119 (66.1)	105 (61.0)	116 (68.6)		340 (65.3)	459 (65.0)
Black or African/American	0	0	0	0		0	0
Asian	34 (18.4)	35 (19.4)	37 (21.5)	28 (16.6)		100 (19.2)	134 (19.0)
Chinese/Japanese	31 (16.8)	25 (13.9)	29 (16.9)	25 (14.8)		79 (15.2)	110 (15.6)
Other ^b	1 (<1)	1 (<1)	1 (<1)	0		2 (<1)	3 (<1)
Study E2007-G000-305							
N	136			129	121	250	386
Sex, Male, n (%)	71 (52.2)			65 (50.4)	50 (41.3)	115 (46.0)	186 (48.2)
Mean (SD) age ^a (years)	34.4 (13.62)			36.7 (14.35)	35.5 (14.12)	36.1 (14.22)	35.5 (14.02)
Age category ^a , n (%)							
< 18 years	17 (12.5)			17 (13.2)	10(8.3)	27 (10.8)	44 (11.4)
18 – 64 years	118 (86.8)			109 (84.5)	109 (90.1)	218 (87.2)	336 (87.0)
65+ years	1 (<1)			3 (2.3)	2 (1.7)	5 (2.0)	6 (1.6)
Race, n (%)							
White	115 (84.6)			107 (82.9)	100 (82.6)	207 (82.8)	322 (83.4)
Black or African/American	1 (<1)			2 (1.6)	1 (<1)	3 (1.2)	4 (1.0)
Asian	12 (8.8)			14 (10.9)	16 (13.2)	30 (12.0)	42 (10.9)
Chinese/Japanese	0			0	0	0	0
Other ^b	8 (5.8)			6 (4.7)	4 (3.3)	10 (4.0)	18 (4.6)
Study E2007-G000-304							
N	121			133	134	267	388
Sex, Male, n (%)	54 (44.6)			65 (48.9)	69 (51.5)	134 (50.2)	188 (48.5)
Mean (SD) age ^a (years)	35.6 (14.67)			35.8 (14.21)	36.7 (14.64)	36.2 (14.41)	36.0 (14.48)
Age category ^a , n (%)							
< 18 years	14 (11.6)			15 (11.3)	10 (7.5)	25 (9.4)	39 (10.1)
18 – 64 years	102 (84.3)			116 (87.2)	119 (88.8)	235 (88.0)	337 (86.9)
65+ years	5 (4.1)			2 (1.5)	5 (3.7)	7 (2.6)	12 (3.1)
Race, n (%)							
White	103 (85.1)			115 (86.5)	116 (86.6)	231 (86.5)	334 (86.1)
Black or African/American	13 (10.7)			6 (4.5)	8 (6.0)	14 (5.2)	27 (7.0)
Asian	0			1 (<1)	1 (<1)	2 (<1)	2 (<1)
Chinese/Japanese	0			1 (<1)	1 (<1)	2 (<1)	2 (<1)
Other ^b	5 (4.1)			10 (7.5)	8 (6.0)	18 (6.7)	23 (5.9)

The subject's epilepsy history is summarized in the sponsor's table below for the Safety Analysis Set in each of the three controlled Phase 3 studies. Subjects in each controlled Phase 3 study had a long history of epilepsy with the mean time since diagnosis for the overall Safety Analysis Set being approximately 19 years for Study 306, 22 years for Study 305, and 24 years for Study 304. In each study, complex partial seizures were the most common seizure type. To qualify for enrollment in the Phase 3 studies, subjects had to have a documented occurrence of at least five partial-onset seizures during the 6-week Prerandomization Phase, with no seizure-free period exceeding 21 days. The median frequency of all partial seizures per 28 days during the Prerandomization Phase was generally consistent across treatment groups within each study: 9.33 to 10.93 in Study 306, 11.79 to 13.69 in Study 305, and 12.00 to 14.34 in Study 304.

Table 12 Subject's epilepsy history

	Placebo	Perampanel				Total	Overall Total
		2 mg	4 mg	8 mg	12 mg		
Study E2007-G000-306							
N	185	180	172	169		521	706
Time since diagnosis (months)							
n	185	180	171	168		519	704
Mean (SD)	209.9 (128.10)	232.4 (145.20)	236.9 (145.32)	239.4 (142.92)		236.1 (144.26)	229.2 (140.58)
Minimum, maximum	23, 608	6, 600	6, 652	7, 760		6, 760	6, 760
Seizure type, n (%)							
Simple partial without motor signs	52 (28.1)	53 (29.4)	48 (27.9)	57 (33.7)		158 (30.3)	210 (29.7)
Simple partial with motor signs	55 (29.7)	53 (29.4)	54 (31.4)	51 (30.2)		158 (30.3)	213 (30.2)
Complex partial	155 (83.8)	153 (85.0)	147 (85.5)	138 (81.7)		438 (84.1)	593 (84.0)
Complex partial with 2 nd generalized	136 (73.5)	115 (63.9)	119 (69.2)	117 (69.2)		351 (67.4)	487 (69.0)
Study E2007-G000-305							
N	136			129	121	250	386
Time since diagnosis (months)							
n	136			129	121	250	386
Mean (SD)	264.2 (155.30)			270.3 (163.36)	255.9 (158.64)	263.3 (160.93)	263.6 (158.77)
Minimum, maximum	9, 819			26, 743	23, 707	23, 743	9, 819
Seizure type, n (%)							
Simple partial without motor signs	48 (35.3)			49 (38.0)	36 (29.8)	85 (34.0)	133 (34.5)
Simple partial with motor signs	30 (22.1)			39 (30.2)	38 (31.4)	77 (30.8)	107 (27.7)
Complex partial	114 (83.8)			114 (88.4)	100 (82.6)	214 (85.6)	328 (85.0)
Complex partial with 2 nd generalized	95 (69.9)			90 (69.8)	77 (63.6)	167 (66.8)	262 (67.9)
Study E2007-G000-304							
N	121			133	134	267	388
Time since diagnosis (months)							
n	121			133	133	266	387
Mean (SD)	289.6 (154.37)			282.8 (162.24)	279.5 (172.44)	281.1 (167.11)	283.8 (163.08)
Minimum, maximum	23, 719			11, 796	19, 797	11, 797	11, 797
Seizure type, n (%)							
Simple partial without motor signs	48 (39.7)			50 (37.6)	45 (33.6)	95 (35.6)	143 (36.9)
Simple partial with motor signs	41 (33.9)			47 (35.3)	40 (29.9)	87 (32.6)	128 (33.0)
Complex partial	107 (88.4)			116 (87.2)	122 (91.0)	238 (89.1)	345 (88.9)
Complex partial with 2 nd generalized	87 (71.9)			91 (68.4)	101 (75.4)	192 (71.9)	279 (71.9)

Source: 306, Table 14.1.6.1; 305, Table 14.1.6.1; 304, Table 14.1.6.1.
 N (n) = number of subjects; SD = standard deviation; 2nd = secondarily.
 Shaded area indicates perampanel dose was not evaluated in a particular study.
 Percentages are based on the total number of randomized and treated subjects in relevant treatment group.

The subject's in each of these Phase 3 studies were permitted to receive treatment with up to three concomitant AEDs. The distribution of the number of concomitant AEDs taken at baseline is summarized by treatment group in the sponsor's table below. Also summarized in this table are the most common concomitant AEDs (i.e., those received by 10% or more of the total Safety Analysis set for each study). Results for the controlled Phase 3 studies were consistent in showing that only a minority of subjects (10.9% to 15.5%) were receiving a single co-administered AED at baseline. The proportion of subjects receiving three concomitant AEDs was somewhat higher for Studies 306 (37.1%) and 305 (38.6%) than for Study 304 (28.9%). Carbamazepine, lamotrigine, levetiracetam, and valproic acid were the most common co-administered AEDs in each Phase 3 study. Results of drug-drug interaction studies, coupled with findings from population-PK modeling using data from the Phase 3 studies, suggest that perampanel is associated with few potential drug interactions, particularly with other AEDs. The AEDs shown to be statistically significant inducers of perampanel were carbamazepine, oxcarbazepine, and phenytoin.

For more detailed discussion refer to section 6.1.7.

Table 13 Subject's background AED therapy in each of the Phase 3 studies

	Placebo	Perampanel				Total	Overall Total
		2 mg	4 mg	8 mg	12 mg		
Study E2007-G000-306							
N	185	180	172	169		521	706
Total AEDs at baseline, ^a n(%)							
Only 1 AED	28 (15.1)	30 (16.7)	19 (11.0)	27 (16.0)		76 (14.6)	104 (14.7)
Exactly 2 AEDs	90 (48.6)	80 (44.4)	88 (51.2)	82 (48.5)		250 (48.0)	340 (48.2)
Exactly 3 AEDs	67 (36.2)	70 (38.9)	65 (37.8)	60 (35.5)		195 (37.4)	262 (37.1)
Common AEDs at baseline, ^b n(%)							
Carbamazepine	64 (34.6)	58 (32.2)	56 (32.6)	53 (31.4)		167 (32.1)	231 (32.7)
Lamotrigine	57 (30.8)	56 (31.1)	68 (39.5)	66 (39.1)		190 (36.5)	247 (35.0)
Levetiracetam	44 (23.8)	48 (26.7)	45 (26.2)	45 (26.6)		138 (26.5)	182 (25.8)
Oxcarbazepine	36 (19.5)	35 (19.4)	25 (14.5)	34 (20.1)		94 (18.0)	130 (18.4)
Topiramate	51 (27.6)	38 (21.1)	40 (23.3)	40 (23.7)		118 (22.6)	169 (23.9)
Valproic acid	77 (41.6)	80 (44.4)	75 (43.6)	63 (37.3)		218 (41.8)	295 (41.8)
Study E2007-G000-305							
N	136			129	121	250	386
Total AEDs at baseline, ^a n(%)							
Only 1 AED	17 (12.5)			16 (12.4)	9 (7.4)	25 (10.0)	42 (10.9)
Exactly 2 AEDs	64 (47.1)			68 (52.7)	63 (52.1)	131 (52.4)	195 (50.5)
Exactly 3 AEDs	55 (40.4)			45 (34.9)	49 (40.5)	94 (37.6)	149 (38.6)
Common AEDs at baseline, ^b n(%)							
Carbamazepine	43 (31.6)			43 (33.3)	47 (38.8)	90 (36.0)	133 (34.5)
Clobazam	18 (13.2)			14 (10.9)	17 (14.0)	31 (12.4)	49 (12.7)
Lamotrigine	37 (27.2)			40 (31.0)	27 (22.3)	67 (26.8)	104 (26.9)
Levetiracetam	52 (38.2)			49 (38.0)	46 (38.0)	95 (38.0)	147 (38.1)
Oxcarbazepine	23 (16.9)			25 (19.4)	24 (19.8)	49 (19.6)	72 (18.7)
Topiramate	24 (17.6)			25 (19.4)	22 (18.2)	47 (18.8)	71 (18.4)
Valproic acid	32 (23.5)			25 (19.4)	26 (21.5)	51 (20.4)	83 (21.5)
Zonisamide	19 (14.0)			12 (9.3)	11 (9.1)	23 (9.2)	42 (10.9)
Study E2007-G000-304							
N	121			133	134	267	388
Total AEDs at baseline, ^a n(%)							
Only 1 AED	15 (12.4)			26 (19.5)	19 (14.2)	45 (16.9)	60 (15.5)
Exactly 2 AEDs	64 (52.9)			70 (52.6)	82 (61.2)	152 (56.9)	216 (55.7)
Exactly 3 AEDs	42 (34.7)			37 (27.8)	33 (24.6)	70 (26.2)	112 (28.9)
Common AEDs at baseline, ^b n(%)							
Carbamazepine	36 (29.8)			42 (31.6)	49 (36.6)	91 (34.1)	127 (32.7)
Clonazepam	22 (18.2)			13 (9.8)	8 (6.0)	21 (7.9)	43 (11.1)
Lamotrigine	31 (25.6)			40 (30.1)	36 (26.9)	76 (28.5)	107 (27.6)
Levetiracetam	29 (24.0)			37 (27.8)	41 (30.6)	78 (29.2)	107 (27.6)
Oxcarbazepine	29 (24.0)			19 (14.3)	20 (14.9)	39 (14.6)	68 (17.5)
Phenytoin	17 (14.0)			18 (13.5)	16 (11.9)	34 (12.7)	51 (13.1)
Topiramate	15 (12.4)			16 (12.0)	23 (17.2)	39 (14.6)	54 (13.9)
Valproic acid	31 (25.6)			32 (24.1)	37 (27.6)	69 (25.8)	100 (25.8)
Zonisamide	11 (9.1)			17 (12.8)	12 (9.0)	29 (10.9)	40 (10.3)

Source: 306, Table 14.1.6.2.1; 306, Table 14.1.6.2.2; 305, Table 14.1.6.2.1; 305, Table 14.1.6.2.2; 304, Table 14.1.6.2.1; 304, Table 14.1.6.2.2.

AED = anti-epileptic drug; N (n) = number of subjects.

Shaded area indicates perampanel dose was not evaluated in a particular study.

Percentages are based on the total number of randomized and treated subjects in relevant treatment group.

a: The subjects are classified by the number of anti-epileptic drugs used at baseline.

b: AEDs used at baseline in at least 10% of subjects in the Overall Total group.

6.1.3 Subject Disposition

The number of randomized and treated subjects who completed the study and the reasons for premature discontinuation from double-blind treatment are summarized for Studies 306, 305, and 304 in the sponsor's table below. For each Phase 3 study, results were consistent in showing that the subject retention rate was relatively high and in a similar range for the placebo and 2 mg, 4 mg, and 8 mg perampanel treatment groups. In each of the three studies, the most common reasons for discontinuation for all treatment groups were adverse events and subject choice. In Studies 305 and 304, the percentage of subjects who completed study treatment was lower for the perampanel 12 mg group than for either the placebo or perampanel 8 mg group, with the difference due to a higher rate of discontinuation due to adverse events in the 12 mg group. In each study, $\leq 1\%$ of all subjects in each study were discontinued due to a lack of therapeutic effect. The overall percentage of subjects in the combined perampanel treatment group who completed the double-blind study was comparable among those whose background AED therapy included carbamazepine (87.2%), oxcarbazepine (86.3%), lamotrigine (86.7%), levetiracetam (84.8%), topiramate (86.4%), or valproic acid (87.7%).

Table 14 Subject Disposition

	Placebo	Perampanel				Total	Overall Total
		2 mg	4 mg	8 mg	12 mg		
Study E2007-G000-306							
Randomized and treated, N	185 ^a	180 ^a	172	169		521	706
Completed study ^b , n (%)	166 (89.7)	154 (85.6)	158 (91.9)	145 (85.8)		457 (87.7)	623 (88.2)
Discontinued prematurely, n (%)	19 (10.3)	26 (14.4)	14 (8.1)	24 (14.2)		64 (12.3)	83 (11.8)
Primary reason for discontinuation							
Adverse event	6 (3.2)	10 (5.6)	5 (2.9)	11 (6.5)		26 (5.0)	32 (4.5)
Subject choice	8 (4.3)	9 (5.0)	8 (4.7)	8 (4.7)		25 (4.8)	33 (4.7)
Lost to follow-up	4 (2.2)	1 (<1)	0	1 (<1)		2 (<1)	6 (<1)
Inadequate therapeutic effect	0	3 (1.7)	0	1 (<1)		4 (<1)	4 (<1)
Administrative/Other	1 (<1)	3 (1.7)	1 (<1)	3 (1.8)		7(1.3)	8 (1.1)
Study E2007-G000-305							
Randomized and treated, N	136			129	121	250	386
Completed study ^b , n (%)	120 (88.2)			108 (83.7)	93 (76.9)	201 (80.4)	321 (83.2)
Discontinued prematurely, n (%)	16 (11.8)			21 (16.3)	28 (23.1)	49 (19.6)	65 (16.8)
Primary reason for discontinuation							
Adverse event	4 (2.9)			11 (8.5)	23 (19.0)	34 (13.6)	38 (9.8)
Subject choice	6 (4.4)			7 (5.4)	4 (3.3)	11 (4.4)	17 (4.4)
Inadequate therapeutic effect	1 (<1)			0	1 (<1)	1 (<1)	2 (<1)
Progressive disease ^c	1 (<1)			0	0	0	1 (<1)
Administrative/Other	4 (2.9)			3 (2.3)	0	3 (1.2)	7 (1.8)
Study E2007-G000-304							
Randomized and treated, n	121			133 ^a	134 ^a	267	388
Completed Study ^b , n (%)	106 (87.6)			114 (85.7)	100 (74.6)	214 (80.1)	320 (82.5)
Discontinued prematurely, n (%)	15 (12.4)			19 (14.3)	34 (25.4)	53 (19.9)	68 (17.5)
Primary reason for discontinuation							
Adverse event	7 (5.8)			9 (6.8)	24 (17.9)	33 (12.4)	40 (10.3)
Subject choice	3 (2.5)			7 (5.3)	4 (3.0)	11 (4.1)	14 (3.6)
Lost to follow-up	0			2 (1.5)	0	2 (<1)	2 (<1)
Inadequate therapeutic effect	2 (1.7)			0	2 (1.5)	2 (<1)	4 (1.0)
Administrative/Other	3 (2.5)			1 (<1)	4 (3.0)	5 (1.9)	8 (2.1)

Sources: 306, Table 14.1.2.1; 305, Table 14.1.2.1; 304, Table 14.1.2.1.

N (n) = number of subjects.

Shaded area indicates perampanel dose was not evaluated in a particular study.

Percentages are based on the total number of randomized and treated subjects in relevant treatment group.

a: One subject was inappropriately randomized (see Section 10.1 of corresponding CSR).

b: As reported on the End of Study (Subject Disposition) case report form, study completion.

c: Subject 24125001 was mistakenly indicated as having progression of disease instead of progression of seizures.

6.1.4 Analysis of Primary Endpoints

The primary efficacy assessment was based on the following:

- **Primary efficacy endpoint: Percent change in seizure frequency per 28 days during the double-blind phase from baseline.**
- **Primary analysis: An ANCOVA was performed on the rank-transformed % change data (both the baseline and % change seizure frequencies per 28 days). The model includes treatment and pooled countries as factors, and the ranked baseline as a covariate.**
- **Multiplicity adjustment for multiple comparisons: A closed, sequential testing procedure was employed to control the family-wise type-I error rate for the analyses of the primary endpoint for different dose groups: first test a lower dose, if the lower dose demonstrates superiority, then the next higher dose will be tested.**

The primary efficacy endpoint was based on seizure counts derived from the subject diaries. Subjects, or a designated caregiver, completed a daily paper diary on which they recorded seizure counts and type throughout the entire study. All simple partial seizures (with or without motor signs), complex partial seizures, and complex partial seizures with secondary generalization were recorded. To try and ensure correct seizure classification, the investigator reviewed the subject diary with the subject at both Visits 1 and 2. The seizure diary was reviewed for completeness at each visit, and subjects were counseled if diary compliance was unsatisfactory.

The prespecified primary efficacy endpoint was the percent change in seizure frequency per 28 days during treatment relative to baseline. The sponsor's table below summarizes the percent change in seizure frequency per 28 days during the Double-blind Phase relative to the Prerandomization Phase for the Full ITT Analysis Set for each controlled Phase 3 study.

The median percent reductions in seizure frequency per 28 days during the Double-blind Phase relative to Prerandomization for the Full ITT Analysis Set were larger in all perampanel treatment groups than in the respective placebo groups, except for the 2 mg group in Study 306. In all 3 studies the treatment differences relative to placebo in the primary efficacy variable for the Full ITT Analysis Set were statistically significant for the 4 mg, 8 mg, and 12 mg perampanel treatment groups based on the rank ANCOVA. These results were

supported by the log transformation-based ANCOVA, which also showed statistical separation from placebo for all perampanel dose groups except for the 2-mg group in Study 306, as detailed in the sponsor's table below.

Table 15 Efficacy Results for all three Phase 3 Studies

Study/Parameter Statistics	Placebo	Perampanel			
		2 mg	4 mg	8 mg	12 mg
Study E2007-G000-306					
N	184	180	172	169	
Prerandomization seizure frequency					
Median	9.33	10.12	10.02	10.93	
Percent change during Double-blind Phase from Prerandomization					
Median	-10.69	-13.63	-23.33	-30.80	
Median difference to placebo ^a		-4.36	-13.71	-20.13	
(95% CI)		(-14.091, 5.227)	(-23.306, -4.500)	(-29.656, -10.425)	
P value vs. placebo ^b		0.4197	0.0026	<0.0001	
Study E2007-G000-305					
N	136			129	121
Prerandomization seizure frequency					
Median	11.79			13.02	13.69
Percent change during Double-blind Phase from Prerandomization					
Median	-9.72			-30.52	-17.57
Median difference to placebo ^a				-19.10	-13.69
(95% CI)				(-29.169, -8.447)	(-25.198, -2.257)
P value vs. placebo ^b				0.0008	0.0105
Study E2007-G000-304					
N	121			133	133
Prerandomization seizure frequency					
Median	13.66			14.34	12.00
Percent Change during Double-blind Phase from Prerandomization					
Median change	-20.95			-26.34	-34.49
Median difference to placebo ^a				-13.53	-14.20
(95% CI)				(-26.172, -1.944)	(-25.030, -2.729)
P value vs. placebo ^b				0.0261	0.0158

Source: 306, Table 14.2.1.1.6.1; 305, Table 14.2.1.1.1.1; 304, Table 14.2.1.1.6.1.

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; N = number of subjects; vs = versus.

a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

b: For analysis windows, the P value is based on rank ANCOVA for percent change from Prerandomization of seizure frequency per 28 days with treatment and pooled country as factors, and Prerandomization seizure frequency per 28 days as covariate. The Prerandomization and post randomization efficacy measurements are rank transformed separately.

Primary Efficacy Result *Study 306*

Efficacy was derived from the change in seizure frequency over the Double-blind Phase relative to the Prerandomization Phase in the Full ITT Analysis Set. For this analysis, both the baseline seizure frequency per 28 days and the percent change per 28 days during treatment were rank transformed separately. An ANCOVA was then conducted on these rank-transformed percent change data, with treatment

and pooled countries as factors, and the ranked baseline seizure frequency per 28 days as a covariate.

To help determine the robustness of the analysis method, a sensitivity analysis was conducted using a protocol-specified log transformation-based ANCOVA. Sequential procedures, pre-specified in the individual study SAPs, were used to control the family-wise Type I error rate at the 0.05 two-sided alpha level due to multiple treatment comparisons of the primary efficacy variable. In this procedure, the perampanel dose groups were compared with placebo, within each study, according to the following hierarchy. The 8-mg dose was compared with placebo at the 0.05 two-sided alpha level. If the treatment difference was statistically significant, this dose was declared efficacious, and the next dose group (12 mg in 305 and 304; 4 mg in 306) was compared with placebo at the 0.05 two-sided alpha level. If this treatment difference was statistically significant, both doses were declared efficacious, and the lowest dose group (2 mg for 306) was compared with placebo at the 0.05 two-sided alpha level. If no statistically significant treatment difference was detected between perampanel and placebo at any dose level (in the specified dose order), the procedure was to stop and to conclude that the specific perampanel dose group and any other dose groups were not statistically significant.

The following table, developed with statistician Dr. Cherry Liu, shows the decrease in seizure frequency per 28 days during the Double-blind Phase relative to Baseline for the three doses of perampanel evaluated in Study 306.

Table 16 Decrease in seizure frequency per 28 days during the Double-blind Phase relative to Baseline for the three doses of perampanel evaluated in Study 306

Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (ITT), Study 306				
Statistic	Placebo	Perampanel		
		2 mg	4 mg	8 mg
n	182	177	168	166
Median	-10.11	-14.13	-23.99	-31.34
Median Difference to Placebo (95% CI)		-23.27 (-63.59, 17.05)	-69.92 (-110.84, -29)	-92.45 (-133.52, -51.38)
P-value		0.26	0.0008	<0.0001

There were no US sites in this study, which was conducted at 116 sites in Australia, Bulgaria, China, Czech Republic, Estonia, Germany, Hong Kong, Hungary, India, Italy, Latvia, Lithuania, Malaysia, Philippines, Poland, Portugal, Romania, Serbia, South Korea, Spain, Taiwan, Thailand and Ukraine.

In Europe, 4 and 8mg doses were effective and in Asia 8mg was effective while there was no effect in Russia.

The table below, jointly prepared with statistician Dr. Cherry Liu, details these findings.

Table 17 Geographic Differences in Seizure Frequency in Study 306

Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (ITT) by Region, Study 306					
Region	Statistic	Placebo	Perampanel		
			2 mg	4 mg	8 mg
Europe	n	103	101	96	100
	Median	-12.66	-13.72	-25.24	-34.89
	Median Difference to Placebo (95% CI)		-25.36 (-79.68, 28.96)	-87.37 (-142.53, -32.2)	-96.71 (-151.18, -42.26)
	P-value		0.36	0.002	0.0005
Asia	n	62	60	60	50
	Median	-8.12	-19.78	-23.45	-36.76
	Median Difference to Placebo (95% CI)		-46.76 (-116.87, 23.35)	-47.41 (-117.35, 22.52)	-116.73 (-190.24, -43.23)
	P-value		0.19	0.18	0.002
Russia	n	17	16	12	16
	Median	-3.28	14.61	-5.83	0.46
	Median Difference to Placebo (95% CI)		-23.27 (-63.59, 17.05)	-47.73 (-184.56, 89.1)	7.85 (-120.73, 136.44)
	P-value		0.26	0.49	0.9

*Statistically significant at $\alpha=0.05$

The ITT analysis showed that only the two higher doses (4 and 8mg) seemed to be effective in showing a statistically significant reduction in percent change in seizure frequency per 28 days during the double-blind phase from baseline. The subgroup analysis supports that the two higher doses were effective in the Europe and Asia region.

Primary Efficacy Result *Study 305*

Efficacy is derived from the change in seizure frequency over the Double-blind Phase relative to the Prerandomization Phase in the Full ITT Analysis Set. For this analysis, both the baseline seizure frequency per 28 days and the percent change per 28 days during treatment were rank transformed separately. An ANCOVA was then conducted on these rank-transformed percent change data, with treatment and pooled countries as factors, and the ranked baseline seizure frequency per 28 days as a covariate. To help evaluate the robustness of the analysis method, a sensitivity analysis was conducted using a protocol-specified log transformation-based ANCOVA. Sequential procedures, pre-specified in the individual study SAPs, were used to control the family-wise Type I error rate at the 0.05 two-sided alpha level due to multiple treatment comparisons of the primary efficacy variable. In this procedure, the perampanel dose groups were compared with placebo, within each study, according to the following hierarchy. The 8-mg dose was compared with placebo at the 0.05 two-sided alpha level. If the treatment difference was statistically significant, this dose was declared efficacious, and the next dose group (12 mg in 305 and 304; 4 mg in 306) was compared with placebo at the 0.05 two-sided alpha level. If this treatment difference was statistically significant, both doses were declared efficacious, and the lowest dose group was compared with placebo at the 0.05 two-sided alpha level. If no statistically significant treatment difference was detected between perampanel and placebo at any dose level (in the specified dose order), the procedure was to stop and to conclude that the specific perampanel dose group and any other dose groups were not statistically significant.

The following table, developed with statistician Dr. Cherry Liu, shows the decrease in seizure frequency per 28 days during the Double-blind Phase relative to Baseline for the three doses of perampanel evaluated in Study 305.

Table 18 Primary Efficacy Results for Study 305

Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (ITT), Study 305			
Statistic	Placebo	Perampanel	
		8 mg	12 mg
n	136	129	121
Median	-9.72	-30.52	-17.57
Median Difference to Placebo (95% CI)		-45.50 (-71.86, -19.14)	-35 (-61.74, -8.26)
P-value		0.0008	0.0105

As detailed in the table below, jointly produced with statistician Dr. Cherry Liu, efficacy was demonstrated in Europe only, while there was no statistically significant effect in the US, India and Russia. 84 sites were involved in Austria, Australia, Belgium, Germany, Finland, France, Greece, India, Israel, Italy, Netherlands, Russia, Sweden, South Africa, UK and US.

Table 19 Geographic Differences in Seizure Frequency in Study 305

Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (ITT) by Region, Study 305				
Region	Statistic	Placebo	Perampanel	
			8 mg	12 mg
Europe	n	84	75	70
	Median	-2.11	-20.04	-14.88
	Median Difference to Placebo (95% CI)		-50.77 (-84.95, -16.6)	-44.08 (-78.87, -9.27)
	P-value		0.004*	0.013*
USA	n	33	31	27
	Median	-23.31	-41.64	-21.64
	Median Difference to Placebo (95% CI)		-35.62 (-86.35, 15.11)	-0.62 (-53.77, 52.53)
	P-value		0.17	0.98
India	n	10	14	14
	Median	-33.79	-45.42	-30.66
	Median Difference to Placebo (95% CI)		3.83 (-110.07, 117.73)	-1.09 (-106.76, 104.59)
	P-value		0.95	0.98
Russia	n	9	10	9
	Median	-5.63	-23.67	-31.02
	Median Difference to Placebo (95% CI)		-70.98 (-173.68, 31.72)	-75.84 (-175.16, 23.49)
	P-value		0.17	0.13

*Statistically significant at $\alpha=0.05$

The ITT analysis showed that both doses, 8 and 12mg, seemed to be effective in showing a statistically significant reduction in percent change in seizure frequency per 28 days during the double-blind phase from baseline. In this analysis, 8mg appears to be more efficacious than 12mg. The subgroup analysis showed that the efficacy was only demonstrated in Europe, but not other regions, including the USA.

Primary Efficacy Result *Study 304*

Efficacy is derived from the change in seizure frequency over the Double-blind Phase relative to the Prerandomization Phase in the Full ITT Analysis Set. For this analysis, both the baseline seizure frequency per 28 days and the percent change

per 28 days during treatment were rank transformed separately. An ANCOVA was then conducted on these rank-transformed percent change data, with treatment and pooled countries as factors, and the ranked baseline seizure frequency per 28 days as a covariate to determine the robustness of the analysis method, a sensitivity analysis was conducted using a protocol-specified log transformation-based ANCOVA. Sequential procedures, pre-specified in the individual study SAPs, were used to control the family-wise Type I error rate at the 0.05 two-sided alpha level due to multiple treatment comparisons of the primary efficacy variable. In this procedure, the perampanel dose groups were compared with placebo, within each study, according to the following hierarchy. The 8-mg dose was compared with placebo at the 0.05 two-sided alpha level. If the treatment difference was statistically significant, this dose was declared efficacious, and the next dose group (12 mg in 305 and 304; 4 mg in 306) was compared with placebo at the 0.05 two-sided alpha level. If this treatment difference was statistically significant, both doses were declared efficacious, and the lowest dose group was compared with placebo at the 0.05 two-sided alpha level. If no statistically significant treatment difference was detected between perampanel and placebo at any dose level (in the specified dose order), the procedure was to stop and to conclude that the specific perampanel dose group and any other dose groups were not statistically significant.

The following table, developed with statistician Dr. Cherry Liu, shows the decrease in seizure frequency per 28 days during the Double-blind Phase relative to Baseline for the three doses of perampanel evaluated in Study 304.

Table 20 Primary Efficacy Results for Study 304

Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (ITT), Study 304			
Statistic	Placebo	Perampanel	
		8 mg	12 mg
n	121	133	133
Median	-20.95	-26.34	-34.49
Median Difference to Placebo (95% CI)		-13.53 (-26.17, -1.94)	-14.20 (-25.03, -2.73)
P-value		0.0261	0.0184

This study was conducted at 77 sites, in five countries, including Argentina, Canada, Chile, Mexico and the US. As detailed in the sponsor's table below, the greatest efficacy was demonstrated in North America, while there was no evidence of effectiveness in Central and South America where there was a high placebo rate.

Table 21 Geographic Differences in Seizure Frequency in Study 304

Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (ITT) by Regions, Study 304				
Region	Statistic	Placebo	Perampanel	
			8 mg	12 mg
North America: CAN, USA	n	73	74	80
	Median	-11.34	-27.63	-36.91
	Median Difference to Placebo (95% CI)		-61.18 (-96.95, -25.41)	-62.96 (-98.01, -27.91)
	P-value		0.0009*	0.0005*
Central & South America: ARG, CHI, MEX	n	48	59	53
	Median	-26.92	-24.88	20.73
	Median Difference to Placebo (95% CI)		14.69 (-27.94, 57.33)	14.72 (-28.91, 58.35)
	P-value		0.50	0.51
USA	n	66	64	72
	Median	-9.52	-25.38	-35.22
	Median Difference to Placebo (95% CI)		-30.94 (-50.46, -11.42)	-37.06 (-56.04, -18.09)
	P-value		0.002	0.0002

*Statistically significant at $\alpha=0.05$

The ITT analysis showed that both doses, 4 and 8mg, seemed to be effective in showing a statistically significant reduction in percent change in seizure frequency per 28 days during the double-blind phase from baseline. A subgroup analysis demonstrates efficacy in North America, but not in Central and South America.

6.1.5 Analysis of Secondary Endpoints

The 50% responder rate was the key secondary efficacy endpoint. The other secondary endpoint was the percent change in the frequency of complex partial plus secondarily generalized seizures.

A responder was defined as a subject who experienced a 50% or greater reduction in seizure frequency per 28 days during the Maintenance Period (with LOCF imputation) relative to the Prerandomization Phase. The responder rate calculations were done using data from the Maintenance Period to avoid the potential confounding influences of dose titration. Results of the analysis of the responder rate for the Full ITT Analysis Set are summarized for each controlled Phase 3 study in the sponsor's table below.

Table 22 50% Responder Rate for all three Phase 3 Studies

Study Parameter/Statistics	Placebo	Perampanel			
		2 mg	4 mg	8 mg	12 mg
Study E2007-G000-306					
N	184	180	172	169	
Responder, n (%)	33 (17.9)	37 (20.6)	49 (28.5)	59 (34.9)	
P value vs. placebo ^a		0.4863	0.0132	0.0003	
Study E2007-G000-305					
N	136			129	121
Responder, n (%)	20 (14.7)			43 (33.3)	41 (33.9)
P value vs. placebo ^a				0.0018	0.0006
Study E2007-G000-304					
N	121			133	133
Responder, n (%)	32 (26.4)			50 (37.6)	48 (36.1)
P value vs. placebo ^a				0.0760	0.0914

Source: 306, Table 14.2.2.3.5; 305, Table 14.2.2.3.5.1; Study 304, Table 14.2.2.3.5.1.

Shaded area indicates perampanel dose was not evaluated in a particular study.

CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; LOCF = last observation carried forward; N (n) = number of subjects; vs = versus.

a: The P value is based on non-missing values and is from the CMH test adjusted for pooled country.

In all three Phase 3 studies the responder rate was numerically greater for all perampanel dose groups than for the respective placebo group. The treatment

differences relative to placebo in the responder rate during the Maintenance Period for the Full ITT Analysis Set were statistically significant for the perampanel 4-mg and 8-mg groups in Study 306 and for the perampanel 8-mg and 12-mg groups in Study 305

While the responder rates for the perampanel 8-mg and 12-mg groups in Study 304 were similar to those for the 8 mg and 12 mg groups in Study 305, the responder rate in the placebo group was higher for Study 304 (26.4% in Study 304 versus 14.7% in Study 305). As a result, the treatment differences relative to placebo for the 8-mg and 12-mg groups in Study 304 did not achieve statistical significance ($P = 0.0760$ and $P = 0.0914$, respectively). The high placebo response in Study 304 appears to have been driven by data from sites in Central and South America (162 of 390 sites, 41.5%). When only data from North American sites were evaluated for this study, the responder rates during the Maintenance Period (LOCF) for the 8-mg and 12-mg perampanel groups were statistically significantly higher than those for the placebo group (P values of 0.0209 and 0.0169, respectively).

The median percent change in the frequency of complex partial plus secondarily generalized seizures during the Double-blind Phase relative to the Prerandomization Phase for the Full ITT Analysis Set is summarized for each controlled Phase 3 study in the sponsor's table below. The results for this seizure type were consistent with those for all seizures in demonstrating that the median percent reductions in the frequency per 28 days of these seizures during the Double-blind Phase (Full ITT Analysis Set) were statistically significantly larger in the perampanel 4 mg and 8 mg groups in Study 306, and in the 8 mg and 12 mg groups in Studies 305 and 304, than in the respective placebo group based on the rank ANCOVA.

Table 23 Median percent change in the frequency of complex partial plus secondarily generalized seizures during the Double-blind Phase in all three Phase 3 Studies

Study/Parameter Statistics	Placebo	Perampanel			
		2 mg	4 mg	8 mg	12 mg
Study E2007-G000-306					
N	169	167	157	154	
Prerandomization seizure frequency					
Median	6.15	6.83	7.51	7.70	
Percent change during Double-blind Phase from Prerandomization					
Median	-17.63	-20.50	-31.18	-38.69	
Median difference to placebo ^a		-3.26	-14.40	-19.32	
(95% CI)		(-13.685, 7.395)	(-25.082, -3.496)	(-29.788, -8.625)	
P value vs. placebo ^b		0.6506	0.0070	0.0005	
Study E2007-G000-305					
N	126			119	113
Prerandomization seizure frequency					
Median	8.20			7.51	10.18
Percent change during Double-blind Phase from Prerandomization					
Median	-8.05			-32.72	-21.89
Median difference to placebo ^a				-23.07	-17.45
(95% CI)				(-34.798, -10.549)	(-29.269, -5.703)
P value vs. placebo ^b				0.0007	0.0045
Study E2007-G000-304					
N	110			120	120
Prerandomization seizure frequency					
Median	9.45			8.20	9.68
Percent Change during Double-blind Phase from Prerandomization					
Median change	-17.88			-33.03	-33.06
Median difference to placebo ^a				-20.37	-17.90
(95% CI)				(-33.164, -7.741)	(-30.313, -4.665)
P value vs. placebo ^b				0.0020	0.0081

Source: 306, Table 14.2.10.1; 305, Table 14.2.2.1.1; 304, Table 14.2.14.1.1

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; N = number of subjects; vs = versus.

a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

b: For analysis windows, the P value is based on rank ANCOVA for percent change from Prerandomization of seizure frequency per 28 days with treatment and pooled country as factors, and Prerandomization seizure frequency per 28 days as covariate. The Prerandomization and post randomization efficacy measurements are rank transformed separately.

6.1.6 Other Endpoints

The primary (section 6.1.4) and secondary endpoints (section 6.1.5), and many of the exploratory endpoints, were based on seizure counts from subject diaries. Other exploratory endpoints were based on the Global Impression of Change questionnaires and the Quality of Life in Epilepsy Questionnaire.

Exploratory Endpoints

Change in the Number of Seizure-free Days

At baseline, the mean number of seizure-free days per 28 days was approximately 17 days in each treatment group for the ITT Analysis Set. In the Double-blind Phase, there were mean increases in the number of seizure-free days of 0.8 days in the placebo group, 1.5 days in the perampanel 2 mg group, 1.8 days in the perampanel 4 mg group, and 2.1 days in the perampanel 8 mg group. The P values for the comparison with placebo were 0.0965 for 2 mg, 0.0153 for 4 mg, and 0.0006 for 8 mg.

Percentage of Subjects Who Achieved Seizure-free Status

Among the subjects in the ITT Analysis Set with at least 28 days of treatment in the Maintenance Period, 7.0% of those in the placebo group, 9.1% of those in the 2 mg group, 9.3% of those in the 4 mg group, and 11.3% of those in the 8 mg group achieved seizure-free status during the last 28 days of treatment. The P values for the comparison with placebo were 0.5487, 0.5478, and 0.2416, respectively. Among those who completed the Maintenance Period, the percentages of subjects who achieved seizure-free status were 1.2% in the placebo group, 1.9% in the 2 mg group, 4.4% in the 4 mg group, and 4.8% in the 8 mg group. The P values for the comparison with placebo were 0.6745, 0.0972, and 0.0875, respectively.

Responder Rates for Complex Partial Seizures plus Secondarily Generalized Seizures

The responder rates during the Maintenance Period (LOCF) were 24.0% in the placebo group, 27.4% in the 2 mg group, 35.9% in the 4 mg group, and 39.1% in the 8 mg group. The P values for the comparison with placebo were 0.4583 for 2 mg, 0.0183 for 4 mg, and 0.0048 for 8 mg.

Responder Rates for Secondarily Generalized Seizures

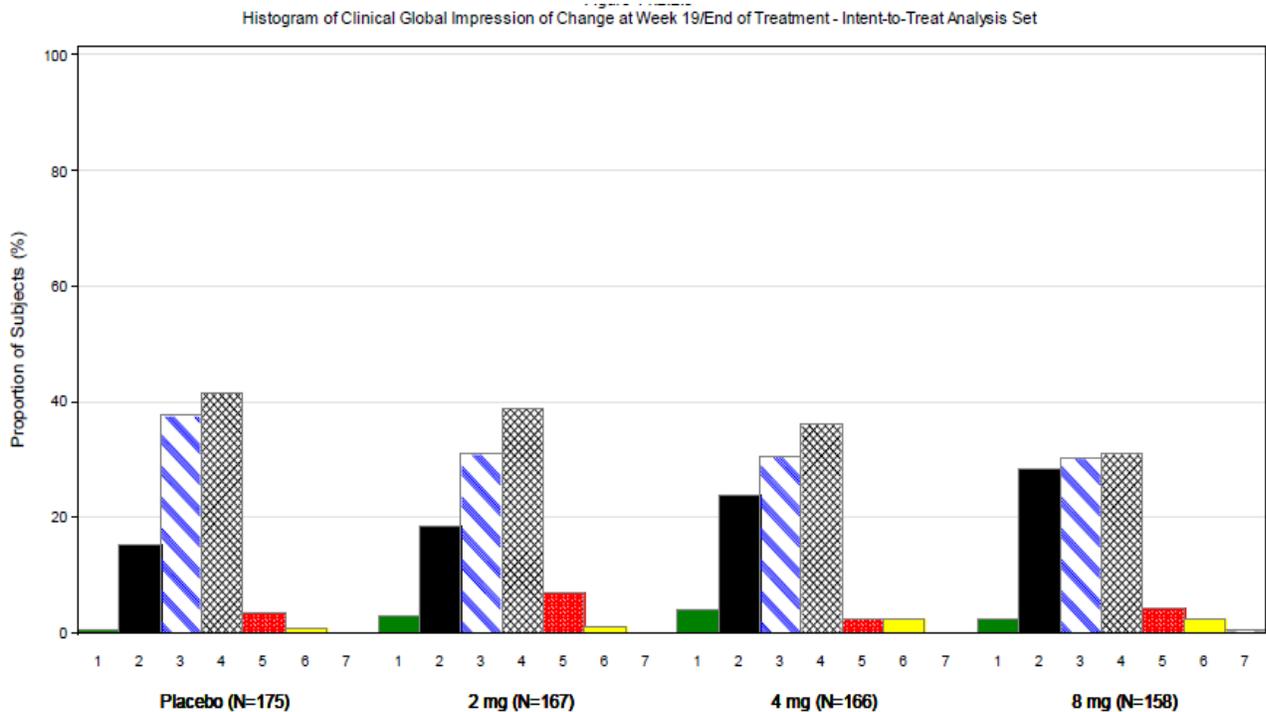
The responder rates during the Maintenance Period (LOCF) were 45.6% in the placebo group, 44.8% in the 2 mg group, 50.0% in the 4 mg group, and 61.7% in the 8 mg group. The P values for the comparison with placebo were 0.5373 for 2 mg, 0.7062 for 4 mg, and 0.2708 for 8 mg.

The following exploratory endpoints were similar in all three Phase 3 studies. Details are shown for Study 306 which appears representative of the others.

Clinical Global Impression of Change

The results for the Clinical Global Impression of Change in Study 306 are illustrated in the sponsor’s figure below. At the end of treatment, 15.9% of the subjects in the placebo group, 21.3% of those in the 2 mg group, 28.1% of those in the 4 mg group, and 30.4% of those in the 8 mg group were considered much or very much improved by the investigators; the remaining subjects were rated minimally improved to very much worse. The P values for the differences relative to placebo were 0.2093 for 2 mg, 0.0063 for 4 mg, and 0.0013 for 8 mg.

Figure 3 Clinical Global Impression of Change in Study 306

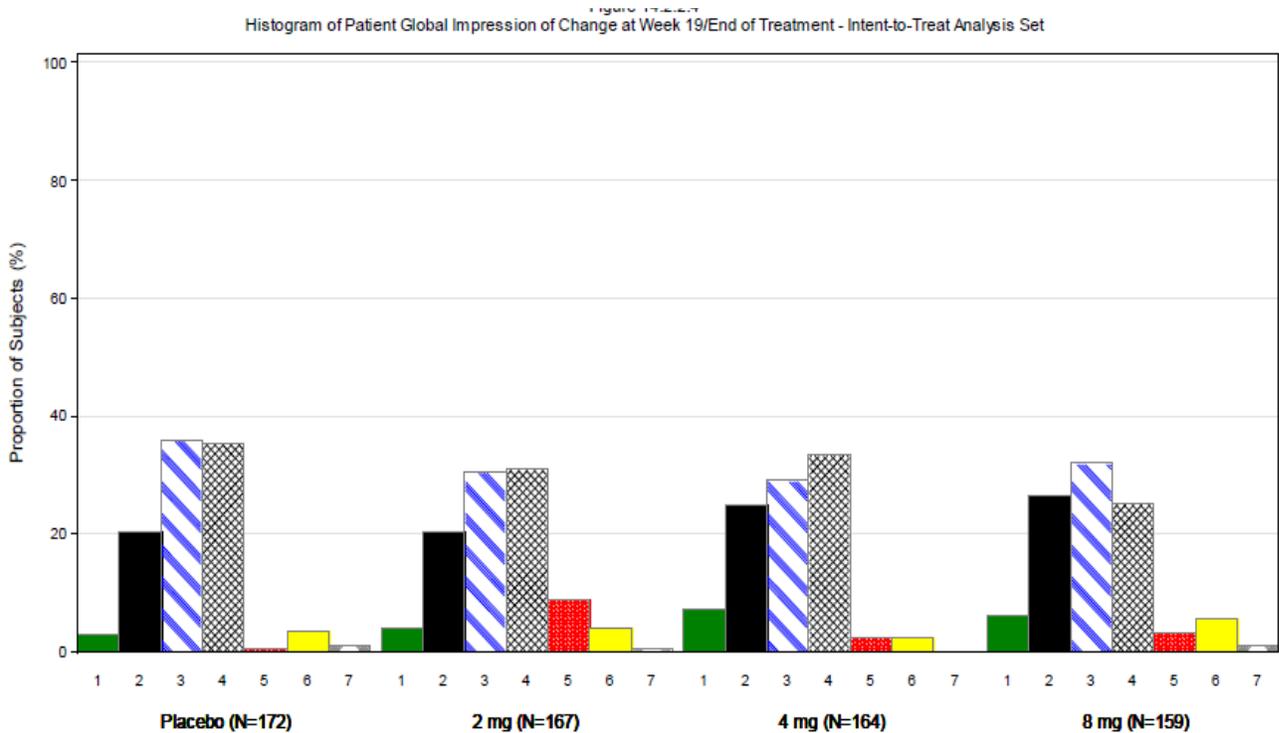


1=Very much improved, 2=Much improved, 3=Minimally improved, 4=No Change, 5=Minimally worse, 6=Much worse, 7=Very much worse

Patient Global Impression of Change

The results for the Patient Global Impression in Study 306 are illustrated in the sponsor's figure below. At the end of treatment, 23.1% of the subjects in the placebo group, 24.3% of those in the 2 mg group, 32.1% of those in the 4 mg group, and 32.3% of those in the 8 mg group considered themselves much or very much improved; the remaining subjects considered themselves minimally improved to very much worse. The P values for the differences relative to placebo were 0.8039 for 2 mg, 0.0618 for 4 mg, and 0.0529 for 8 mg.

Figure 4 Patient Global Impression of Change in Study 306

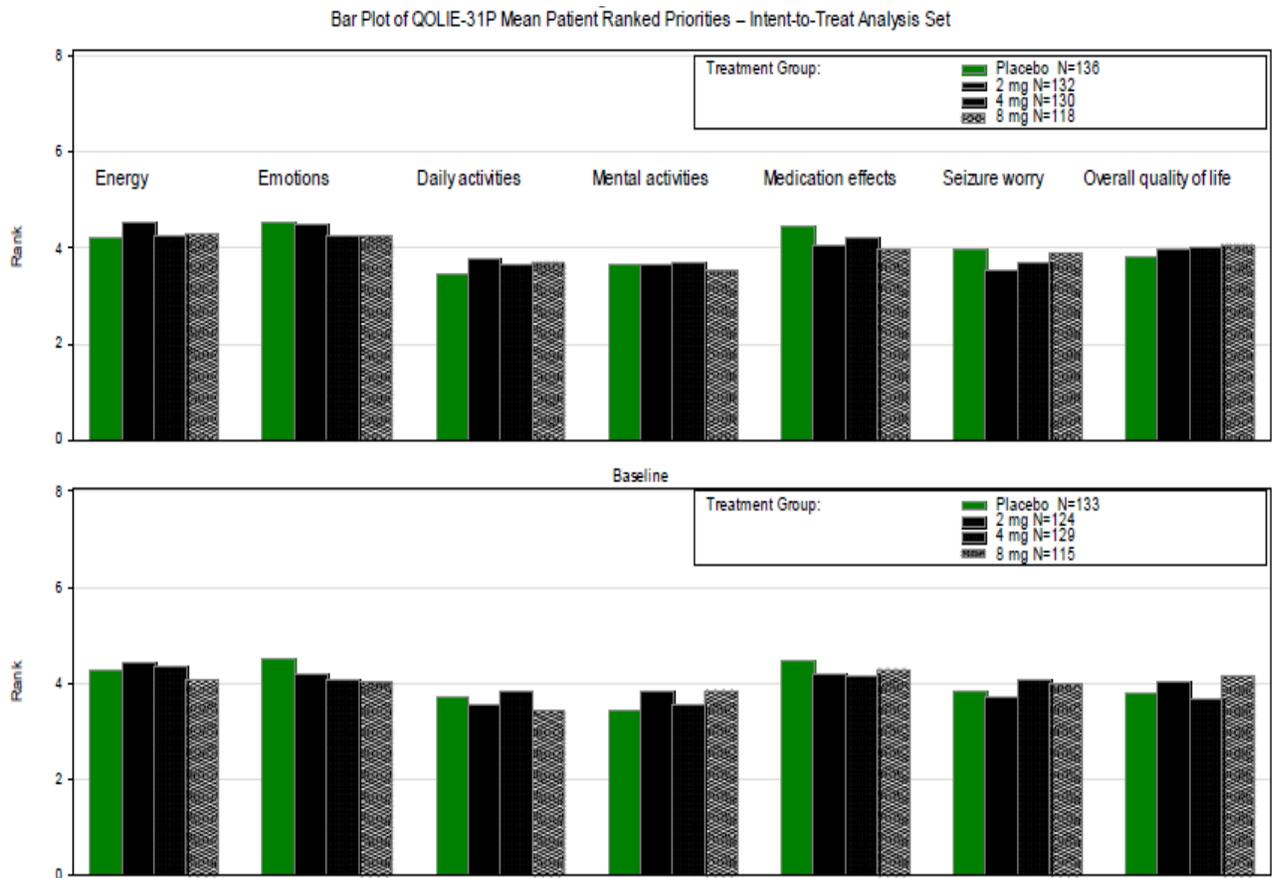


Note: 1=Very much improved, 2=Much improved, 3=Minimally improved, 4=No Change, 5=Minimally worse, 6=Much worse, 7=Very much worse.

QOLIE-31-P

The QOLIE-31-P results for the ITT Analysis Set including: change from baseline to end of treatment, percent change from baseline to end of treatment and percentages of subjects with ≥ 12 -point improvement (i.e., clinically meaningful improvement) in the seven QOLIE-31-P subscales, plus the overall score at the end of treatment are shown in the sponsor's figure below. The changes in quality of life were similar in the placebo, 2 mg, 4 mg, and 8 mg treatment groups.

Figure 5 QOLIE-31-P Results for the ITT Analysis Set in Study 306



6.1.7 Subpopulations

Data from Studies 306, 305, and 304 were pooled for additional analyses of efficacy in various subpopulations. This pooling was especially helpful for perampanel doses of 8 mg and 12 mg, as the 8 mg dose was evaluated in all three studies and the 12 mg dose was evaluated in two of the three studies.

The consistency of the perampanel treatment effects relative to placebo was analyzed for subgroups of subjects with different demographic backgrounds (age, sex, race, concomitant AEDs) and for subjects enrolled at US sites. The subgroup analyses for demographic background and geographic region were performed using the primary (median change in seizure frequency per 28 days during the Double-blind Phase) and secondary (responder rate and median change in frequency of complex partial plus secondarily generalized seizures per 28 days during the Double-blind Phase) efficacy variables. In addition, subgroup analyses explored the perampanel treatment effects based upon the specific concomitant AEDs being used.

Overall, the effects of perampanel, based on results of the primary and secondary efficacy variables, were consistent across all subgroups analyzed. Treatment with perampanel, at doses of 4 to 12 mg, was effective regardless of the subjects' demographic background or co-administered AEDs and for subjects enrolled at US sites.

Efficacy by Age Group

Subjects were categorized into three age subgroups: < 17 years, ≥ 17 to < 65 years, and ≥ 65 years. Of the 1478 subjects in the integrated Full ITT Analysis Set, 110 (7.4%) subjects were younger than 17 years, 1340 (90.7%) were aged from 17 years to < 65 years, and 28 (1.9%) were aged 65 years or older. The distribution of age subgroups was similar for the placebo and perampanel groups.

A summary of the results for the three efficacy variables (median percent change in seizure frequency per 28 days in the Double-blind Phase, responder rate for the Maintenance Period, median percent change in frequency of complex partial plus secondarily generalized seizures per 28 days in the Double-blind Phase) by treatment group is summarized for the age subgroups of < 17 years and ≥ 17 to < 65 years (integrated Full ITT Analysis Set) in the sponsor's table below. Because of the small number of subjects aged ≥ 65 years, differences among the treatment groups for this age subgroup would not allow a meaningful evaluation.

Results for the < 17 years of age subgroup analyses indicated that perampanel at doses of 4 mg to 12 mg was effective relative to placebo in reducing the frequency of all partial-onset seizures as well as complex partial plus secondarily

generalized seizures, during the Double-blind Phase relative to Prerandomization. Additionally, treatment with perampanel doses of 4 mg to 12 mg resulted in higher responder rates during the Maintenance Period (when doses were more stable). The magnitude of the treatment effect (median difference relative to placebo) for the median percent change in seizure frequency per 28 days for perampanel doses of 4, 8, and 12 mg was similar among the < 17 and 17 to < 65 year-old subgroups.

Table 24 Summary of Efficacy Variables by Age Group

Subgroup Parameter/Statistics	Placebo	Perampanel			
		2 mg	4 mg	8 mg	12 mg
Age: < 17 years					
All partial seizure frequency per 28 days					
Total N	38	14	9	31	18
Median percent change to Double-blind Phase	-21.59	17.32	-23.91	-33.55	-40.01
Median difference to placebo (95% CI) ^a		32.60 (6.086, 58.817)	-10.19 (-41.304, 17.407)	-18.98 (-41.827, 4.491)	-23.66 (-48.172, 2.996)
Responder rate					
Total N	38	14	9	31	18
Responders, n (%)	10 (26.3)	0	2 (22.2)	12 (38.7)	9 (50.0)
Complex partial plus secondarily generalized seizures per 28 days					
Total N	32	13	8	29	13
Median percent change to Double-blind Phase	-4.27	17.46	-40.12	-32.72	-44.59
Median difference to placebo (95% CI) ^a		27.95 (-2.723, 59.931)	-33.59 (-59.712, -6.267)	-19.15 (-49.081, 12.277)	-32.71 (-60.935, 5.243)
Age: ≥ 17 to < 65 years					
All partial seizures per 28 days					
Total N	395	163	162	391	229
Median percent change to Double-blind Phase	-12.77	-15.34	-23.41	-28.07	-26.47
Median difference to placebo (95% CI) ^a		-4.96 (-13.331, 3.161)	-12.97 (-21.326, -5.032)	-18.43 (-24.926, -12.062)	-15.48 (-22.992, -7.942)
Responder rate					
Total N	395	163	162	391	229
Responders, n (%)	73 (18.5)	34 (20.9)	47 (29.0)	138 (35.3)	77 (33.6)
Complex partial plus secondarily generalized seizures per 28 days					
Total n	366	151	148	356	214
Median percent change to Double-blind Phase	-13.87	-22.03	-29.43	-35.65	-28.39
Median difference to placebo (95% CI) ^a		-8.18 (-17.242, 0.935)	-16.05 (-25.525, -6.442)	-21.16 (-28.288, -14.070)	-15.33 (-23.548, -6.879)

Source: Table 14.2.1.2.1; Table 14.2.2.2; Table 14.2.3.2.1.

CI = confidence interval, ITT = intent-to-treat; N (n) = number of subjects.

a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

Efficacy Based on Sex

The integrated Full ITT Analysis Set was comprised of 759 (51.4%) females and 719 (48.6%) males. The demographic and medical history characteristics for males and females were similar. The mean age was 34.1 and 35.5 years for males and females, respectively. The mean time since diagnosis was approximately 20 years for males and females (244.9 and 260.1 months, respectively), and about 85% of subjects in both subgroups (83.2% and 87.7%, respectively) had complex

partial with or without secondarily generalized seizures. Efficacy results for perampanel were consistent in males and females, with both subgroups showing improved seizure control with perampanel 4 mg, 8 mg, and 12 mg relative to placebo. The magnitude of the treatment effect relative to placebo for the median percent change in seizure frequency per 28 days (all partial seizures and complex partial plus secondarily generalized seizures) was higher for females than for males, as detailed in the sponsor's table.

Table 25 Treatment Effect by Sex

Subgroup Parameter/Statistics	Perampanel				
	Placebo	2 mg	4 mg	8 mg	12 mg
Sex: Males					
All partial seizure frequency per 28 days					
Total N	220	85	88	207	119
Median percent change in Double-blind Phase	-15.00	-16.33	-17.91	-22.82	-24.84
Median difference to placebo (95% CI) ^a		-2.07 (-13.832, 9.533)	-5.87 (-16.695, 5.065)	-11.48 (-20.045, -2.538)	-11.76 (-22.451, -0.971)
Responder rate					
Total n	220	85	88	207	119
Responders, n (%)	38 (17.3)	20 (23.5)	23 (26.1)	64 (30.9)	40 (33.6)
Complex partial plus secondarily generalized seizures per 28 days					
Total N	203	78	79	185	107
Median percent change in Double-blind Phase	-16.42	-13.47	-30.53	-31.67	-22.93
Median difference to placebo (95% CI) ^a		0.48 (-12.171, 12.628)	-9.81 (-22.484, 3.643)	-13.78 (-23.311, -3.630)	-8.80 (-20.603, 3.250)
Sex: Females					
All partial seizures per 28 days					
Total N	221	95	84	224	135
Median percent change in Double-blind Phase	-11.61	-12.20	-26.19	-34.15	-30.16
Median difference to placebo (95% CI) ^a		-3.54 (-14.633, 7.219)	-18.94 (-30.126, -7.843)	-23.99 (-32.732, -15.614)	-19.61 (-29.371, -9.484)
Responder rate					
Total N	221	95	84	224	135
Responders, n (%)	47 (21.3)	17 (17.9)	26 (31.0)	88 (39.3)	49 (36.3)
Complex partial plus secondarily generalized seizures per 28 days					
Total n	202	89	78	208	126
Median percent change in Double-blind Phase	-12.35	-25.07	-32.31	-39.54	-33.45
Median difference to placebo (95% CI) ^a		-11.39 (-23.901, 0.514)	-24.72 (-35.932, -8.957)	-27.72 (-37.296, -17.948)	-22.67 (-33.407, -11.799)

Source: Table 14.2.1.4.1; Table 14.2.2.4; Table 14.2.3.4.1.

CI = confidence interval, ITT = intent-to-treat; N (n) = number of subjects.

a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

Efficacy Based on Race

About three-quarters of the 1478 subjects in the integrated Full ITT Analysis Set were White. The distribution of the remaining subjects was 19.6% Asian or Pacific Islander, 2.1%, Black or African American, and 3.0% of other racial origins. The distribution of racial subgroups was similar for the placebo and perampanel groups. In all racial subgroups, a complex partial plus secondarily generalized seizure was the most common seizure type at baseline. The percentage of female subjects was higher for the Black/African American subgroup (64.5%) than for the other three racial subgroups, and the mean time since epilepsy diagnosis was shorter for the Asian or Pacific Islander subgroup than for the other three racial subgroups.

Because of the very small number of subjects in the Black/African American or other racial subgroups, the principal subgroup analyses of efficacy based on race compare Whites and Asian or Pacific Islanders. A summary of the results for the three efficacy variables by treatment group is summarized for the racial subgroups of White and Asian or Pacific Islander (pooled Full ITT Analysis Set) is detailed in the sponsor's table below.

Table 26 Summary of efficacy variable by race

Subgroup Parameter/Statistics	Perampanel				
	Placebo	2 mg	4 mg	8 mg	12 mg
Race: White					
All partial seizure frequency per 28 days					
Total N	337	119	105	338	215
Median percent change in Double-blind Phase	-12.77	-10.71	-23.91	-25.87	-25.77
Median difference to placebo (95% CI) ^a		0.05 (-9.565, 9.583)	-15.76 (-25.337, -5.920)	-15.53 (-22.394, -8.634)	-14.75 (-22.665, -7.009)
Responder rate					
Total N	337	119	105	338	215
Responders, n (%)	63 (18.7)	24 (20.2)	34 (32.4)	110 (32.5)	69 (32.1)
Complex partial plus secondarily generalized seizures per 28 days					
Total n	310	112	100	309	199
Median percent change in Double-blind Phase	-13.08	-12.53	-35.61	-32.72	-28.41
Median difference to placebo (95% CI) ^a		-3.38 (-13.862, 7.260)	-19.38 (-29.659, -8.179)	-18.80 (-26.565, -11.038)	-15.75 (-24.563, -6.850)
Race: Asian or Pacific Islander					
All partial seizures per 28 days					
Total N	76	60	66	69	18
Median percent change in Double-blind Phase	-11.57	-19.78	-22.04	-39.29	-33.82
Median difference to placebo (95% CI) ^a		-8.86 (-22.053, 7.786)	-4.95 (-20.769, 9.972)	-26.19 (-41.473, -10.814)	-15.49 (-39.780, 14.635)
Responder rate					
Total N	76	60	66	69	18
Responders, n (%)	16 (21.1)	13 (21.7)	15 (22.7)	33 (47.8)	9 (50.0)
Complex partial plus secondarily generalized seizures per 28 days					
Total N	68	54	56	62	15
Median percent change in Double-blind Phase	-19.18	-26.59	-28.87	-47.20	-11.54
Median difference to placebo (95% CI) ^a		-8.78 (-25.437, 7.352)	-9.38 (-28.709, 7.866)	-26.33 (-42.840, -9.225)	-7.54 (-36.970, 28.901)

Source: Table 14.2.1.3.1; Table 14.2.2.3; Table 14.2.3.3.1.

CI = confidence interval, ITT = intent-to-treat; N (n) = number of subjects.

a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

Improvements in seizure control were seen for perampanel compared to placebo in both racial subgroups. The efficacy for the White subgroup was consistent with that described for the overall study population. (This would be expected since this race comprised about three-quarters of all subjects in the integrated Full ITT Analysis Set.) For the Asian or Pacific Islander subgroup, reductions in seizure frequency per 28 days during the Double-blind Phase, as well as the proportion of subjects achieving at least a 50% reduction in seizure frequency during the Maintenance Period, were consistently larger for the perampanel 8-mg and 12-mg groups than for the placebo group.

Among the Asian and Pacific Islander subgroup, the magnitude of the treatment effect relative to placebo for median changes in seizure frequency was less in the perampanel 2-mg and 4-mg groups, and the responder rates for perampanel 2 mg and 4 mg were similar to those for placebo.

There were fewer than 10 Black/African American subjects within each treatment group (none in the 2 mg or 4 mg groups). It is not possible to meaningfully evaluate differences among the treatment groups for these racial subgroups. (For this reason, data for these two subgroups are not included in the table.) There was no indication that the pattern of efficacy for perampanel (4 mg to 12 mg) compared with placebo differed in the Black/African American or other racial subgroups relative to the larger racial subgroups or to the overall population.

Effect of Concomitant AEDs

The results of the population PK analysis indicated a two- to three-fold increase in the clearance of perampanel in both male and female subjects receiving co-administered carbamazepine (three-fold increase), oxcarbazepine (two-fold increase), or phenytoin (two-fold increase). The therapeutic effects of perampanel were examined for subgroups treated concomitantly with at least one of the three inducer AEDs (perampanel inducer subgroups) compared to the subgroup whose background AED therapy did not include one of these AEDs (perampanel noninducer subgroup).

Using data from Studies 305 and 304 to further assess the effects at 8 mg and 12 mg, the median treatment difference versus placebo in the percent change in seizure frequency per 28 days in the Maintenance Period among subjects in the perampanel noninducer AED subgroup was similar to that for subjects receiving concomitant therapy with carbamazepine or oxcarbazepine at the 8 mg perampanel dose, higher in subjects receiving the 12 mg dose. Higher responder rates during the Maintenance Period for perampanel 8 mg and 12 mg compared

with placebo were seen regardless of perampanel AED inducer use. The response rate during the Maintenance Period was higher for subjects on adjunctive perampanel 8 mg or 12 mg therapy in the perampanel noninducer AED subgroup compared to subjects in either of the two perampanel AED inducer subgroups. These results suggest that the induction effects of carbamazepine and oxcarbazepine on perampanel clearance have a small effect on perampanel response at these higher doses. The explanation for this observation remains unclear.

Results were similar for Study 306. The median percent reductions in seizure frequency per 28 days in the Maintenance Period were larger, and the responder rates were higher, for perampanel doses of 4 and 8 mg compared with placebo or perampanel 2 mg for subjects receiving concomitant therapy with perampanel AED inducers than those not on a co-administered perampanel AED inducer. Once again, the explanation for this clinical vs. PK discrepancy remains unclear.

The sponsor's table below shows the median percent change in seizure frequency and responder rate during the maintenance period by last dose and baseline co-administered AEDs, completer analysis set for Studies 305 and 304, excluding central and South American sites.

Table 27 Effect of Concomitant AEDs on Efficacy in Studies 305 and 304

Parameter/ Statistics	Concomitant CBZ, OXC, PHY			Concomitant CBZ or OXC			No Concomitant CBZ, OXC, or PHY		
	Placebo	Perampanel Last Dose		Placebo	Perampanel Last Dose		Placebo	Perampanel Last Dose	
		8 mg	12 mg		8 mg	12 mg		8 mg	12 mg
All partial seizure frequency per 28 days									
Total N	102	94	79	91	77	67	80	64	35
Median frequency – Prerandomization	14.74	10.21	12.78	12.98	10.50	13.66	10.72	13.84	17.18
Median percent change in Maintenance Period	-8.68	-25.82	-22.62	-5.87	-32.37	-27.82	-19.96	-50.63	-54.17
Median difference to placebo (95% CI) ^a		-17.77 (-31.807, -3.872)	-19.21 (-34.269, -4.409)		-25.92 (-40.446, -11.170)	-26.92 (-42.396, -11.338)		-24.37 (-37.818, -10.163)	-33.22 (-47.253, -17.673)
Responder rate									
Total N	102	94	79	91	77	67	80	64	35
Responders, n (%)	21 (20.6)	29 (30.9)	26 (32.9)	17 (18.7)	27 (35.1)	24 (35.8)	12 (15.0)	32 (50.0)	19 (54.3)

Source: 5.3.5.3, Table 14.2.6.6; 5.3.5.3, Table 14.2.6.7.

AED = antiepileptic drug; CBZ = carbamazepine; CI = confidence interval, N (n) = number of subjects; OXC = oxcarbazepine; PHY = phenytoin.

Note: Subjects who were completers and with actual last dose equal to perampanel 8 or 12 mg were included in the analysis.

a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

The sponsor’s table below shows the median percent change in seizure frequency and responder rate during maintenance period by last (actual) dose and baseline co-administered AED, Completer Analysis set for Study 306.

Table 28 Effect of Concomitant AEDs on Efficacy in Study 306

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

Source: 5.3.5.3, Table 14.2.6.9; 5.3.5.3, Table 14.2.6.10; 5.3.5.3, Table 14.2.6.11; 5.3.5.3, Table 14.2.6.12.

AED = antiepileptic drug; CBZ = carbamazepine; CI = confidence interval, N (n) = number of subjects; OXC = oxcarbazepine; PHY = phenytoin.

Note: Subjects who were completers and with actual last dose equal to perampanel 8 or 12 mg were included in the analysis.

a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

Efficacy at US Sites

Of the 1478 subjects in the integrated Full ITT Analysis Set, 293 (19.8%) were enrolled at sites in the US. These subjects came from Study 304 and Study 305; no US sites were involved in Study 306. For this reason, there are no data for perampanel doses of 2 mg and 4 mg in the US subgroup.

The US subjects in the integrated Full ITT Analysis Set had a mean age of 36.8 years and were predominately White (80.2%); 48.8% of subjects were male and 51.2% were female. The mean time since diagnosis was approximately 24 years and 89.1% of subjects had complex partial with or without secondarily generalized seizures. Approximately one-third of US subjects were receiving background therapy with three AEDs (32.1%), and 53.9% were receiving concomitant therapy with two AEDs. This pattern of demographic and epilepsy-specific characteristics was consistent with that of all subjects in the Full ITT Analysis Set for the Phase 3 studies.

Improved seizure control was demonstrated for adjunctive therapy with perampanel 8 mg and 12 mg among US subjects having partial-onset seizures, as detailed in the sponsor's table below.

Table 29 Seizure Control in US sites

Parameter/Statistics	Perampanel		
	Placebo	8 mg	12 mg
All partial seizure frequency per 28 days			
Total N	99	95	99
Median percent change in Double-blind Phase	-15.90	-32.72	-33.86
Median difference to placebo (95% CI) ^a		-22.26 (-35.303, -9.413)	-20.81 (-33.766, -8.767)
Responder rate			
Total N	99	95	99
Responders, n (%)	17 (17.2)	38 (40.0)	42 (42.4)
Complex partial plus secondarily generalized seizures per 28 days			
Total N	90	92	90
Median percent change in Double-blind Phase	-16.16	-39.92	-34.90
Median difference to placebo (95% CI) ^a		-26.03 (-39.138, -12.783)	-21.00 (-34.393, -8.179)

Source: Table 14.2.1.5.1; Table 14.2.2.5; Table 14.2.3.5.1.

CI = confidence interval, ITT = intent-to-treat; N (n) = number of subjects.

a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

The magnitude of the treatment differences relative to placebo for the median percent changes in all partial-onset seizures as well as for complex partial plus secondarily generalized seizures for the US subgroup was numerically greater than the corresponding values for the 8 mg and 12 mg perampanel groups for the entire integrated Full ITT Analysis Set. The same was true for the magnitude of the responder rate for the US subgroup compared with the entire integrated Full ITT Analysis Set. To further assess this, data from all regions across the three Phase 3 studies, data from the common treatment groups of placebo and 8 mg in Studies 304, 305 and 306 were pooled. A rank ANCOVA was used to analyze the percent change from baseline per 28 days during the treatment period for the Full ITT analysis set. The ANCOVA included the rank-transformed percent change from baseline as the dependent variable, rank-transformed baseline seizure frequency as a covariate, and treatment, region, and treatment-by-region as factors.

These results are displayed in the sponsor's table below as the percent change in seizure frequency per 28 days during the double-blind phase relative to prerandomization for subjects who received placebo or 8mg perampanel (Studies 306, 305 and 304) by region (Full Intent-to-Treat Analysis Set).

Table 30 Percent Change in Seizure Frequency by Region

Region/Statistics	Placebo	8 mg Perampanel
North America		
N	106	105
Mean	1.65 (77.898)	-31.86 (44.521)
Median	-16.16	-34.20
Min, Max	-100.0, 404.3	-100.0, 103.1
Median Difference to Placebo		-23.74
(95% Confidence Interval) ^a		(-36.364, -10.879)
Central and South America		
N	48	59
Mean	-26.92 (35.932)	-17.42 (52.707)
Median	-26.18	-24.88
Min, Max	-88.8, 111.5	-95.6, 150.7
Median Difference to Placebo		5.02
(95% Confidence Interval) ^a		(-11.263, 24.568)
Europe		
N	192	181
Mean	7.07 (71.840)	-14.90 (61.780)
Median	-7.13	-23.25
Min, Max	-95.5, 420.6	-100.0, 390.6
Median Difference to Placebo		-19.26
(95% Confidence Interval) ^a		(-28.869, -10.097)
Asia Pacific		
N	74	65
Mean	-6.05 (51.131)	-29.24 (45.858)
Median	-11.57	-38.89
Min, Max	-100.0, 192.9	-93.9, 127.3
Median Difference to Placebo		-22.83
(95% Confidence Interval) ^a		(-37.687, -6.533)

Among US sites, the treatment differences relative to placebo in the median percent change in seizure frequency per 28 days during the Double-blind Phase were -28.06% for the 8 mg group and -31.25% for the 12 mg group; the P values associated with these treatment differences were 0.0020 and 0.0002, respectively (rank ANCOVA). Among US sites, the responder rates during the Maintenance Period (with LOCF imputation) were 37.5% and 43.1% for the 8 mg and 12 mg groups, compared with 16.7% for the placebo group; the P values for the differences to placebo were 0.0077 for 8 mg and 0.0008 for 12 mg. Among US sites, the treatment differences relative to placebo in the median percent change in the frequency of complex partial plus secondarily generalized seizures per 28 days during the Double-blind Phase were -31.5% for the 8 mg group and -31.17% for the 12 mg group; the P values associated with these treatment differences were 0.0002 and 0.0002, respectively (rank ANCOVA). Results of subgroup

analyses based on region for sites in North America were consistent with those for the US subgroup (202 of 227 subjects in North America were from US).

In the subgroup from Central and South America, there was no difference between either perampanel group and the placebo group in the median percent change in seizure frequency per 28 days during the Double-blind Phase (P = 0.5121 for the 8 mg group; P = 0.5151 for the 12 mg group) or in the responder rate during the Maintenance Period (P = 0.9335 for the 8 mg group; P = 0.7925 for the 12 mg group).

The lack of efficacy observed for perampanel in the Central and South American subgroup in Study 304 appears to be related to the high response to placebo in this regional subgroup. In the placebo group for the Central and South American subgroup, the median percent change in seizure frequency during Double-blind Phase was -26.18%, and the responder rate was 33.3%. Corresponding figures for the placebo group in the North American subgroup were -11.34% and 21.9%, respectively. The median change in seizure frequency per 28 days during the Double-blind Phase for the placebo group in the US subgroup (or North American subgroup) was consistent with results seen for placebo in Studies 306 and 305. The dose-response analysis focused on the Maintenance Period (Full ITT Analysis Set, LOCF) when the doses of perampanel became more stable. The median percent change in the frequency of all partial seizures was greater in the 12 mg group (-34.49%) than in the 8 mg group (-26.34%).

The sponsor attempted to explain the high placebo rate in Central and South America by performing multiple analyses. These explorations include evaluating the influence of demographic and baseline characteristics (age and baseline body weight) and concomitant AEDs on the efficacy results for the Central and South American region. For these analyses, data from the integrated Phase 3 Full ITT Analysis Set were used; in this integrated analysis set, only subjects from Study 304 contributed to the Central and South American regional subgroup.

The mean age for subjects in Central and South America (34.7 years) was younger than that for subjects in North America (36.6 years), and there were fewer adolescent subjects (<18 years) enrolled in sites in Central and South America (6.9% vs. 15.1% for North America). It is unlikely, however, that this age difference contributed to the high placebo response in Central and South America for Study 304, as subjects enrolled at sites in Asia-Pacific study sites were also younger (mean age of 31.1 years) and had fewer adolescents (4.0%) compared to subjects enrolled at North American sites. There was no indication of a greater placebo response among Asia-Pacific subjects.

The mean body weight and body mass index (BMI) was lower for Central and South American subjects (67.36 kg and 25.21 kg/m², respectively) compared to North American subjects (75.64 kg and 26.90 kg/m², respectively). Again, the mean body weight and BMI values for Central and South American subjects was comparable to those for Asian-Pacific subjects (60.13 kg and 22.54 kg/m²), and it therefore seems unlikely that a difference in these parameters contributed to the high placebo response in Central and South America for Study 304. The individual AEDs at baseline were similar across regions both for the relative incidence of individual AEDs as well as for the incidence of use of carbamazepine, oxcarbazepine, and phenytoin (perampanel inducers) The use of concomitant non-AED medication also showed no notable differences among regions. In this reviewer's opinion, no reasonable explanation has been proposed which might explain this high placebo rate in Central and South America.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The time to the onset of activity for perampanel, up to the minimum effective dose of 4 mg, was explored in analyses of the percent change in seizure frequency relative to the Prerandomization Phase during the first 2 weeks of the Titration Period for the Full ITT Analysis Set based on integrated data from Studies 306, 305, and 304. As designated in the Protocol, all subjects randomized to perampanel received a daily dose of 2 mg during Week 1 of the Titration Period, and subjects randomized to the perampanel 4 mg, 8 mg, or 12 mg groups received a daily dose of 4 mg during Week 2 of the Titration Period.

The minimally effective dose for perampanel as adjunctive therapy in partial-onset seizures in Study 306 appears to be 4 mg. Thus, the onset of clinically meaningful seizure improvement with perampanel seems to appear as early as the second week of treatment if the subject is titrated at a rate increase of 2 mg/week. This observation is consistent with PK simulations based on plasma concentration data obtained from healthy subjects which showed that, for the 4 mg perampanel dose (with titration), about 85% of average steady-state perampanel concentration is achieved at the start of the second week of treatment, and 97% of the average perampanel concentration is achieved at the start of the third week of 4 mg/day treatment.

A once daily dose regimen was established by Phase 2 Study 206 where subjects who were randomly assigned to adjunctive perampanel treatment were titrated over the dose range of 1 mg to 4 mg, and perampanel was administered either once or twice daily. Results were similar for the QD and BID perampanel groups. Based on this finding, the once-daily dosing regimen was used in all subsequent

clinical studies of perampanel in partial-onset seizures. In the Phase 3 studies, perampanel was administered with food at bedtime. Administration with food is supported by results of Phase 1 studies which showed that dosing with food slowed drug absorption without changing the extent of absorption. Dosing before bedtime was selected to minimize sedation and/or somnolence. Once-daily dosing of perampanel is further supported based on its half-life, which averages more than 72 hours in healthy subjects not receiving a perampanel AED inducer, and still more than 24 hours in healthy subjects receiving carbamazepine.

Because of perampanel's long half life, a 2-week interval (the time likely needed to reach steady state) between doses was evaluated in Phase 2 Studies 206 and 208. Although steady states may not have been completely reached in less than two weeks, weekly titration was chosen because of the good tolerability shown for perampanel at doses up to 12 mg/day in these studies. In the Phase 3 studies, perampanel treatment was initiated at a dose of 2 mg/day and doses were adjusted upward in 2 mg increments on a weekly basis to the randomly assigned dose.

Due to its half-life of 70 to 110 hours, none of the clinical studies with perampanel included a down-titration schedule. There was no increased seizure activity following discontinuation of perampanel doses of 2 mg to 12 mg in the Phase 3 studies and no adverse event reports.

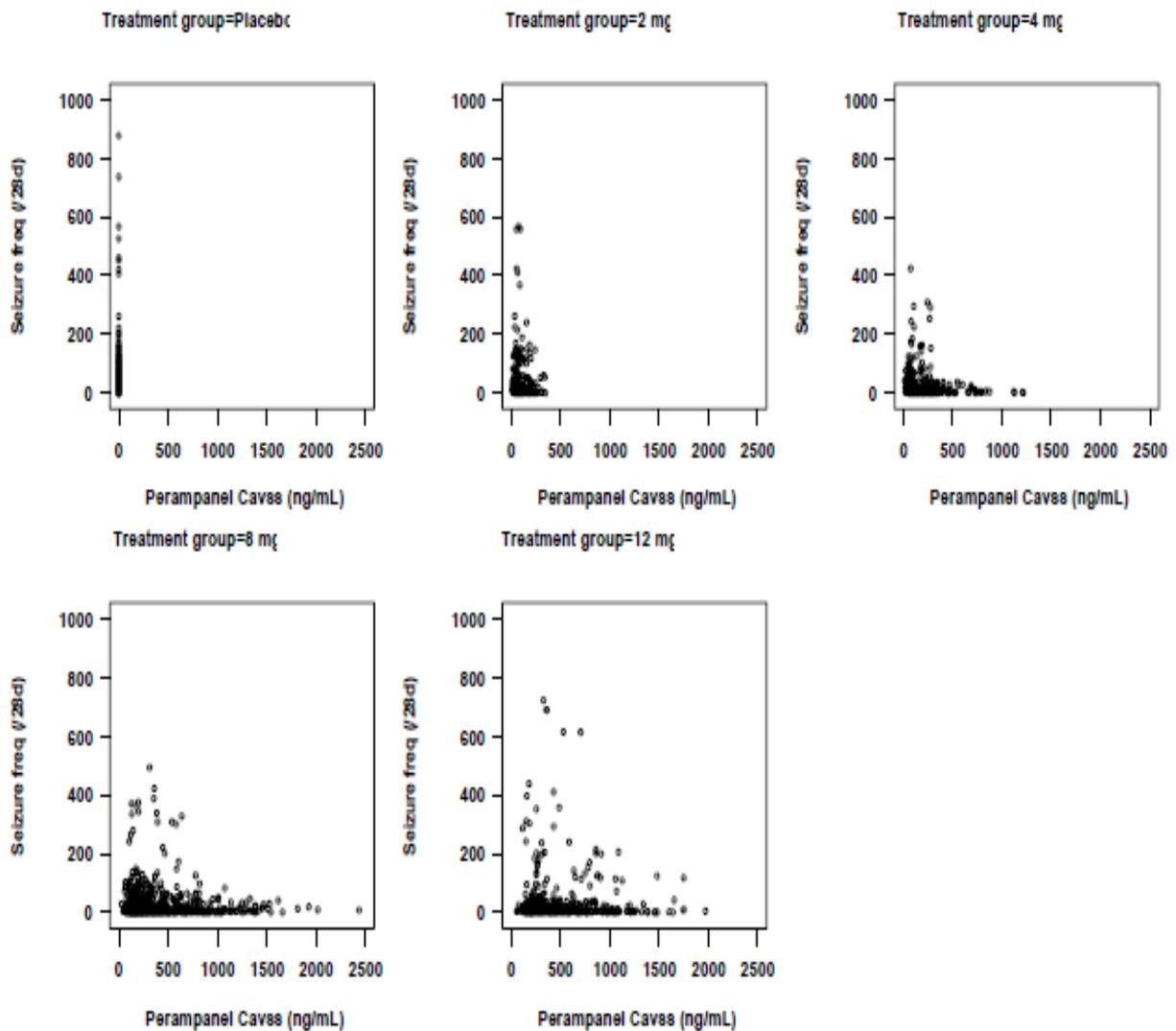
The selection of the dosage range evaluated in the Phase 3 studies was based on data gathered from Phase 2 studies. In Study 208, subjects randomly assigned to adjunctive perampanel treatment were titrated to their MTD over the dose range of 2 mg to 12 mg. Results from this study, together with those from Study 206, showed benefit and tolerability across the dose range tested. Results of the PK/PD analysis of these Phase 2 studies were used to select the doses to evaluate in the Phase 3 studies (no effect = 2 mg, minimum effective dose = 4 mg, mid-range effective dose = 8 mg, and high effective dose = 12 mg).

Results of the population PK analysis for the Phase 3 studies showed that exposure to perampanel increased approximately proportionally with doses between 2 and 12 mg. The geometric mean concentrations of perampanel were 71, 138, 272, and 349 ng/mL for the perampanel dose groups of 2 mg, 4 mg, 8 mg and 12 mg, respectively.

The relationship between plasma concentration of perampanel and anti-seizure effects was explored in the population PK/PD analysis using data from the Phase 3 studies. There was an inverse relationship between steady-state perampanel plasma concentration and seizure frequency. The slope for the relationship between seizure frequency and plasma concentrations associated with doses of 8 to 12 mg was not significantly different from the slope for the relationship

between seizure frequency and concentrations associated with doses of 4 to 8 mg. The sponsor's figure below shows the total seizure frequency as a function of perampanel concentration.

Figure 6 Total seizure frequency as a function of perampanel concentration



Analyses of the percent change in seizure frequency per 28 days relative to the Prerandomization Phase and responder rate using the integrated Full ITT Analysis Set for the Phase 3 studies were performed based on each randomized dose group. These analyses were limited to the Maintenance Period (with LOCF imputation) where doses of perampanel were more stable. The lowest perampanel dose of 2 mg did not provide any benefit in terms of improved seizure control compared with placebo. Once daily perampanel doses of 8 mg and 12 mg produced greater reductions in seizure frequency and improved responder rates compared with the once daily dose of 4 mg. However, in these analyses there was an apparent plateau at 8 mg, with no greater improvement in seizure control seen with the 12 mg dose. The median differences versus placebo in change in seizure frequency during the Maintenance Period for the 8 and 12 mg groups were -16.43% and -15.79%, respectively, while the responder rates were 35.3% and 35.0%, respectively. These results were consistent with results for Study 305 and to a lesser extent for Study 304, when analyzed individually.

Additional analyses were performed on the percent change in seizure frequency and responder rate during the Maintenance Period in each randomized dose group using the integrated Full ITT Analysis Set, but excluding subjects from sites in Central and South America where there was an unusual outcome, perhaps due to the high placebo response rate. Results of these analyses were consistent in showing better efficacy for the 8 and 12 mg dose groups than for the 4 mg dose group, but no clear separation between these two highest randomized perampanel dose groups.

In order to further compare the potential benefit of 12mg over 8mg of perampanel daily, the sponsor attempted to see if there was an incremental benefit associated with the 12-mg dose of perampanel relative to the 8-mg dose in individual patients. This was an attempt to examine efficacy responses in subjects who received treatment with both doses, rather than comparing separate groups of subjects. Subjects who completed a double-blind Phase 3 study were enrolled into the long-term OLE study (Study 307) and underwent blinded titration to a maximum dose of 12 mg/day. Thus, data from controlled Phase 3 studies, coupled with those from the blinded Conversion Period (16 weeks), permitted an investigation of effectiveness in the same subject in both doses of 8 and 12 mg.

The results were consistent in showing better efficacy in the same subjects when the dose of perampanel was increased from 8 mg to 12 mg. Of particular note, seizure frequency decreased further from -32.42% at the double-blind Maintenance Period to -43.27% at the blinded Conversion Period, and the 50% responder rate rose from 37.8% on a dose of 8 mg in the double-blind Maintenance Period to 43.5% in the same subjects on a dose of 12 mg in the

blinded Conversion Period. It therefore appears that some patients might benefit from perampanel 12 mg, if the associated adverse side-effects could be tolerated.

The change in seizure frequency per 28 days and responder rate for subjects who were randomized to and completed the double-blind Maintenance Period (Studies 304, 305, and 306) on 8 mg and received 12 mg as their last dose in the blinded conversion period (Study 307) (Full ITT Analysis Set) are shown in the sponsor's table below.

Table 31 Change in Seizure Frequency and Responder Rate in those on 8 mg Blindly Converted to 12 mg

Parameter	DB Actual Dose → Conversion Period Actual Dose
Statistic/ Timepoint	8 mg → 12 mg
Seizure frequency per 28 days	
N	209
Median Prerandomization	10.50
Median percent change from Prerandomization	
DB Maintenance Period	-32.42
Blinded Conversion Period (Study 307, Weeks 1-16)	-43.27
Responder rate	
Response, n (%)	
DB Maintenance Period	79 (37.8)
Blinded Conversion Period (Study 307, Weeks 1-16)	91 (43.5)

Source: [Table 14.2.7.4.1](#); [Table 14.2.7.5.1](#)

DB = double-blind; ITT = intent-to-treat; N = number of subjects; n = subset of N; OLE = open-label extension.

Note: Only subjects who had valid seizure data in the blinded Conversion Period in Study 307 are presented. Data exclude Central and South America sites.

The results were very similar in showing incremental benefit when the perampanel dose was increased from 8 mg in the double-blind Maintenance Period compared to 12 mg in Weeks 1-13 of the OLE Maintenance Period. The sponsor's table below shows the change in seizure frequency and responder rate for subjects who were randomized to and completed the double-blind maintenance period (Studies 304, 305 and 306) on 8 mg and received 12 mg as

their last dose in the open-label maintenance period Study 307 (Full ITT Analysis Set).

Table 32 Change in Seizure Frequency and Responder Rate from those on 8 mg in Maintenance Period to 12 mg in the OLE Maintenance Period

Parameter Statistic/ Timepoint	DB Actual Dose → OLE Actual Dose 8 mg → 12 mg
Seizure frequency per 28 days	
N	143
Median Prerandomization	9.77
Median percent change from Prerandomization	
DB Maintenance Period	-31.67
OLE Maintenance Week 1-13	-49.31
Responder rate, n (%)	
N	143
DB Maintenance Period	55 (38.5)
OLE Maintenance Week 1-13	69 (48.3)

Source: Table 14.2.7.1.1; Table 14.2.7.2.1.

DB = double-blind; ITT = intent-to-treat; N = number of subjects; n = subset of N; OLE = open-label extension study.

Note: Only subjects who had valid seizure data in OLE Maintenance Weeks 1-13 are presented.

Seizure-free status for subjects who were randomized to and completed the double-blind Maintenance Period at a dose of 8 mg perampanel and completed Weeks 1-13 of the open-label Maintenance Period (Study 307) on 12 mg were analyzed. Seizure-free status among subjects who completed both Maintenance Periods increased from 5.4% (during the double-blind Maintenance Period) to 15.5% (during the open-label Maintenance Period Weeks 1-13). Similarly, in subjects who completed both Maintenance Periods and who were titrated from 8 mg to 12 mg, there was an increase in the proportion that were seizure-free during the last 28 days from 13.2% (double-blind Maintenance Period) to 20.9% (open-label Maintenance Period Weeks 1-13). There was also an increase in the proportion of subjects who were seizure-free among subjects who had a last dose of 12 mg perampanel in both the double-blind and open-label Maintenance Periods.

The number of seizure free days for subjects who were randomized to and completed the double-blind maintenance period (Studies 304, 305, and 306) on 8

mg and completed week 1-13 of the open-label maintenance period (Study 307) on 12 mg (Full ITT analysis Set) are shown in the sponsor's table below.

Table 33 Seizure Free Days for those on 8 mg in Maintenance Period to 12 mg in the OLE Maintenance Period

Statistic/ Timepoint	DB Actual Dose → OLE Actual Dose 8 mg → 12 mg
Subjects who completed both Maintenance Periods	
N	129
Seizure-free, n (%)	
During the entire DB Maintenance Period	7 (5.4)
During the entire OLE Maintenance Weeks 1-13	20 (15.5)
During the last 28 Days of DB Maintenance Period	17 (13.2)
During the last 28 Days of OLE Maintenance Weeks 1-13	27 (20.9)

Source: [Table 14.2.7.3.1](#)

DB = double-blind; ITT = intent-to-treat; N = number of subjects; n = subset of N; OLE = open-label extension study.

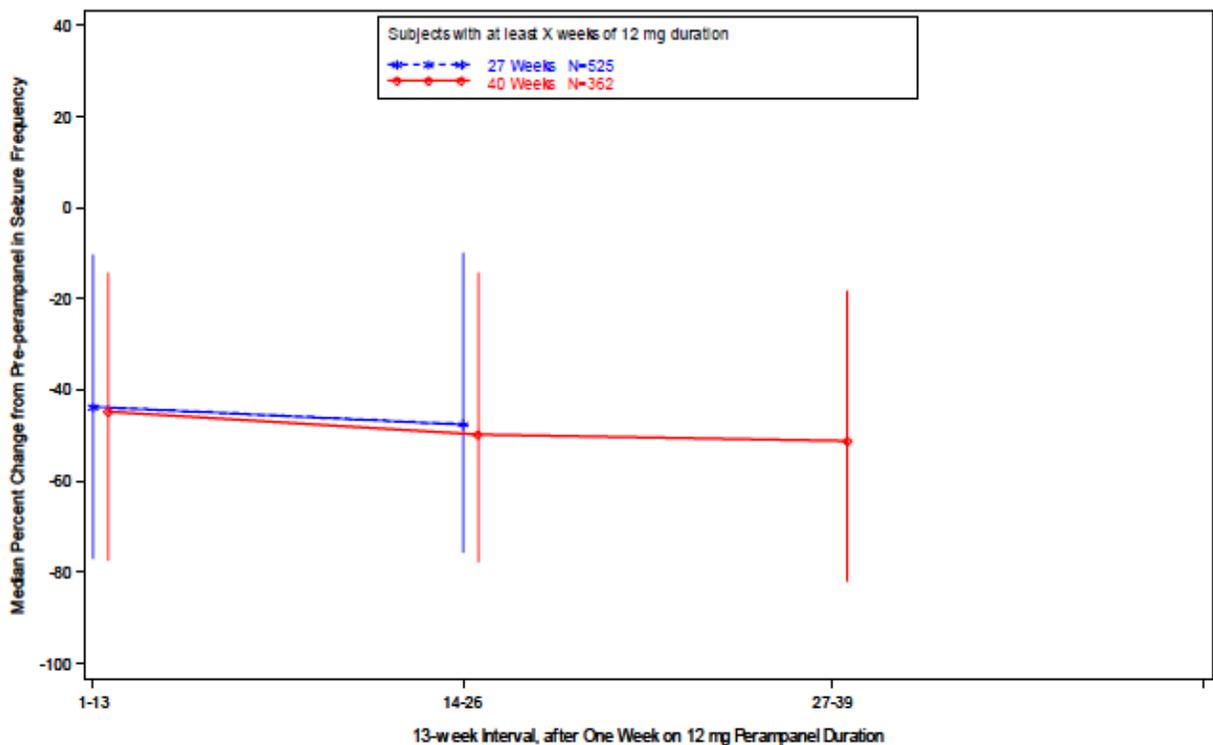
Therefore, even though there was an apparent plateau at 8 mg, with no greater improvement in seizure control seen with the 12 mg dose in the Phase 3 efficacy studies, there does appear to be an incremental benefit associated with the 12-mg dose of perampanel relative to the 8-mg dose in individual patients who received treatment with both doses. Once again, the 12 mg dose was associated with a greater number of AEs, many of which could not be tolerated.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Results relevant to the safety of long-term treatment with perampanel come from the three ongoing OLE studies (Studies 307, 207, and 233). A total of 703 subjects in those studies have received perampanel for at least 1 year and 95 have received perampanel for at least 2 years (combined exposure to double-blind and open-label perampanel). Some subjects have been treated for as long as 3 years (n=57) or 4 years (n=26). Among these subjects, no new safety signals were seen during long-term treatment with perampanel and, according to the sponsor, there was no clinically notable worsening in the frequencies of safety findings.

The data from the OLE studies show sustained improvement in seizure control for subjects who remained on the same efficacious dose of perampanel for up to approximately 9 months. There was no decrement in efficacy over this period. The sponsor's figure below shows the median percent change from pre-perampanel baseline in seizure frequency per 28 days, by 13-week intervals, after one week on 12 mg perampanel, full ITT Analysis Set for Study 307 with at least 27 or 40 weeks of 12-mg perampanel treatment duration.

Figure 7 Maintenance of Seizure Control with a Fixed Dose of Perampanel



A vertical line denotes the 3rd quartile to the 1st quartile, and a symbol in the vertical line stands for the median percent change. The X weeks of 12 mg perampanel duration starts on the first day of 12 mg and ends X weeks later on 12 mg. The 13-week intervals start one week after starting 12 mg. For example, Weeks 1-13 is the first 13-week interval, one week after starting 12 mg.

6.1.10 Summation of Efficacy Analyses of Primary and Secondary Endpoints

The following is a summary tabulation of the key efficacy results (primary and secondary) for each of the three adequate and well controlled Phase 3 clinical trials analyzed in order to render an opinion on the efficacy of perampanel as adjunctive treatment partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. Once-daily administration of perampanel doses of 4 mg, 8 mg, and 12 mg appears to have significantly improved seizure control in these subjects when compared to placebo, as shown by larger reductions in the frequency of partial-onset seizures and complex partial plus secondarily generalized seizures and greater responder rates.

Study 306

Results for the primary and secondary efficacy variables in Study 306 were examined for subgroups for different countries. Although the number of subjects was small for several countries, results were consistent across countries in showing greater improvements in seizure control for perampanel compared with placebo. No US sites were included in this study. The following sponsor's table shows an overview of key primary and secondary results for the full ITT analysis set for Study 306.

Table 34 An overview of key primary and secondary results for the full ITT analysis set for Study 306

Parameter Statistic	Placebo (N=184)	Perampanel 2 mg/d (N=180)	Perampanel 4 mg/d (N=172)	Perampanel 8 mg/d (N=169)
Percent change in partial seizure frequency per 28 days during Double-blind Phase from Prerandomization				
N		180	172	169
Median change	-10.69	-13.63	-23.33	-30.80
Median difference from placebo (95% CI) ^a		-4.36 (-14.091, 5.227)	-13.71 (-23.306, -4.500)	-20.13 (-29.656, -10.425)
P value (vs. placebo) ^b		0.4197	0.0026	<0.0001
Responder Rate during Maintenance-LOCF Period				
N		180	172	169
Number (%) responders ^c	33 (17.9)	37 (20.6)	49 (28.5)	59 (34.9)
P value (vs. placebo) ^d		0.4863	0.0132	0.0003
Percent change in complex partial plus secondarily generalized seizures per 28 days during Double-blind Phase from Prerandomization				
N		167	157	154
Median change	-17.63	-20.50	-31.18	-38.69
Median difference from placebo (95% CI) ^a		-3.26 (-13.685, 7.395)	-14.40 (-25.082, -3.496)	-19.32 (-29.788, -8.625)
P value (vs placebo) ^b		0.6506	0.0070	0.0005

Source: 306, Table 14.2.1.1.6.1; 306, Table 14.2.2.3.5; 306, Table 14.2.10.1.

ANCOVA = analysis of covariance; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; d = day; ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects; vs = versus.

a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

b: For analysis windows, the value is based on rank ANCOVA for percent change from Prerandomization of seizure frequency per 28 days with treatment and pooled country as factors, and Prerandomization seizure frequency per 28 days as a covariate. The Prerandomization and post-randomization efficacy measurements are rank transformed separately.

c: A responder is a subject who experienced a 50% or greater reduction in seizure frequency per 28 days from the Prerandomization Phase.

d: The P value is based on non-missing values and is from the CMH test adjusted for pooled country.

Study 305

Results for the primary and secondary efficacy variables in Study 305 were examined, and are shown for the Full ITT Analysis Set in the sponsor's table below. Although the number of subjects was small for several countries, the results were consistent across countries in showing greater improvements in seizure control for perampanel compared with placebo. Approximately 25% of subjects in this study were enrolled at sites in the US. In the pooled US subgroup, the median percent change in seizure frequency per 28 days during the Double-blind Phase was -23.31%, -41.64%, and -21.64% for the placebo, perampanel 8 mg, and perampanel 12 mg groups, respectively. The responder rates (Maintenance Period) for each treatment group were 16.1%, 45.2%, and 44.0%, respectively.

The dose-response analysis was based on the Maintenance Period (Full ITT Analysis Set) when the doses of perampanel became stable. The median percent change in the frequency of all partial seizures was greater in the 8 mg group (-32.37%) than in the 12 mg group (-24.91%).

The following sponsor's table is an overview of the key efficacy results for the full ITT analysis set in study 305.

Table 35 An overview of key primary and secondary results for the full ITT analysis set for Study 305.

Parameter Statistic	Placebo (N=136)	Perampanel 8 mg/d (N=129)	Perampanel 12 mg/d (N=121)
Percent change in partial seizure frequency per 28 days during Double-blind Phase from Prerandomization			
N		129	121
Median change	-9.72	-30.52	-17.57
Median difference from placebo (95% CI) ^a		-19.10 (-29.169, -8.447)	-13.69 (-25.198, -2.257)
P value (vs placebo) ^b		0.0008	0.0105
Responder rate during Maintenance			
N		129	121
Number (%) responders ^c	20 (14.7)	43 (33.3)	41 (33.9)
P value (vs. placebo) ^d		0.0018	0.0006
Percent change in complex partial plus secondarily generalized seizures per 28 days during Double-blind Phase from Prerandomization			
N		119	113
Median change	-8.05	-32.72	-21.89
Median difference from placebo (95% CI) ^a		-23.07 (-34.798, -10.549)	-17.45 (-29.269, -5.703)
P value (vs placebo) ^b		0.0007	0.0045

Source: 305, Table 14.2.1.1.1.1; 305, Table 14.2.2.3.5.1; 305, Table 14.2.2.1.1.

ANCOVA = analysis of covariance; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; d = day; ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects; vs = versus.

a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

b: For analysis windows, the value is based on rank ANCOVA for percent change from Prerandomization of seizure frequency per 28 days with treatment and pooled country as factors, and Prerandomization seizure frequency per 28 days as a covariate. The Prerandomization and post-randomization efficacy measurements are rank transformed separately.

c: A responder is a subject who experienced a 50% or greater reduction in seizure frequency per 28 days from the Prerandomization Phase.

d: The P value is based on non-missing values and is from the CMH test adjusted for pooled country.

Study 304

Results for the primary and secondary efficacy variables are detailed in the sponsor's table below. In the ITT Analysis Set, the treatment differences relative to placebo in the median percent change in seizure frequency per 28 days during the Double-blind Phase for the 8 mg (-13.17) and 12 mg (-14.47) groups were statistically significant (P = 0.0290 and P = 0.0120, respectively; rank ANCOVA). The treatment comparisons to placebo for the median percent change in seizure frequency per 28 days during the Maintenance Period (using LOCF imputation) were -11.67 for the 8 mg group (P = 0.0812) and -12.64 for the 12 mg group (P = 0.0304) (rank ANCOVA). In the ITT Analysis Set, the responder rate during the Maintenance Period (using LOCF imputation) was 26.1% in the placebo group, 37.1% in the 8 mg group (P value vs. placebo of 0.0871), and 36.2% in the 12 mg group (P value vs. placebo of 0.0776).

In Study 304, approximately half (52%) of the subjects were from sites in the US, with the remaining subjects from sites in Canada (6%) or Central and South America (42% [Chile, Argentina, Mexico]). A significant treatment-by-region difference was detected (P = 0.0035) from the analysis of the median percent change in seizure frequency per 28 days during the Maintenance Period (with LOCF imputation) using the rank ANCOVA for the ITT Analysis Set. This regional difference reflected a strong treatment effect in the North America region (mainly US), in contrast to a high placebo response and no treatment difference in the Central and South America region. Results of the primary and secondary efficacy, using the Full ITT Analysis Set for Study 304, are detailed in the sponsor's table below.

See section 6.1.7 for details.

Table 36 An overview of key primary and secondary results for the full ITT analysis set for Study 304

Parameter Statistic	Placebo (N=121)	Perampanel 8 mg/d (N=133)	Perampanel 12 mg/d (N=133)
Percent change in partial seizure frequency per 28 days during Double-blind Phase from Prerandomization			
N		133	133
Median change	-20.95	-26.34	-34.49
Median difference from placebo (95% CI) ^a		-13.53 (-26.172, -1.944)	-14.20 (-25.030, -2.729)
P value (vs placebo) ^b		0.0261	0.0158
Responder Rate during Maintenance-LOCF Period			
N		133	133
Number (%) responders ^c	32 (26.4)	50 (37.6)	48 (36.1)
P value (vs placebo) ^d		0.0760	0.0914
Percent change in complex partial plus secondarily generalized seizures per 28 days during Double-blind Phase from Prerandomization			
N		120	120
Median change	-17.88	-33.03	-33.06
Median difference from placebo (95% CI) ^a		-20.37 (-33.164, -7.741)	-17.90 (-30.313, -4.665)
P value (vs placebo) ^b		0.0020	0.0081

Source: 304, Table 14.2.1.1.6.1; 304, Table 14.2.2.3.5.1; 304, Table 14.2.14.1.1

ANCOVA = analysis of covariance; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; d = day; ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects; vs = versus.

a: The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

b: For analysis windows, the value is based on rank ANCOVA for percent change from Prerandomization of seizure frequency per 28 days with treatment and pooled country as factors, and Prerandomization seizure frequency per 28 days as a covariate. The Prerandomization and post-randomization efficacy measurements are rank transformed separately.

c: A responder is a subject who experienced a 50% or greater reduction in seizure frequency per 28 days from the Prerandomization Phase.

d: The P value is based on non-missing values and is from the CMH test adjusted for pooled country.

7 Review of Safety

The review of safety will be completed by Dr. Mary Doi. The only safety issue to be addressed in this review will be treatment emergent adverse events (TEAEs) related to seizures and status epilepticus.

Phase 3 Studies

In the phase 3 double-blind pool of patients, the most common event, in all treatment groups, was convulsions. This had a pattern of occurrence similar to

that of all TEAEs related to status epilepticus (preferred term) and convulsions (preferred term). There were no apparent dose-related trends for any of these, while status epilepticus occurred in one subject in the placebo group and two in the total perampanel group. There were no deaths due to status epilepticus.

Convulsion was an SAE in three (0.7%) subjects in the placebo group and six (0.6%) subjects in the total perampanel group (one, three, and two subjects in the 4, 8, and 12 mg/d groups, respectively). This resulted in discontinuation in five (1.1%) placebo treated subjects and 10 (1.0%) perampanel-treated subjects (two, one, four, and three subjects in the 2, 4, 8, and 12 mg/d groups, respectively), and led to dose interruption or reduction in two placebo-treated subjects (0.5%) and two (0.2%) perampanel treated subjects (one each in the 2 and 12 mg/d groups). There were no deaths due to convulsions.

The sponsors table shows the treatment-emergent adverse events (selected preferred terms for status epilepticus/convulsions) by decreasing frequency and randomized treatment in the phase 3 double blind pool (Safety Analysis set).

Table 37 Convulsions/Status Epilepticus in Phase 3 Studies

MedDRA Preferred Term ^b	Placebo ^a (N=442) n (%)	Perampanel ^a				
		2 mg/day (N=180) n (%)	4 mg/day (N=172) n (%)	8 mg/day (N=431) n (%)	12 mg/day (N=255) n (%)	Total (N=1038) n (%)
Subjects with any TEAE	25 (5.7)	4 (2.2)	5 (2.9)	22 (5.1)	13 (5.1)	44 (4.2)
Convulsion	16 (3.6)	3 (1.7)	3 (1.7)	15 (3.5)	9 (3.5)	30 (2.9)
Simple Partial Seizures	0	0	1 (0.6)	3 (0.7)	0	4 (0.4)
Grand Mal Convulsion	2 (0.5)	0	0	1 (0.2)	1 (0.4)	2 (0.2)
Status Epilepticus	1 (0.2)	0	0	0	2 (0.8)	2 (0.2)
Postictal Headache	0	0	0	1 (0.2)	1 (0.4)	2 (0.2)
Epilepsy	2 (0.5)	0	1 (0.6)	0	0	1 (0.1)
Aura	0	0	0	1 (0.2)	0	1 (0.1)
Febrile Convulsion	0	1 (0.6)	0	0	0	1 (0.1)
Partial Seizures With Secondary Generalization	0	0	0	1 (0.2)	0	1 (0.1)
Complex Partial Seizures	2 (0.5)	0	0	0	0	0
Postictal Psychosis	1 (0.2)	0	0	0	0	0
Tongue Biting	1 (0.2)	0	0	0	0	0

A TEAE is defined as an adverse event that either begins on or after the first dose date and up to 30 days after the last dose date of study drug; or begins before the first dose date and increases in severity during the treatment period.

Subject with two or more adverse events with the same preferred term is counted only once for that preferred term.

MedDRA = Medical Dictionary for Regulatory Activities, TEAE = treatment-emergent adverse event

a: Subjects treated during the double-blind study.

b: MedDRA preferred terms are sorted in descending order of frequency in the total perampanel column.

Phase 2 Studies

The incidence of the most common event, convulsions, was slightly higher in the placebo group than in the total perampanel group, while status epilepticus occurred in only one (1.5%) subject in the placebo group and one (0.7%) subject in the total perampanel group. There were no deaths and these TEAEs were SAEs in three (4.4%) subjects in the placebo group (one with status epilepticus and two with convulsion) and two (1.3%) subjects in the total perampanel group (one each with status epilepticus and post ictal state). These TEAEs led to discontinuation in two (2.9%) placebo-treated subjects (one each with status epilepticus and convulsion) and one (0.7%) perampanel-treated subject (with status epilepticus). No subject in any treatment group had dose interruption or reduction due to these TEAEs. There were no deaths due to convulsions.

The sponsors table shows the treatment-emergent adverse events (selected preferred terms for status epilepticus/convulsions) by decreasing frequency and randomized treatment in the phase 2 double blind pool (Safety Analysis set).

Table 38 Convulsions/Status Epilepticus in Phase 2 Studies

MedDRA Preferred Term ^b	Placebo ^a (N=68) n (%)	Perampanel ^a				Total (N=151) n (%)
		<4 mg/day (N=12) n (%)	4 mg/day (N=101) n (%)	>4-8 mg/day (N=0) n (%)	>8-12 mg/day (N=38) n (%)	
Subjects with any TEAE	6 (8.8)	2 (16.7)	5 (5.0)	NA	2 (5.3)	9 (6.0)
Convulsion	3 (4.4)	0	1 (1.0)	NA	2 (5.3)	3 (2.0)
Complex Partial Seizures	0	1 (8.3)	1 (1.0)	NA	0	2 (1.3)
Grand Mal Convulsion	1 (1.5)	1 (8.3)	0	NA	0	1 (0.7)
Partial Seizures	1 (1.5)	1 (8.3)	0	NA	0	1 (0.7)
Status Epilepticus	1 (1.5)	0	1 (1.0)	NA	0	1 (0.7)
Postictal State	0	0	1 (1.0)	NA	0	1 (0.7)
Simple Partial Seizures	0	0	1 (1.0)	NA	0	1 (0.7)

A TEAE is defined as an adverse event that either begins on or after the first dose date and up to 30 days after the last dose date of study drug; or begins before the first dose date and increases in severity during the treatment period.

Subject with two or more adverse events with the same preferred term is counted only once for that preferred term.

MedDRA = Medical Dictionary for Regulatory Activities, NA = not applicable, TEAE = treatment-emergent adverse event

a: Subjects treated during the double-blind study.

b: MedDRA preferred terms are sorted in descending order of frequency in the total perampanel column.

Convulsions/Status Epilepticus in All Treated Pool

In this group, status epilepticus occurred in 15 (0.9%) subjects in the total perampanel group, compared with two (0.4%) subjects who received placebo in the pooled double-blind studies. The exposure-adjusted rates were 0.0008 and 0.001 subjects per subject-month, respectively. In the analysis by actual dose at onset, this event occurred in three (0.2%) subjects at doses of < 4 mg/d, two (0.1%) subjects at doses of > 4-8 mg/d, and 10 (0.8%) subjects at doses of > 8-12 mg/d. The most common event was convulsion (5.7% of all perampanel-treated subjects), compared with 3.9% in the placebo group from the pooled double-blind studies. The exposure-adjusted rate for this event was 0.01 subjects per subject-month in the placebo group and 0.005 subjects per subject-month in the total perampanel group.

Convulsion was an SAE in five (1.0%) subjects in the placebo group and 31 (1.9%) subjects in the total perampanel group and led to treatment discontinuation in

six (1.2%) and 16 (1.0%) subjects, respectively. There were no deaths due to any TEAEs related to status epilepticus or convulsion.

Although the incidence of status epilepticus in the 12 mg group was higher than that seen in the other dosages, the actual number (2 compared to 0) is too low to draw any meaningful conclusions regarding the possibility of increased seizure activity associated with higher dosages of perampanel. The exposure-adjusted rates suggest that the risk of seizure-related TEAEs, including status epilepticus, was lower with perampanel than with placebo.

The sponsor's table shows the treatment-emergent adverse events (selected preferred terms for status epilepticus/convulsions) by decreasing frequency and randomized treatment in the all treated pool (safety analysis set).

Table 39 Convulsions/Status Epilepticus in the All Treated Pool

MedDRA Preferred Term^b	Total Perampanel^a (N=1639) n (%)
Subjects with any TEAE	147 (9.0)
Convulsion	93 (5.7)
Status Epilepticus	15 (0.9)
Simple Partial Seizures	10 (0.6)
Grand Mal Convulsion	9 (0.5)
Epilepsy	8 (0.5)
Complex Partial Seizures	5 (0.3)
Partial Seizures	4 (0.2)
Postictal Headache	4 (0.2)
Partial Seizures With Secondary Generalization	2 (0.1)
Postictal State	2 (0.1)
Aura	1 (0.1)
Drug Withdrawal Convulsions	1 (0.1)
Epileptic Aura	1 (0.1)
Febrile Convulsion	1 (0.1)
Postictal Psychosis	0
Tongue Biting	0

A TEAE is defined as an adverse event that either begins on or after the first dose date and up to 30 days after the last dose date of study drug; or begins before the first dose date and increases in severity during the treatment period.

Subject with two or more adverse events with the same preferred term is counted only once for that preferred term.

MedDRA = Medical Dictionary for Regulatory Activities, TEAE = treatment-emergent adverse event

a: Subjects treated with perampanel in any study.

b: MedDRA preferred terms are sorted in descending order of frequency in the total column.

8 Postmarket Experience

None

9 Appendices

9.1 Literature Review/Reference

None

9.2 Labeling Recommendations

Once daily perampanel doses of 8 mg and 12 mg produced greater reductions in seizure frequency and improved responder rates compared with the once daily dose of 4 mg. However, there was an apparent plateau at 8 mg, with no greater improvement in seizure control seen with the 12 mg dose. The median differences versus placebo in change in seizure frequency during the Maintenance Period for the 8 and 12 mg groups were -16.43% and -15.79%, respectively, while the responder rates were 35.3% and 35.0%, respectively in Study 306. These results were consistent with results for Study 305 and to a lesser extent for Study 304, when analyzed individually.

Additional analyses were performed on the percent change in seizure frequency and responder rate during the Maintenance Period in each randomized dose group using the integrated Full ITT Analysis Set, but excluding subjects from sites in Central and South America (where there was a treatment-by-region interaction of outcome largely due to high placebo response rate). Results of these analyses were consistent in showing better efficacy for the 8 and 12 mg dose groups than for the 4 mg dose group, but no clear separation between these two highest randomized perampanel dose groups.

In contrast to these findings, an analysis of the difference between two doses of perampanel was compared in the same patient who actually received each dose. This approach did show an incremental benefit associated with the 12 mg dose of perampanel over the 8 mg dose. Studies of this design appeared to show benefit from 12 mg over 8 mg. These were derived from examining efficacy responses in subjects who received treatment with both doses, rather than separate groups of subjects.

This reviewer feels that perampanel is safe and effective at doses of 4 mg to 8 mg daily. Some patients might benefit from dosages as high as 12 mg daily, although this could not be clearly demonstrated in the three Phase 3 clinical trials. Additionally, daily dosages of 12 mg are associated with an increased number of adverse side effects, many of which may be unacceptable to patients.

9.3 Advisory Committee Meeting

None

**Martin S. Rusinowitz, MD
Medical Review Officer
Division of Neurology Products**

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

/s/

MARTIN S RUSINOWITZ
10/19/2012

NORMAN HERSHKOWITZ
10/19/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2				
	Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	please see CLINICAL EFFICACY checklist for efficacy issues
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	please see CLINICAL EFFICACY checklist for efficacy issues
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	please see CLINICAL EFFICACY checklist for efficacy issues
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			However, doses higher than 12 mg were not studied (requested during EOP2 meeting with the Sponsor)
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	Perampanel is first in class
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission	X			See #19 comment

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	discussions?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	please see pediatric checklist
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	please see controlled substance checklist
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	please see CLINICAL EFFICACY checklist
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	please see CLINICAL EFFICACY checklist for efficacy issues
34.	Are all datasets to support the critical safety analyses available and complete?	X			discrepancies in #TEAEs and subjects between the ISS and the individual studies
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	please see CLINICAL EFFICACY checklist for efficacy issues
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	please see CLINICAL EFFICACY checklist
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	please see CLINICAL EFFICACY checklist

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

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

Please provide the following as previously requested on pages 5-6 of the Refuse to File letter dated July 21, 2011:

1. A summary table of the original AE coding dictionaries for ALL studies (epilepsy, nonepilepsy, and Phase 1).
2. Narratives for discontinuations due to subject choice and “other” reasons for subjects in the Sponsor’s “second category” (subjects with no safety-related comments on the disposition page of the CRF, with AEs or markedly abnormal laboratory values, but no ongoing severe AEs or markedly abnormal laboratory values within 2 weeks of discontinuation/last visit) listed on pages 56 and 64 of the ISS.
3. The subjects’/investigators’ verbatim terms described in the CRFs for every AE (in addition to the preferred terms). Please include these verbatim terms as a column in the line listing of serious adverse events for ALL studies (epilepsy and non-epilepsy studies). For example, in Table 20.7-5, the verbatim terms were not provided.
4. Tables of Common TEAEs by preferred term for TEAEs in $\geq 2\%$ of the Subjects by dose group for every pooled safety analysis group (formatted tables that fit on 1-2 pages instead of the SAS output tables in the ISS appendix) with the TEAE sorted by MedDRA SOC and then MedDRA Preferred Term (instead of descending order of preferred terms). Please also include a summary table for TEAEs reported by $\geq 2\%$ of perampanel-treated subjects by study pool (specifically with two columns representing the Epilepsy Study Pool and Other Indications Study Pool).
5. A table of all “normal” reference values (in addition to Table 20.15, Modified NCI-CTC Criteria).
6. Summary tables of laboratory and vital sign analyses using Tables 1, 2, and 3 in the Appendix of this document. Please provide these summary tables in addition to the tables provided in the ISS Appendix with one laboratory value listed for every page (e.g., Table 20.11-1.4).
7. A line listing, narrative, and case report form of all subjects who fit the criteria of Hy’s Law case definition. In the ISS, it is stated that “Hy’s Law is satisfied when AST or ALT $> 3xULN$, Total Bilirubin $> 2xULN$, and ALP $< 2xULN$ at the same visit.” However, please include subjects who had laboratory values of AST or ALT $> 3xULN$, total Bilirubin $> 2xULN$, and ALP $< 2xULN$ during the study (not necessarily at the same visit).

Please also provide the following items:

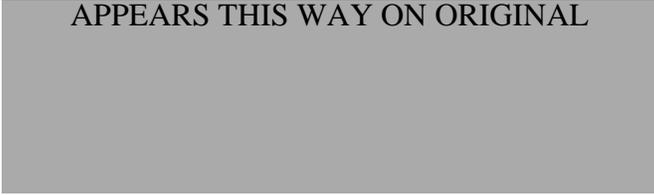
8. Please provide a listing of the unique subject ID for all of the 12 pregnancies and 17 subjects with a TEAE related to suicidality (in the epilepsy all treated pool) with hyperlinks to narratives and case report forms.
9. Please perform additional searches for AEs of particular interest to identify subjects with AEs coded to the MedDRA SMQs listed in Table 7 (in the Appendix).
10. There were discrepancies (in the number of subjects and adverse events) between the ISS and the individual clinical study reports identified for both the Parkinson’s Disease Double-blind Pool and the Neuropathic Pain Double-blind Pool. For example, for the Neuropathic Pain Double-blind Pool, it is unclear why in the ISS (which includes 7 additional subjects than the individual study reports) the number of subjects with TEAEs is less than the number in the clinical study reports for Studies 218 and 227. There were no discrepancies identified for the Epilepsy Phase 3 Double-blind Pool.
Please provide tables similar to Tables 4, 5, and 6 in the Appendix of this document for every pooled group. And please explain the discrepancies between the numbers (of subjects and adverse events) in the ISS and the individual clinical study reports.
11. In the individual study AE datasets, please provide an “emergent flag” similar to AEEMFL in the integrated datasets and a “safety flag” similar to SAFFL in the integrated datasets.
12. Please provide the step-by-step algorithms that were used for the ISS ADaM datasets (to use with the JMP software) to populate all of the tables in the ISS.

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Mary Doi, M.D., M.S. <i>{See appended electronic signature page}</i>	02/06/2012
_____ Reviewing Medical Officer	_____ Date
Sally Yasuda, Pharm D., M.S. <i>{See appended electronic signature page}</i>	
_____ Clinical Team Leader	_____ Date

APPEARS THIS WAY ON ORIGINAL



CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

APPENDIX

Table 1 – Mean Change from Baseline for Laboratory Parameters

Parameter	Placebo			Dose 1			(Similar columns for other doses)
	n	mean	SD	n	mean	SD	
Albumin (<i>units</i>)							
Alkaline Phosphatase							
Bilirubin, total							
(etc. - list all laboratory parameters making separate tables for hepatobiliary, renal, hematologic, electrolytes, and other chemistry parameters)							

Table 2 – Incidence of Potentially Clinically Significant Changes in Laboratory Parameters (for subjects who were normal at baseline)

Parameter	Placebo			Dose 1			(Similar columns for other doses)
	n	# abnormal	%	n	# abnormal	%	
Albumin < 2.5 g/dl							
Alkaline Phosphatase > 400 U/L							
Bilirubin, total > 2 mg/dl							
(etc - list all laboratory parameters making separate tables for hepatobiliary, renal, hematologic, electrolytes, and other chemistry parameters)							

Table 3 – Summary of changes from baseline in supine vital sign measurements and body weight

Parameter	Placebo			Dose 1			(Similar columns for other doses)
	n	mean	SD	n	mean	SD	
SBP (mmHg)							
baseline							
change end of treatment							
DBP (mmHg)							
baseline							
Δ end of treatment							
Pulse rate (bpm)							
baseline							
Δ end of treatment							
Weight (kg)							
baseline							
Δ end of treatment							
Δ end of 6 months							
Δ end of 12 mos							
Δ end of 24 mos							
Δ end of 36 mos							
Δ end of 48 mos							
Δ end of 60 mos							

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Table 4 - **Epilepsy Phase 3 Double-blind Pool** - TEAEs by Randomized Treatment Groups (Safety Analysis Set)

	ISS Table 46, p 145		Study Reports (304, 305, 306)		Using the Epilepsy ADAE Dataset, ISS	
	Placebo	Perampanel	Placebo	Perampanel	Placebo	Perampanel
Total # of subjects	442	1038	442	1038		
Subjects with TEAEs	294	799	294	799	294	799
Treatment-related	182	630	182	630	182	630
Severe	24	92	24	92	24	92
SAEs	22	57	22	57	22	57

Table 5 - **Parkinson's Disease Double-blind Pool** - TEAEs by Randomized Treatment Groups (Safety Analysis Set)

	ISS Table 49, p 148		Study Reports (202, 204, 214, 301, 302, 309)		Using the Non- epilepsy ADAE Dataset, ISS	
	Placebo	Perampanel	Placebo	Perampanel	Placebo	Perampanel
Total # of subjects	845	1517	843	1517		
Subjects with TEAEs	543	1058	540	1059	543	1058
Treatment-related	328	691	331	700	328	691
Severe	80	164			80	164
SAEs	60	108	60	110	60	108

Table 6 - **Neuropathic Pain Double-blind Pool** - TEAEs by Randomized Treatment Groups (Safety Analysis Set)

	ISS Table 50, p 149		Study Reports (218 and 227)		ADAE Dataset - ISS	
	Placebo	Perampanel	Placebo	Perampanel	Placebo	Perampanel
Total # of subjects	121	377	119	372		
Subjects with TEAEs	79	282	82	283	79	282
Treatment-related	40	178	42	179	40	178
Severe	9	39			9	39
SAEs	4	29	5	29	4	29

*In the ISS, it is noted that seven subjects were included in the ISS who were not in the clinical study reports for Studies 218 and 227.

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Table 7 – List of Relevant MedDRA SMQ

Adverse Events of Particular Interest	MedDRA 13.0 SMQ
Events related to Alertness or Cognition	Dementia
Psychiatric Disorders	Hostility/aggression
	Psychosis and psychotic disorders
Suicidality	Depression and suicide/self-injury
Status Epilepticus/Convulsions	Convulsions
TEAEs Suggestive of Abuse Potential	Drug abuse, dependence and withdrawal
Cardiac and ECG Adverse Events	Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias)
	Arrhythmia related investigations, signs and symptoms
	Cardiac failure
	Cardiomyopathy
	Ischaemic heart disease
	Torsade de pointes/QT prolongation
Adverse Events, Related to Laboratory Abnls	Drug-related hepatic disorders – comprehensive search

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

/s/

MARY DOI
02/07/2012

SALLY U YASUDA
02/07/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2				
	Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	please see CLINICAL EFFICACY checklist for efficacy issues
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	please see CLINICAL EFFICACY checklist for efficacy issues
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	please see CLINICAL EFFICACY checklist for efficacy issues
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?		X		Lack of analysis of studies performed for non-epilepsy indications and Phase I studies in ISS (TEAEs of special interest, subgroups, vital signs, laboratory tests, ECG)
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?		X		Doses higher than 12 mg were not studied
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?		X		Lack of analysis of studies performed for non-epilepsy indications
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			Coding for non-epilepsy studies were done using different coding dictionaries/versions
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	Perampanel is first in class
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?		X		Some narrative summaries for adverse dropouts and SAEs are missing

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?		X		See #19
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	please see pediatric checklist
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	please see controlled substance checklist
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	please see CLINICAL EFFICACY checklist
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?		X		Non-epilepsy study datasets not all in SDTM format
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?		X		Non-epilepsy study datasets not all in SDTM format
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	please see CLINICAL EFFICACY checklist for efficacy issues
34.	Are all datasets to support the critical safety analyses available and complete?		X		Non-epilepsy study datasets were not provided in the initial application on 5/25/11
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	please see CLINICAL EFFICACY checklist for efficacy issues
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	no additional CRFs previously requested
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	please see CLINICAL EFFICACY checklist
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	please see CLINICAL EFFICACY checklist

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___No___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Datasets:

- a. Datasets for the studies performed for the non-epilepsy indications were not submitted in the initial NDA application package. For the non-epilepsy studies, fifteen datasets were submitted after May 25, 2011, many of which were submitted after June 17, 2011. Twelve of these datasets are raw datasets and are not in SDTM format conforming to CDISC standards that would allow reasonable review of the data.
- b. Please provide an integrated dataset for these non-epilepsy studies in SDTM format conforming to CDISC standards (similar to the integrated dataset provided for the epilepsy studies in eCTD section 5.3.5.3).
- c. Please also provide datasets for all 27 Phase 1 studies (although this is not a filing issue).

Format/Organization:

- a. Please be comprehensive in providing hyperlinks in documents; some hyperlinks are missing. For example:
- b. Hyperlinks from ISS to individual CRFs and narratives are missing for deaths (page 148).
- c. Hyperlinks in other Clinical Study Reports were not provided (e.g. Clinical Study Report E2007-E044-301 page 104, hyperlinks to various Sections are missing).
- d. Please correct this throughout the ISS and pertinent study reports.

Safety:

- a. Narratives for some Serious Adverse Events and Dropouts due to AEs are missing (e.g., in study E2007-G000-304, the narratives are missing for subjects 17014011, 51164007, 51284011). Please make sure that narrative summaries from all studies for all deaths, serious adverse events, and dropouts due to adverse events are included.
- b. Analysis and presentation of the integrated safety data in the ISS for the studies performed for the non-epilepsy indications (and Phase 1 studies) are inadequate. The ISS should not merely summarize findings in the 15 non-epilepsy and 27 Phase 1 studies. The ISS should comprehensively integrate safety findings and provide an analysis for all TEAEs, deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups analyses, vital sign analyses, laboratory analyses, ECG analyses. For these studies, the ISS lacked analyses for TEAEs of special interest, subgroups, vital signs, laboratory tests, ECGs, and a pooled analysis for all TEAEs.
- c. Please conduct and present ALL safety data analyses (for all treatment-emergent adverse events including deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups analyses, vital sign analyses, laboratory analyses, ECG analyses) for the 15 studies for the non-epilepsy indications and the 27 Phase 1 studies pooled according to Table 1 (in the Appendix).
- d. Please conduct and present all analyses of demographic characteristics (including baseline disease characteristics, concomitant diseases, and concomitant medications [both AEDs and non-AEDs]), disposition, and extent of exposure for the 15 studies for the non-epilepsy indications pooled according to Table 1 (in the Appendix). Please also conduct and present all analyses of demographic characteristics, disposition, and extent of exposure for the 27 Phase 1 studies pooled together. Please provide summaries of these analyses at the end of each section (e.g. Summary of subject disposition).
- e. Please include the information from the non-epilepsy studies and the Phase 1 studies in the ISS Section 1.2.3 Analysis Populations. Please provide a table similar to Table 4 of the ISS (Number of Subjects From Each Study Included in the Pool of...) for these other studies.

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

Please provide the following:

1. The reasoning for not performing the QT interval studies at doses higher than 12 mg/day to cover the anticipated increases in perampanel plasma concentrations in the patient population due to CYP3A4 inhibition and hepatic impairment (please refer to the End of Phase 2 meeting minutes, QT-IRT Comments for Question 11 on page 6).
2. A summary table of the original AE coding dictionaries for ALL studies (epilepsy, nonepilepsy, and Phase 1). Please recode all investigator terms to MedDRA, Version 13.1 to standardize the terminology for the summary of the 15 studies non-epilepsy studies.
3. The subjects'/investigators' verbatim terms described in the CRFs for every AE (in addition to the preferred terms). Please include these verbatim terms as a column in the line listing of treatment emergent adverse events, adverse events identified as leading to discontinuation, and serious adverse events for ALL studies (epilepsy and non-epilepsy studies).
4. A Case Report Form summary page (with hyperlinks to CRFs) for every study.
5. A summary page of all of the narratives (with hyperlinks to individual narratives) for every study.
6. Narratives and CRFs for discontinuations due to subject choice and "other" reasons.
7. A table of all "normal" reference values and your proposed thresholds for each potentially clinically significant/markedly abnormal high and low values.
8. Change the age categories for the subgroup analysis to <17 years, ≥17 to <65 years, and ≥65 years to reflect the definition of pediatric population in 21 CFR 201.57 (c)(9)(iv).
9. Results of orthostatic changes for vital signs for every study that included these measurements in the study protocol. Please make this a TEAE of special interest. Please include the criteria for clinically significant orthostatic values that were used (if any).
10. Tables using modal dose (or daily dose of maximum duration) for analyses presented in the body of the ISS for the following pools: Epilepsy study pool and Other Indications pool (see Table 1 for list of analysis pools). Please use randomized treatment dose group for analyses presented in the body of the ISS for all other study pools. Other tables using mean daily dose, last daily dose, and maximum daily dose should be included in the Appendix.
11. Tables of Common TEAEs by preferred term for TEAEs in ≥ 2% of the Subjects by dose group for every pooled safety analysis group. Please also include a summary table for TEAEs reported by ≥ 2% of perampanel-treated subjects by study pool (specifically with two columns representing the Epilepsy Study Pool and Other Indications Study Pool).
12. Tables of TEAEs leading to discontinuation of study drug in ≥ 1% of the subjects by dose group for every pooled safety analysis group.
13. Tables of Demographics stratified by an additional category of Geographic region.
14. Table of Exposure to perampanel by dose (see Table 2 in the Appendix). Please include a table of overall perampanel exposure with total number of unique exposures listed for each pooled group based upon modal dose.
15. Tables of laboratory analyses using Tables 3, 4, 5 in the Appendix. In each section (e.g. hepatobiliary, renal, etc) of the Clinical Laboratory Tests, please also include a subsection which summarizes abnormal values reported as TEAEs.
 - a. For example, in the hematology laboratory section, please include a table that summarizes the hematology abnormalities reported as TEAEs. Specifically, this table would include the number of subjects in each dose group who reported an AE in the MedDRA SOC, Blood and lymphatic system disorders (including all relevant preferred terms such as neutropenia, anemia, etc) and the MedDRA SOC, Investigations (including all relevant preferred terms such as WBC count decreased, hemoglobin decreased, occult blood, etc).
 - b. For the other sections, relevant preferred terms may be found in the following MedDRA SOCs: investigations, metabolism and nutrition disorders, renal and urinary disorders, endocrine disorders, and hepatobiliary disorders.
 - c. Please be comprehensive in providing all relevant preferred terms.
16. A line listing, narrative, and case report form of all subjects who fit the criteria of Hy's Law case definition.

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17. Tables of vital sign and body weight analyses using Tables 6, 7, 8 in the Appendix. Please provide an analysis of the metabolic effects of perampanel. Specifically, please provide a table with the number of subjects in each study who had weight gain (categorized as >5%, >7%, and >10%) stratified by the number of subjects who also developed the other metabolic syndrome parameters during the study (triglycerides \geq 150 mg/dl, BP \geq 130/85 mmHg, HDL < 40 mg/dl, fasting BG \geq 100 mg/dl, and BMI > 30 kg/m²). Please also stratify these tables by dose.
18. Tables of ECG analyses using Table 9 and 10 in the Appendix for all studies in which ECGs were performed. Please also provide a table with the incidence of treatment-emergent cardiac and ECG AEs by dose group (using preferred terms in the MedDRA SOCs, cardiac disorders, investigations, and general disorders and administration site conditions).

Mary Doi, M.D., M.S. *{See appended electronic signature page}*

Reviewing Medical Officer

Date

Sally Yasuda, Pharm D., M.S. *{See appended electronic signature page}*

Clinical Team Leader

Date

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Appendix

Table 1 - Overview of Integrated Analysis Pools

Pool	Pool definition	Trials included
Subjects with partial-onset seizures		
Epilepsy study pool (10 studies)	Subjects with epilepsy who received ≥ 1 dose of perampanel from DB studies and subjects who received ≥ 1 of perampanel in OLE studies	G000-304, -305, -306, -307, -207 E049-203 A001-206 G000-208 J081-231, -233
Epilepsy Phase 3 Study pool	Subjects with epilepsy who received ≥ 1 dose of perampanel from Phase 3, DB studies	G000-304, -305, -306
Epilepsy Phase 2 Study pool	Subjects with epilepsy who received ≥ 1 dose of perampanel from Phase 2, DB studies	E049-203 A001-206 G000-208 J081-231
Subjects with non-epilepsy indications		
Other indications study pool (15 studies)	Subjects (with PD, MS, neuropathy, migraine) who received ≥ 1 dose of perampanel from DB studies and subjects who received ≥ 1 of perampanel in OLE studies	E044-301, -202, -204, -214 A001-302 G000-309 E044-205, -318, -220, -303 A001-218 G000-227, -228 E049-201 A001-210
Other indications double-blind (DB) pool	Subjects who received ≥ 1 dose of perampanel from DB trials	E044-301, -202, -204, -214 A001-302, -218 G000-309, -227 E049-201 A001-210
Parkinson's disease (PD) double-blind pool	Subjects with PD who received ≥ 1 dose of perampanel from DB trials	E044-301, -202, -204, -214 A001-302 G000-309
Neuropathy double-blind pool	Subjects with diabetic neuropathy or postherpetic neuropathy who received ≥ 1 dose of perampanel from DB trials	A001-218 G000-227
Healthy subjects		
Phase I study pool (27 studies)	Subjects who received ≥ 1 dose of perampanel	E044-017, -003, -016, -037 A001-008, -040, -039 E044-001, -002 J081-010, -026 E044-015, -004, -007 E044-005, -006, -025, -029, -030 A001-014 E055-019 E044-009, -020, -028 A001-013, -023, -024

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Table 2 – Exposure to perampanel by dose

** (please make separate tables for modal, maximum daily dose, and mean daily dose)

Duration (weeks)	Placebo	Dose 1	Dose 2	Dose 3	Dose 4	Any dose (%)
0-1 week						
>1 to 2						
>2 to 4						
>4 to 6						
>6 to 8						
>8 to 10						
>10 to 12						
>12 to 14						
>14 to 16						
>16 to 18						
>18 to 20						
>20 to 26						
>26 to 51						
>51 to 102						
>102 to 153						
>153 to 204						
>204 to 255						
...						
Duration of exposure (wks)						
n						
mean (SD)						
median						
min, max						
Number of subject-weeks						

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Table 3 – Mean Change from Baseline for Laboratory Parameters

Parameter	Placebo			Dose 1			(Similar columns for other doses)
	n	mean	SD	n	mean	SD	
(list here all laboratory parameters including hepatobiliary, renal, hematologic, electrolytes, and other chemistry parameters)							

Table 4 – Incidence of Potentially Clinically Significant Changes in Laboratory Parameters (for subjects who were normal at baseline)

Parameter	Placebo			Dose 1			(Similar columns for other doses)
	n	# abnormal	%	n	# abnormal	%	
list here all laboratory parameters (including hepatobiliary, renal, hematologic, electrolytes, and other chemistry parameters)and potentially clinically significant changes (e.g. WBC count $\leq 3.0 \times 10^9/L$)							

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Table 5 – Shift from baseline to maximum value during treatment by multiple of ULN for LFTs and Creatinine

Parameter	Maximum Post-Baseline				Missing
	<1x ULN	1 to <2x ULN	2 to <3x ULN	≥3x ULN	
ALT					
Placebo					
Dose 1					
Dose 2					
Dose 3					
Dose 4					
AST					
Placebo					
Dose 1					
Dose 2					
Dose 3					
Dose 4					
Total bilirubin					
Placebo					
Dose 1					
Dose 2					
Dose 3					
Dose 4					
GGT					
Placebo					
Dose 1					
Dose 2					
Dose 3					
Dose 4					
Alkaline phosphatase					
Placebo					
Dose 1					
Dose 2					
Dose 3					
Dose 4					
Creatinine					
Placebo					
Dose 1					
Dose 2					
Dose 3					
Dose 4					

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Table 6 – Incidence of Abnormal Vital Signs During Treatment

Abnormal Vital Sign (VS) Parameters Relative to Baseline/Pre-treatment VS	Placebo	Dose 1	Dose 2	Dose 3	Dose 4	Any dose
Supine						
SBP increment ≥ 20 mm Hg						
SBP increment ≥ 40 mm Hg						
SBP decrement ≥ 20 mm Hg						
SBP decrement ≥ 40 mm Hg						
DBP increment ≥ 10 mm Hg						
DBP increment ≥ 20 mm Hg						
DBP decrement ≥ 10 mm Hg						
DBP decrement ≥ 20 mm Hg						
Pulse increment ≥ 15 bpm						
Pulse increment ≥ 30 bpm						
Pulse decrement ≥ 15 bpm						
Pulse decrement ≥ 30 bpm						
Standing						
SBP increment ≥ 20 mm Hg						
SBP increment ≥ 40 mm Hg						
SBP decrement ≥ 20 mm Hg						
SBP decrement ≥ 40 mm Hg						
DBP increment ≥ 10 mm Hg						
DBP increment ≥ 20 mm Hg						
DBP decrement ≥ 10 mm Hg						
DBP decrement ≥ 20 mm Hg						
Pulse increment ≥ 15 bpm						
Pulse increment ≥ 30 bpm						
Pulse decrement ≥ 15 bpm						
Pulse decrement ≥ 30 bpm						
Change from Supine to Standing						
SBP increment ≥ 20 mm Hg						
SBP increment ≥ 40 mm Hg						
SBP decrement ≥ 20 mm Hg						
SBP decrement ≥ 40 mm Hg						
DBP increment ≥ 10 mm Hg						
DBP increment ≥ 20 mm Hg						
DBP decrement ≥ 10 mm Hg						
DBP decrement ≥ 20 mm Hg						
Pulse increment ≥ 15 bpm						
Pulse increment ≥ 30 bpm						
Pulse decrement ≥ 15 bpm						
Pulse decrement ≥ 30 bpm						

SBP = systolic blood pressure

DBP = diastolic blood pressure

Patients are counted once during treatment regardless of number of times achieving the threshold change.

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Table 7 – Summary of changes from baseline in supine vital sign measurements and body weight

Parameter	Placebo			Dose 1			(Similar columns for other doses)
	n	mean	SD	n	mean	SD	
SBP (mmHg)							
baseline							
change end of treatment							
DBP (mmHg)							
baseline							
Δ end of treatment							
Pulse rate (bpm)							
baseline							
Δ end of treatment							
Weight (kg)							
baseline							
Δ end of treatment							
Δ end of 6 months							
Δ end of 12 mos							
Δ end of 24 mos							
Δ end of 36 mos							
Δ end of 48 mos							
Δ end of 60 mos							

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Table 8 – Summary of orthostatic changes in vital signs

Parameter	Placebo			Dose 1		
	n	mean	SD	n	mean	SD
SBP (mmHg)						
placebo						
dose 1						
dose 2						
dose 3						
dose 4						
DBP (mmHg)						
placebo						
dose 1						
dose 2						
dose 3						
dose 4						
Pulse rate (bpm)						
placebo						
dose 1						
dose 2						
dose 3						
dose 4						

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Table 9 – Summary of changes from Baseline in ECG parameters

Parameter	Placebo			Dose 1			(Similar columns for other doses)
	n	mean	SD	n	mean	SD	
Heart rate (bpm)							
baseline							
Δ end of treatment							
PR interval (ms)							
baseline							
Δ end of treatment							
QRS duration (ms)							
baseline							
Δ end of treatment							
QTcF (ms)							
baseline							
Δ end of treatment							
QTcB (ms)							
baseline							
Δ end of treatment							

Table 10 – Summary of subjects with selected treatment-emergent ECG abnormalities

ECG findings	Placebo	Dose 1	Dose 2	Dose 3	Dose 4	Any dose
Rate						
Sinus bradycardia (HR<60 bpm)						
Sinus tachycardia (HR>100 bpm)						
Atrial-related conduction						
First-degree AVB (PR>200 ms)						
Ventricular-related conduction						
Intraventricular block (QRS>120 ms)						
Repolarization-related						
Prolonged QT						
Ischemia and infarction-related						

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