CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202834Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	10/19/2012
From	Norman Hershkowitz, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA	202834 (000)
Applicant	Eisai, Inc.
Date of Submission	12/22/2012
PDUFA Goal Date	10/22/2012
Proprietary Name / Established (USAN) names	Fycompa/perampanel
Dosage forms / Strength	Tablets: 2 mg, 4 mg, 6 mg, 8 mg, and 12mg
Proposed Indication(s)	Adjunctive Treatment of Partial onset epilepsy in children 12 years and older and adults.
Recommended:	Approval

1. Introduction

Perampanel is a non-competitive AMPA receptor antagonist developed by Eisai. The Sponsor is now submitting an original application with trial evidence for the therapeutic use of perampanel for partial onset seizures (POS) in adults and children 12 years of age and older. The Sponsor has also examined this drugs potential therapeutic effect in a number of other neurologic conditions, including Parkinson's disease, neuropathic pain, multiple sclerosis and migraine. AMPA is subtype receptor of glutamate, the principal excitatory neurotransmitter in the brain, While no approved anticonvulsant has specifically been developed based upon its AMPA activity, post-hoc investigation of at least one anticonvulsant, topiramate[1], has demonstrated AMPA antagonism.

2. Background

Pre-IND meetings were held with the Sponsor in 2007. At the at meeting agreement was reached on change in frequency as a primary endpoint during the titration and maintenance period, with allowance to exclude the first 2 weeks of titration. In 2010 issues regarding the statistical methodology were addressed as a response to a Statistical Assessment Plan (see below). In response to a prior submission of this NDA in 2011, a Refuse to File letter was issued, predominately because 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. Other issue regarding safety datasets, which needed correction, was described in this action. Perampanel has recently (July 2012) been approved in Europe for the same indication that the Sponsor is seeking in the present application.

[1] Rogowski, MA and Loscher W, Nat. Rev of Neurosci, 5: 553-564, 2004.

3. CMC/Device

The CMC review was performed by Dr. Lyudmila Soldatova.

Perampanel comes in the form of a film coated tablets of 2 mg, 4 mg, 6 mg, 8 mg, and 12mg strengths. Excipients used in this products formulation are common to those found in other oral medicines.

In her review dated the CMC reviewer found the application acceptable pending the following:

1. Pending overall OC recommendation
2. Pending submission of the translated executed packaging batch records.
3. (b) (4) The results of Method Validation Consult for (b) (4) are pending but validation of the analytical methods was found acceptable by this reviewer."

I inquired as to these pending issues by email to the reviewer Dr. L. Soldatova who responded in an email (10/9/12) by noting: 1) item 1 is still pending, but a later email from Tra Gooen indicated that OC found the inspection acceptable., 2) item 2 was resolved, 3) an action for approval can be taken prior to the completion of the analytical procedure validation.

The CMC reviewer did not recommend any PMCs or PMRs.

The ONDQA review was performed by Tien-Mien Chen. The reviewer found the application acceptable. But, before approval ONDQA had to negotiate a change in the dissolution acceptance criterion from Q (b) (4) (b) (4) to Q= (b) (4) at 15 min and 2 through a series of information requests and teleconferences. This new agreed upon criteria was found acceptable by both the FDA and Sponsor. The Sponsor was to update the specification section of the drug product, Module 32P51. These were submitted to the FDA on 08/14/12.

4. Nonclinical Pharmacology/Toxicology

The Dr. Toscano, performed the Pharmacology/Toxicology review. Dr Freed, the Pharmacology/Toxicology Team Leader, provided a supervisory review.

The efficacy of perampanel was suggested in a number of animal seizure models, including AMPA-induced seizures, audiogenic seizures, maximal electroshock, pentylenetetrazol-induced seizures, corneal kindling, and amygdale kindling.

The reviewer noted that there were a number of tissues of high "residence time." These included most notably the eyes (e.g. iris and retina) and aorta. Dr. Toscano concludes that

perampanel's effect on the eye has no clinical significance as there is no evidence of ocular toxic effects of the drug in long term toxicological studies. Dr. Toscano notes that the binding to the aorta was a very unusual finding, the residence time being at lest 106 weeks following a single dose. There was no evidence of venous binding. The binding appears to be a result of covalent linking, possibly to elastin. Some other drugs, such as rofecoxib, exhibit similar binding characteristics and have proven to have clinically deleterious effects of arterial structure. Although when examined by conventional light microscopy there was no abnormality, ultrastructure was not examined. . In the case of rofecoxib changes were observed in the ultrastructure through EM. Dr. Dr. Toscano notes that binding of rofecoxib to vessel walls have not been proven to cause vascular pathology and because of this the decision, final approval must be left to the clinical team. As will be described below, there was no obvious cardiac clinical signal. Dr. Toscano recommends further studies to more clearly examine whether perampanel binds covalently to human Aorta as a post-marketing requirement. He also recommends a rat aorta ultrastructure studies if covalent binding is observed. Dr. Freed does not believe that any information would be gleaned from such a study, particularly with the lack of clinical evidence of a vascular signal.

Dr. Toscano noted that toxicology studies were performed in mice, rats, dogs and monkeys. All were being adequately designed. The principal effect of perampanel was referable to the CNS, including abnormal gait/ ataxia, reduced activity, prostration and behavioral stereotypy (excessive grooming, scratching and serious excoriations). Dr. Freed notes that such stereotypy behavior indicates that the drug had the potential of producing OCD type behavior. However she also that "what, if any, implications these findings have to possible effects of perampanel on human behavior is unknown?" Dr Freed suggests that this information be included in the label. I believe that these may be related to some of the behavioral anomalies described in the safety section, which will be prominently described in the label (see below). The general toxicity studies revealed such affects were dose dependent and reversible upon drug discontinuation.

Convulsions were observed after long term exposures in the 2 year carcinogenicity studies in rats at low doses at exposures consistent with low human therapeutic doses. Dr. Toscano notes that the significance for the seizures are not understood. This was not observed at higher doses. This was not observed in mice. There were no obvious signs in the clinical data for increasing seizures. The significance of this single species finding is at present unknown,

There is no evidence that perampanel is genotoxic or carcinogenic. However, a phototoxicity battery demonstrated it was clastogenic but not mutagenic. Moreover, the presence of (b) (4) may result in degradation to (b) (4), which is a mutagen containing. Because of this, as noted above, there are specifications that limit (b) (4) in the drug product. Two-year studies in rat and mice did not indicate evidence of carcinogenicity.

Reproductive/developmental toxicity studies were performed in rat and rabbit. Rat studies indicted teratogenicity in the form of intestinal divertcilum. This occurred within the range of clinically recommended range. Dr. Toscano notes that this should be noted in the label. An increase in early resorption and stillborn pups was noted in litters of dams exposed to >1

mg/kg perampanel. Alterations in the estrous cycle were observed, but this was not associated with changes in fertility.

Juvenile studies revealed toxicity similar to that observed in adults, but at lower doses. Again, CNS symptoms were the most common observed effects. Learning was evaluated in juvenile rats using a Cincinnati water maze during subchronic treatment and several weeks after a period of subchronic seizures. Errors appeared to be dose dependent during treatment and appeared to only partially reverse several weeks after drug withdrawal. It does not appear that there was a statistical examination of the data. I would note that this effect is observed with other anticonvulsant drugs. Similar learning deficit appeared only in female rats, and Dr. Toscano does not believe that this resulted from differences in exposures. Dr. Toscano recommends that this be included in the label. This is seen at exposures within the expected therapeutic range and appears to be partly reverse upon drug discontinuation.

In summary Dr. Toscano notes that toxicities, described above, should not preclude approval. Dr Freed agrees. He notes that the most worrisome finding include learning deficits observed in female rats and teratogenesis, which he recommends should described in the label. Also noted above are recommendations for certain toxicities to be included in the label. He also notes a PMR should be performed examining the issue effects on the vasculature (see above). Dr. Freed does not agree with the latter point. She does not believe that any information would be gleaned from such a study, particularly with the lack of clinical evidence of a vascular signal as noted above and elsewhere in this review. I agree with this.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Xinning Yang performed the primary OCP review, with Dr Joo-Yeon Lee performing the pharmacometric review. These reviews were performed under the oversight of Dr Ta-Chen Wu (Acting Team Leader) and Atul Bhattaram (Team Leader).

In single dose studies perampanel was absorbed in a proportional fashion from 0.2 to 8 mg. At higher doses there is a less than proportional relation to Cmax; data on the AUC is inconclusive. This was confirmed in multiple dosing in seizure patients through a pop-PK analysis of the phase 3 trials. Oral dosing results in near complete absorption, with a Tmax of 0.5 to 2.5 hours under fasting conditions; high fat meals delays the Tmax by 2 to 3 hours, and reduces the Cmax by 28 % to 40%, but had no effect on the AUC. Plasma protein binding is about 95%, with the parent drug being principally bound to albumen and α1-acid glycoprotein.

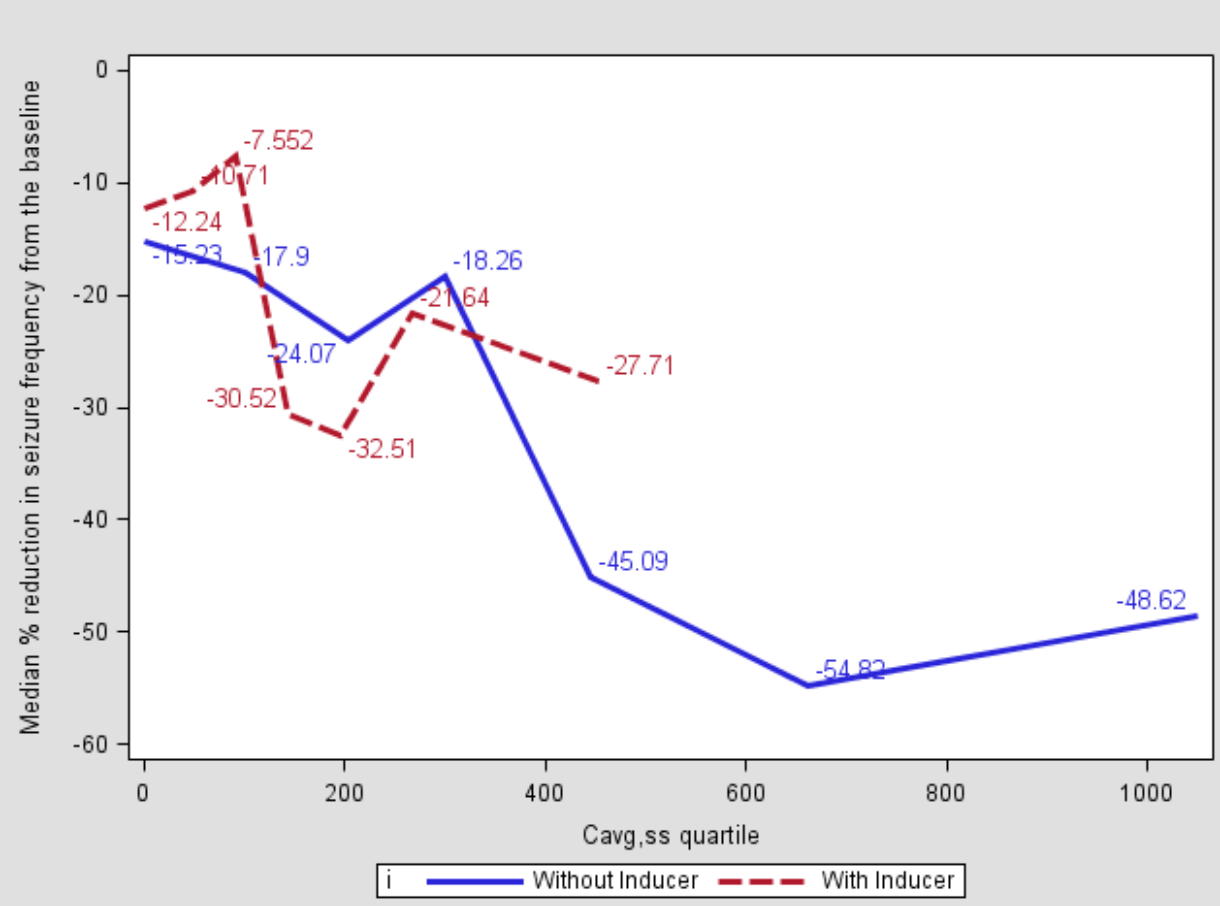
Perampanel is extensively metabolized, principally by oxidative metabolism with, in some cases, additional subsequent glucuronidation. In vitro studies indicate CYP3A4/5 metabolism, but *in vivo* studies with ketoconazole, a strong inhibitor of the isozyme, resulted in only a modest increase in perampanel levels (20%). Dr. Yang notes that this latter observation suggests that other CYP or non-CYP enzymes must be involved in this drugs metabolism.

Nonetheless carbamazepine (a broad-spectrum enzyme inducer with notable effects on CYP3A4/5) increased clearance of perampanel by 3-fold. Moreover, phenytoin and oxcarbazepine (both CYP3A4/5 inducers) increased perampanel clearance to 2-fold in patients. Phenobarbital and primidone, which are also inducers, did not show an effect, but Dr. Yang notes there was insufficient data for these drugs for a definitive conclusion . In general Dr. Yang notes this effect on clearance should have an effect to decrease the blood levels of perampanel by 1/3 to 1/2. These effects on clearance, and therefore levels, may have a significant effect on efficacy and toxicity, and complicate dosing labeling. Thus, there can be up to a 2 fold difference in therapeutic effect at the anticipated recommended doses of 8 and 12 mg/day (see below) when a comparison is made between patients on concomitant inducer and non inducer AEDs. When the full review group examined these data appeared the actual effect appeared to be small; therefore, it was decided to maintain information about a possible interaction in the PK section, but to not make any recommendations on dosage.

Dr. Yang notes that "there were clear exposure-response relationships for both efficacy and safety and the relationships support the maximum recommended dose of 8 mg." However, effect of concomitant AED CYP3A4/5 inducers, described above must be considered in dosing. For this reason OCP was requested to perfom the following analysis to derive a dosing schedule for patients who were and were not using concomitant inducer AEDs:

> 1. Construct two concentration/response curves for patients on inducers and non -inducers concomitant AEDs. This should accomplish two goals. First a comparison of the curves (eyeball comparisons of scattergrams and fitted curves, or actual statistical examination of the curves) and will allow one to demonstrate that there is no PD component to the inducer effect. Second it allows the determination of dosing for these two populations, which is described in the next few steps
>
> 2. Next determine, based upon these curves, the optimal dose for the two separate populations of patients (on and not on inducers). This may be done by determining the point that occurs before the concentration/curve flattens. Also, examination of adverse events may assist in this determination. Presumably may allow the identification pf a concentration in both populations that produce similar optimal effects.
>
> 3. After the optimal dose is determined, calculate back to the approximate mg/kg that will produce that concentration based on PK information. Assuming the calculations are based upon pop-PK in the studies, not only will the dose group need to be considered, but the modal dose as there was a great deal of step-backs in the higher dose groups.

The following figure was provided, which performs a concentration response based upon quartiles of concentration in the presence (red) and absence (blue) of inducers. What is apparent is that the concentration response may overlap. Therefore pharmacodynamic response may be similar. This however is theoretical and there was still some concern that inducers may result in an alteration in metabolites, and while theoretically the dosing may be adjusted based upon such information, empirical data should be obtained. A PMR requesting safety/efficacy studies in the presence of inducers will be requested.



Dr. Yang notes that the effect of perampanel on other AEDs is not significant However, multiple doses of 12 mg perampanel reduced AUC0-24hr and Cmax of single-dose levonorgrestrel by 40% and 42%, respectively. For this reason Dr. Yang notes that caution (multiple birth control methods) should be noted in the label when using hormonal birth control with perampanel use.

Administration of perampanel under fasting conditions, compared to a high fat meal, resulted in a Cmax of 39% to 67% greater and a Tmax reduced by about 2 hours. Perampanel was administered the efficacy studies under feed conditions Because of this Dr. Yang recommends that "perampanel be taken before bedtime preferably with food. If taken without food, perampanel should be administered immediately before bedtime."

Perampanel has an extremely long half life of 105 hours, with steady state being achieved after 21 days. Of note, with the present dosing titration used in the pivotal study (see below), if the target dose is 8 mg/day, the steady state is achieved approximately one week after the initial 8 mg dose. If titration is halted at lower doses, the time to achieve steady state after the target dose (e.g.4 mg) is longer, with that being achieved after the first dose of occurring in about 2 weeks.

Dr. Yang notes only small, non-significant differences in clearance in patients of different sex and race. Adolescent and elderly also did not differ significantly from the adult population. Mild reduction in clearance was noted in patients with mild renal impairment, but the clearance in these cases overlapped with normal. Data on moderate renal clearance impairment was limited and no data exists on severe renal disease. Dr Yang recommends monitoring in moderate impairment, and that perampanel not is used in severe renal impairment.. Dr Yang recommends modification of target dose and titration regimen in such cases in these cases.

OCP recommends approval but asks for additional in vitro studies, which will be included as PMRs, to further elucidate the metabolism of perampanel.

6. Clinical Microbiology

Does not apply.

7. Clinical/Statistical- Efficacy

The Clinical efficacy review was performed by Dr Rusinowitz and statistical review by Dr Liu (Team leader Dr. Kun Jin).

A demonstration of clinical efficacy for perampanel as adjunctive treatment of partial seizures was based upon three randomized, double-blinded, parallel-group, placebo–controlled pivotal trials (studies 304, 305 and 306). Studies were multinational with 2 of the studies containing 23 and 59 percent of patients from the US. All studies were of similar design and consisted of a 6 week prospective baseline period followed by a double-blind period that included a 6 week titration phase and a 13 week maintenance phase. The studies principally differed by the number of arms (3 to 4), with each arm representing a placebo and a variety of dose groups (2, 4, 8 and 12 mg/D). Titration was similar across arms and studies, except they were truncated when the target doses were achieved. Thus, patient's dose was increased by 2 mg every week during the titration phase until the target dose was achieved. Step backs were permitted during the double blind phase, but subsequent attempts were made to return the dosage to target if possible. Dr Rusinowitz notes that demographic features were generally well balanced across arms. My examination of the data suggests that the baseline mean frequency of seizures tend to be lower in the composite placebo groups than the dosage arms, but the medians were well matched. The percent of patients varied in study to study who were: 1) black/African American - 0 to 7%, 2) younger than 18 years of age - 8.5 to 11.4%, 3) older than 64 years of age- 1.3 to 3.1%.

The primary endpoint was the percent change in seizure frequency (per 28 days) during the maintenance phase as compared to the baseline. According to Dr. Liu the primary analysis was carried out such that the baseline seizure frequencies per 28 days and the percent change per 28 days during treatment were rank transformed separately and an analysis of covariance (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 then conducted to assess the robustness of the analysis method. The Sponsor corrected for multiple comparison's by using a hierarchy sequential analysis starting with the lower dose (8 mg/day) in study 304 and 305 and subsequently examining the higher dose (12 mg QD). Study 306 used the more conventional analysis of starting with the highest dose in the study (8 mg QD) and sequentially testing lower doses. All analyses were two sided with the alpha set at 0.05.

As per Dr. Liu the Sponsor specified, in the original SAP , the primary analysis noted the analysis set would include only in patients who had at least 2 weeks of seizure data from the baseline (pre-randomization) and double blind phase. This does not constitute a true modified-ITT (mITT) analysis. Because of this, in response to the SAP, the Division recommended a true ITT analysis (i.e. include the titration period). The Sponsor did not actuate this recommendation until studies 304 and 306 were completed. Therefore the only true protocol driven mITT analysis occurs in study 304 and 305. All analyses used last observation carried forward imputation.

Secondary endpoints included percent change in the frequency of partial and secondarily generalized seizures, responder rate and dose response analysis. Other exploratory endpoints included measures based upon diary frequency data (e.g. e.g. seizure free days), Global impression of change, quality of life measures etc.

Primary endpoint analysis, transcribed for the mITT analysis, from the sponsor's application, as it appears in the statistics review, is presented in the following three tables. The statistical reviewer confirmed and agrees with the Sponsor's analysis. As apparent from below an mITT analysis of the data reveals statistically significant effects for doses of 4 mg, 8 mg and 12 mg QD. Analysis mITT set differed little from the originally planned protocol analysis, except for study 304, where the 8 mg dose produced a slightly smaller effect, which was not statistically significant. I would defer to a true mITT analysis set, as that would be the Division's recommended analysis set. The protocol driven versus a more conventional correction for hierarchal analysis did not affect the results. Examination of these data by dosage from individual trials would suggest an optimal effect at 8 mg, with little or no further effect at 12 mg.

Table 1 mITT analysis for the primary endpoint (percent change from baseline) of 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	0.0158

Table 2 mITT analysis for the primary endpoint (percent change from baseline) of 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)		-19.10 (-29.17, -8.45)	-13.69 (-25.20, -2.26)
P-value		0.0008	0.0105

Table 3 mITT analysis for primary endpoint (percent change from baseline) of study 306.

Statistic	Placebo	Perampanel		
		2 mg	4 mg	8 mg
n	184	180	172	169
Median	-10.69	-13.63	-23.33	-30.80
Median Difference to Placebo (95% CI)		-4.36 (-14.09, 5.22)	-13.71 (-23.31, -4.50)	-20.13 (-29.66, -10.43)
P-value		0.42	0.0026	<0.0001

With a minor difference, the responder rate analysis revealed a similar effect. Evaluating combined complex partial and generalized seizures also revealed a similar effect.

The statistics reviewer performed a subset analysis according to age, race (white vs, non-white), sex and region (USA/ Europe/India/Russia/Central and South America). With some minor exceptions, no major differences were apparent that could not be explained by sampling error. The exceptions included a slightly greater trend for efficacy in women and non-white patients (my conclusion and not the statistics reviewer). These, however, reveal only minor differences. Most importantly patients under 18 years of age exhibited a very robust effect. The statistics reviewer agrees with the conclusion of efficacy; however because of the issue of the selection of the wrong analysis for study 304 the reviewer considers study 304 only supportive.

Dr. Liu concludes that "In conclusion, 2400mg SPN-804O administered QD demonstrated an effective treatment for refractory partial epilepsy, and 1200mg QD demonstrated numerically better than placebo in reducing the partial seizure frequency."

When the efficacy data is divided by the presence of potential perampanel metabolism inducers (e.g. carbamazepine, phenytoin and oxcarbazepine, See Pharmacokinetics), which represented slightly greater than half of the studied patients studied, it appears that in general the presence of inducers substantially reduces the magnitude of efficacy by approximately 2 fold. This is consistent with the effect of these inducers on clearance (increasing clearance by 2 to 3 fold, see Pharmacokinetics). This is best demonstrated by the table constructed below, which is derived from Dr. Rusinowitz's Tables 27 and 28. It presents the percent reduction in

seizure frequency from baseline, treatment difference from placebo (drug group median percent change from baseline – placebo group median percent change from baseline) for studies 304 and 305 (combined for analysis) and study 302. This presents the issue as to the dosing recommendations in the presence and absence of inducers.

	Treatment Groups							
	2 mg/day		4 mg/day		8 mg/day		12 mg/day	
	Without Inducers	With Inducers	Without Inducers	With Inducers	Without Inducers	With Inducers	Without Inducers	With Inducers
Studies304 and 305					24.4%	17.8%	33.2%	19.2%
Study 306	8.5%	0.46%	15.3%	11.9%	27.6%	10.82%		

Examiantion of this data reveals a larger effect when increasing dose from 8 to 12 mg per day in the absence of inducers. . This the slope of the dose response between these two doses was greater than that observed when both inducers and non-inducers were analyzed together (see above). I believe that the difference between the shape of the composite (inducer plus non-inducer) dose-response relation and the separate (inducer or non-induce) dose-response analyses represents the adding of different sections of a sigmoidal shaped concentration-response curve.

I believe that the Sponsor demonstrated efficacy for doses of 4 to 12 mg per day in POS. The optimal dose appears between 8 and 12 mg per day, but this is complicated by the issues as to whether inducers are present or not. The optimal dose of may have been empirically identified in the absence of inducers, but not in its presence. This will be reflected is dosing recommendations in the label. A short term safety/efficacy study will be requested as a PMR to better define the optimal dosing in the presence of inducers.

8. Safety

Dr. Mary Doi performed the initial safety review and Dr. Sally Yasuda performed the supervisory review.

Exposure and Demography

The safety database includes a total of 5,284 perampanel exposed patients from a total of 52 trials. Of these there were 916 healthy volunteers, 2717 patients with non-seizure neurologic diagnoses (Parkinson's disease, neuropathic pain, multiple sclerosis and migraine) and 1,615 patients with partial-onset epilepsy. Of the studies involving patients with partial onset seizures a total of 1038 were studied in the double blind phase 3 studies, 442 receiving placebo and the remainder receiving drug (2mg to 12 mg per day). Exposures in these studies were up

to 19 weeks. The remaining epilepsy patient exposures included patients participating in a phase 2 double blind study as well as open label extension trials. In total 1,615 epilepsy patients received perampanel, with 1231 patients exposed for a period of 6 months and 996 exposed for a period of one year. Dr. Doi notes that 739 patients, receiving 8 to 12 mg, were treated for over 51 weeks and that this exposure alone fulfills the ICH guidelines for an NME. As per Dr. Doi's review, exposures to patients in non-epilepsy trials tended to be at lower doses than epilepsy, with the majority of exposures being 4 mg and less. Exposure duration was less in non-epilepsy indication with a median exposure of 21 weeks.

One-hundred and four pediatric epilepsy patient form 12 to 16 years of age are included in the safety database, with 82 and 65 being exposed for greater than 6 months and one year, respectively. Only 2% of epilepsy patients were 65 years or older. Dr. Doi does not believe that there are sufficient safety information provided for adolescent patients to approve this age range. She notes that some preliminary data was supplied on cognition, growth safety and tolerability in an ongoing double-blind, placebo-control study in adolescents, but the information is incomplete. She recommends for the completion of this trial. I do not agree. The amount of data included in this study is similar to that provided for other approved and pediatric labeled anticonvulsants. While there was an animal signal for interference in higher cognitive function, the signal does not differ much from some other labeled anticonvulsants. The patient signal for this was also not that clear (see below). Moreover, studies on cognition and growth are difficult to interpret because of the underlying disease. Lastly, epilepsy is a serious condition, for which I believe the community is best served with approving this drug in the studied adolescent population studied. Some of these effects can be labeled and/or be requested as part of PREA and BPCA requirements. Lastly, except for growth and sexual maturation, adverse effects are usually similar to that observed in adults.

There was approximately equal number of patients in both sexes. Most patients were Caucasian (75%) with Asian patients (19%) being the second most common; the remaining was of Hispanic and black/African American. Off the patients studied 44% were in Europe and 22% were from North American, the remaining was from Asia and Latin America.

Deaths

Dr. Doi notes 9 deaths were reported in the epilepsy trials. One occurred prior to receiving drug and the remaining 8 occurred during the open label extension trials. Three deaths sere described as "sudden deaths" with one of these described as a death from SUDEP. The other 2 cases included: 1) a 48 year old female patient who died of cardiac arrest (myocardial infarction on the death certificate/ no autopsy) who was morbidly obese and had other cardiac risk factors including hypertension, hypercholesterolemia, and 2) a 27 year old who died of a" cause unknown" who was noted to have fallen and observed to have ventricular fibrillation. In the latter case electrolytic abnormalities were suspected, but no laboratories performed. Dr. Doi notes that, based upon a single death attributed to SUDEP, the SUDEP rate is 0.44 deaths per 1,000 person years. This is lower than published values of 3.5 to 9.3 per 1000 person years. I would add that a more liberal analysis, including all sudden deaths, also results in lower than expected SUDEP rate. The remaining 5 deaths occurring on drug were due to a

number of different pathological causes and could not be linked to one general shared toxicity/disease process. One death was classified as a neonatal death (potential aspiration) associated with maternal use; the mother, however, was on other drugs that may influence neonatal mortality (carbamazepine and clobazam).

Drs. Yasuda and Doi notes that there are an additional 33 deaths in non-epilepsy trials that included 26 in Parkinson's disease and 6 in neuropathic pain patients, bringing the death rate in this population to 13.2 per 1,000 patient-years. These deaths appeared to occur in older patients with a number of co-morbidities and both Drs. Doi and Yasuda believe these rates are more explainable by the susceptibility of this generally aged population and their associated co-morbidities than a drug related phenomena. Thus, there were a number of different neoplasm- and cardiovascular-related deaths. Support of this comes when examining the deaths in placebo control trials: i.e. rates were in fact greater in the placebo treatment groups than in the drug treatment groups, albeit by only a small degree. Both Drs. Doi and Yasuda believe that such deaths do not appear associated with drugs use. Of interest, there were 3 cases deaths associated with traumatic injuries resulting from falls in the Parkinson's studies (cervical hematoma, hip fracture, femoral neck fracture). While such falls are not uncommon in Parkinson's, Dr. Doi points out a potential contribution of the sedative quality of this drug. Falls will be discussed in the Warnings and Precautions of the label as will associated neurologic events that increases the risk of falls (e.g. dyscoordination and vertigo). An additional death associated with pancreatitis and chololithiasis is discussed below.

Serious Adverse Events

In the total epilepsy trial database a total of 17.3% (285 /1,651) of patients experienced a serious adverse event. The common serious adverse events, in declining order based upon MEDRA SOC were Nervous System disorders (6.7%), Poisoning and Procedural Complications (3.9%) and psychiatric (3.6%). The most common preferred term SAE, in descending order were Convulsions (2.7%), Status Epilepticus (2.7%) and Aggression (0.8%). Convulsion related preferred terms are certainly not unexpected in this population. The general trend , based upon data collected indicates better control of seizures. When corrected for exposures the incidence of serious adverse events in the non-epilepsy pool was somewhat less. As noted, doses in these studies tended to be lower. For the non-epilepsy pool Dr. Doi notes that SOC SAEs of Cardiac, Neoplasms, Musculoskeletal, General, Renal, Respiratory, and Vascular disorders are more common than that observed in the epilepsy pools. This is consistent with the differences in population age. According to calculations from Dr. Doi the grouped incidence of serious adverse events in the double-blind phase 3 epilepsy studies in the drug treatment groups at doses of 2 to 8 mg was similar (3.3% to 5.6%) and less than the incidence in the placebo groups (5.0%). Dr. Doe notes that for the complete 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 liver failure, angioedema, or anaphylaxis. There, however, were cases coded to acute renal failure, and rhabdomyolysis. None of which, according to Dr, Yasuda, appeared to be related to drug. There were two cases of acute pancreatitis (one associated with chololithiasis), one in the drug treatment groups and one in placebo. Dr Yasuda also noted

that she does not feel this represents a signal. Some of the serious adverse events are discussed below in the section "Events of Interest."

Discontinuations

Dr. Doi identified, in a comparison in phase 2/3 double blind epilepsy studies, that discontinuation rates of 11.5 % were observed in patients receiving placebo and 15.1% in patients receiving perampanel. The common reasons for the discontinuations in both groups differed. The most common in the drug treatment groups were adverse events and subject choice and the most common in the placebo group were inadequate therapeutic effect, lost to follow-up, and "other." Of importance, Dr. Doi notes that while an obvious dose response is not obvious for all discontinuations in the double–blind epilepsy trials it is apparent when one only examines discontinuations for adverse events. When one examines the phase 3 double-blind epilepsy studies the treatment emergent adverse events leading to treatment discontinuation occurred in 19.5% of the perampanel subjects. The most frequent SOC categorization for discontinuations from adverse events were Nervous system disorders (9.4%), followed by Psychiatric disorders (6.0%) and General disorders (3.9%). The rates increased from 14.8% to 24.3% when one compares patients exposed to doses of >4- mg to >8-12 mg. When all phase 1 and 3 epilepsy trials (blinded and open labeled) are examined, 46.1 % of patients were noted to have discontinued treatment. The most common adverse event related reason for discontinuations, greater than placebo (in descending order) in epilepsy control trials included dizziness, vertigo, fatigue, ataxia, somnolence, rash aggression, anger, dysarthria, vision blurred nausea and balance disorder.

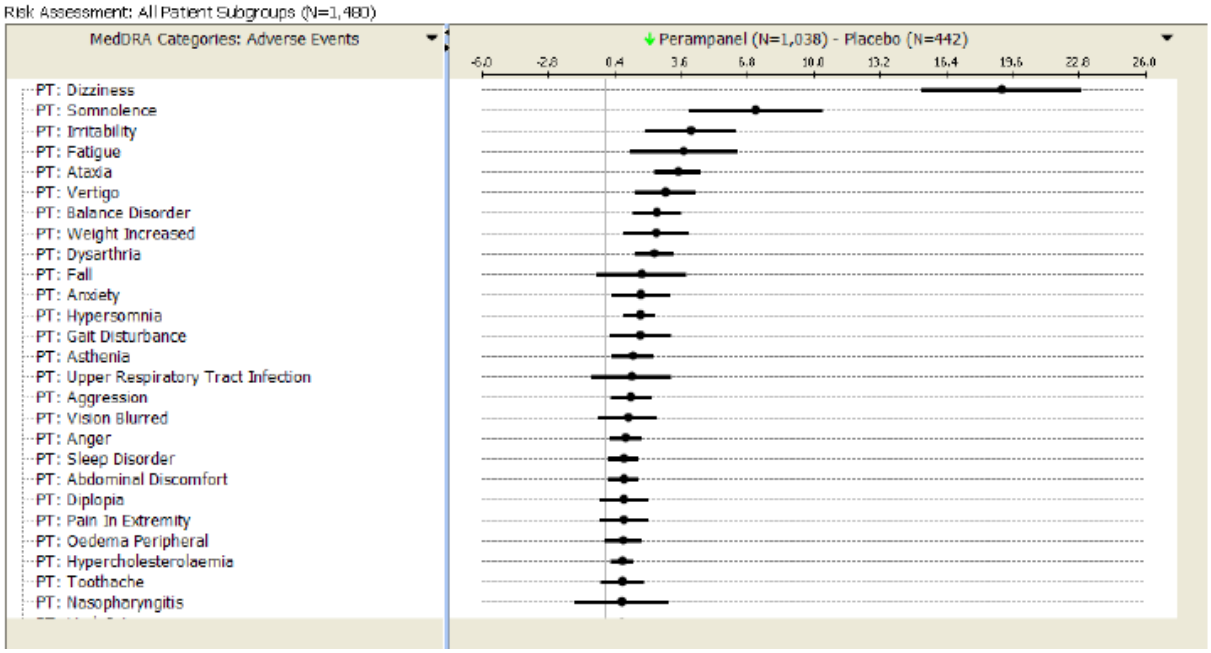
Dr Yasuda notes that in the epilepsy and non-epilepsy studies, no subjects discontinued for Stevens Johnson syndrome, toxic epidermal necrolysis, acute liver failure, aplastic anemia, agranulocytosis, pancytopenia, or anaphylaxis. There were, however, , discontinuations due to thrombocytopenia, CK elevation, QT prolonged, toxic skin, rhabdomyolysis, acute renal failure, CK elevation, and QT prolonged, and transaminase elevations, acute pancreatitis, which will be discussed below

Common Adverse Events

The following table, from Dr. Doi's review, presents common adverse events occurring in the drug treated groups in the pivotal epilepsy trials at rates equal to or greater than 2%, at any dose, and greater than placebo.

MedDRA System Organ Class Preferred Term	Placebo n=442 %	Perampanel % 2 mg n=180	4 mg n=172	8 mg n=431	12 mg n=255	Total n=1038
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
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

Dr. Doi also presents the following helpful figure which represents the risk difference for the most common adverse events: i.e. risk ratio (experimental period/baseline) for drug minus the risk ratio for placebo. The bars represent the 95% confidence intervals. The events largely followed a dose response (see the above table).



As apparent from the above table and figure the most common adverse events are referable to neurologic and behavioral symptoms with the most common symptoms being referable to the preferred terms of dizziness, somnolence, irritability, fatigue, ataxia, vertigo, balance disorder, weight increased, dysarthria, fall, anxiety, hypersomnia, and gait disturbance.

Events of Interest

Psychiatric

Dr. Doi, with the concurrence of Dr. Yasuda, has identified psychiatric disorders as a significant drug related risk of perampanel. This is supported by SOC for psychiatric adverse events comparison in placebo control trials in both epilepsy and non-epilepsy conditions. The data is represented in the table extracted from Dr. Doi's review below. SOC Psychiatric events were consistently greater in epilepsy trials in the form of treatment emergent adverse events, SAEs and discontinuations from such events.

	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	

Of the TEAEs observed in control epilepsy trials irritability, anxiety, sleep disorder anger were reported in greater than 1% of patients and greater than approximately three times that of placebo. Other psychiatric TEAEs occurring in drug groups at rates greater than the placebo groups, but less than 1%, in the placebo control trials included nervousness, confusional state, mood swings, mood altered, euphoric attack, panic attack and abnormal behavior. Other psychiatric events occurred less commonly in drug than placebo (hallucinations) but these differences did not appear very large. Certainly seizure patients are known to have a high rate of psychiatric co-morbidity. Nonetheless, the increased rates suggest drug causality. This is also supported by a variety of reports of psychiatric adverse events in normal subjects including euphoria, insomnia, disassociation, flat affect etc. Dr. Doe also identified a number of adverse events that were identified in the drug treatment groups, but not in placebo groups, which were classified as serious, in both epilepsy and non epilepsy trials. Such events were not common, but included preferred term such as aggression, adjustment disorder, and belligerence confusional state.

Dr. Doi performed a comparison of two general Standardized MedDRA Queries (SMQ) to investigate the psychiatric signal. She examined the epilepsy trials using both a broad and narrow SMQ search. When doing so there was not a consistent difference between placebo and drug treated groups. However when she examined an SMQ for "hostility and aggression" and corrected for, seizure related terms, she consistently observed greater risk in the drug treated group. Similar trends were observed in non-epilepsy trials. Hostility and Aggression in the double blind epilepsy studies tended to have more dramatic consequences (e.g. were rated as severe, serious or resulted in discontinuations or dose reductions). Included in the total database describing "hostility and aggression" were 23 physical assaults, physical threats (e.g. with a knife), suicidal ideations, homicidal ideations (but, no actual homicides), and damage to property. Most patients (two-thirds) described as such had no documented psychiatric history. Some cases were confounded, but both Dr. Doi and Yasuda agree that the role of perampanel cannot be ruled out. There appeared to be an increased risk for patients on perampanel with a prior psychiatric history of developing hostility than those without in the double blind phase. Because of this Dr. Doi has suggested that labeling include the recommendation that one should avoid "the use in patients with a history of aggression or any unstable psychiatric Disorder." Dr Yasuda does not feel an absolute restriction is necessary. I agree with Dr. Yasuda and would also add that this comparison is not an adequate comparison as patients

with a prior psychiatric history may already have a proclivity for such behavior. Nonetheless, the data does suggest that patients with such a history may be at a higher risk although the one caveat to this is that this study excluded patients with active psychotic disorder(s) and/or unstable recurrent affective disorder(s) In sum, I believe there should not be an absolute restriction but a description of the increased frequency in this population of patients.

A latter, post review, examination of the placebo controlled data revealed that paranoia and delusions are slightly greater in the drugs arms of such studies

Dr. Doi notes that the risk of this behavior markedly increases in doses 8 mg and greater..

Dr. Doi recommends that this adverse event should appear as boxed. The review team has decided to concur with the boxed warning because of the seriousness of such events.

Generally there did not appear to be a consistent difference between suicidal ideation between placebo and drug treated patients in controlled studies, with different analyses revealing a different result. Nonetheless, there was some suggestion of an increased risk on drug. Thus, according to Dr. Doi's 4 patients in the complete epilepsy and 1 in the non-epilepsy database were noted to have had a suicide attempt. There were no suicide attempts in the epilepsy double blind database, but there were 2 in the non-epilepsy database. All such analyses were retrospective. Perampanel will receive class suicidality labeling for antiepileptic drugs.

Nervous System Disorders

This SOC group of disorders was reported as one of the most common adverse events. Dizziness/coordination and somnolence were the most common under this general rubric. Dizziness exhibited an obvious dose response and occurred at a remarkably high rate in the 12 mg dose in the placebo controlled trials. Other related neurologic symptoms (vertigo, ataxia, gait disturbance, balance disorder, coordination) occurred at lower rates but also appeared to exhibit dose dependency. Somnolence, fatigue (and to a lesser extent lethargy and sedation) were also commonly reported in the drugs groups at rates greater than in the placebo groups in the epilepsy controlled trials and appeared to be dose dependent. Thus, somnolence occurred at the highest dose of nearly 2 to 3 times that of placebo in the highest exposure groups (12 mg). Dr. Doi also noted a signal suggesting a decrease in cognitive function based upon a grouped analysis of a number of cognitive associated preferred terms. Dr Yasuda points out this analysis were driven by the preferred term dysarthria, which she notes should be classified under weakness/coordination and therefore suggest a false signal. Off course a drugs that produces somnolence may be expected to reduce cognitive function, but as noted by Dr. Yasuda examination of adverse event preferred terms do not permit a definitive conclusion. Dr. Doi also notes greater number of paresthesia and other sensory symptoms (e.g. hypoesthesia's) in the drug treated group than placebo. The absolute size of this effect is small and differences with placebo are not great (1.58% in placebo and 2.22% in drug, but exhibit substantially higher rates in the high dose group). The significance of this unknown, but has been seen with other anticonvulsants.

Some of the above neurologic events were classified as serious and served as a common reason for drug discontinuation. An examination by Dr. Doi indicates that elderly (>65 years of age) are at higher risk for coordination and somnolence related adverse events. Examination of her tables indicates an increased risk for such adverse events. The analysis is slightly confounded by the small number of elderly patients.

Lastly an analysis by Dr. Doi of completers indicates that these neurologic events are more common during the titration than the maintenance phase, suggesting some degree of habituation, a phenomena observed with other anticonvulsants.

Dr. Doi's analysis indicated a rather high percent of patients in the epilepsy double blind studies with falls, with a step dose response (10.2% in the 12 mg dose group). This effect was more common in the elderly. Injuries, associated with seizures and associated without seizures, were also more common in drug than placebo treated patients in both epilepsy and non epilepsy studies. Dr. Doi believes that such events may have a serious outcome as indicated by a slightly greater increase in serious injuries (e.g. head injury, facial bone fractures) in drug treated patients compared to placebo treated patients in both epilepsy and non-epilepsy trials. An analysis of falls and injuries in the absence of seizures confirmed that non-seizure events can be associated with such falls and injuries.

Dr, Doi and Yasuda believe that these nervous system effects belong in the Warnings and Precautions section of the label. I agree. The principal problematic events involve somnolence, fatigue, coordination, dizziness, gait disturbance and falls.

Eye Disorders

Dr. Doi notes that blurred vision and diplopia were more commonly seen in the drugs treatment at greater rates than the placebo treatment groups in the controlled epilepsy trials. The treatment difference was rather small and there were no serious events. Again the significance of this is unknown. It is also noteworthy that other anticonvulsants produce similar adverse events.

Weight, lipids, glucose and blood pressure (Metabolic syndrome)

Dr. Doi identified weight gain as a significant adverse event. Thus, in the double-blind epilepsy trials adult perampanel subjects gained an average of 1.12 kg, compared to an average 0.3 kg weight gain in placebo subjects. A lesser effect was observed in adolescence. There was no obvious alteration in appetite as pointed out by Dr. Yasuda. Weight gain was also seen in non-epilepsy studies. This effect exhibited a dose response relation.

Dr. Doi noted that a higher percent of patients in adults than adolescent exhibited an increase in shifts to high level and outliers for cholesterol in patients treated with perampanel than those treated with placebo (e.g. the increase to > 40mg/dl in placebo was 2.9% in placebo and 8.3%

in perampanel patients). Shits table only revealed a very subtle signal. No obvious effect was apparent for glucose and a suggestion of an effect was observed for an increase in triglycerides in adolescents, but this effect was not sufficiently strong for confirmation.

Dr. Doi also identified a small, increase in blood pressure in patients on perampanel when compared to placebo an outlier analysis in epilepsy trials. The first analysis of blood pressure, using large outlier (e.g. SBP >180 mmHg or change of 20 and 40 mm HG) did not reveal a signal. Moreover, mean changes in blood pressure was small and not consistently in a particular direction. To analyze blood pressure more thoroughly she requested a more granular examination. She noted a small, but consistent, increase. To summarize some of this data I have created the below tables with data from Dr. Doi's review that allows examination of all patients who have blood pressures greater than > 5 mmHg or >10 mmHg. The percent of patients with increases of 5-10 mg HG for systolic blood pressures were greater in the drug than placebo by 2% to 3% into titration but was less 12 weeks into the maintenance period and again increases at the end of maintenance. Examination of her data reveals the difference between drug and placebo practically disappears when higher blood pressures (>10 mmHg) are examined, see tables below. This suggest a very small effect.

	Percent of Patients with blood pressure increase >5 mm Hg			
	Systolic Blood Pressure		Diastolic Blood Pressure	
	Placebo	perampanel	Placebo	perampanel
End of Titration (6 week)	30.5%	33.2%	24.7%	31.4%
Maintenance (week 12)	32.2%	32.5%	27.6%	29.6%
End of Maintenance	16.2%	18.3%	18.6%	21.4%

	Percent of Patients with blood pressure increase > 10 mm Hg			
	Systolic Blood Pressure		Diastolic Blood Pressure	
	Placebo	perampanel	Placebo	perampanel
End of Titration	14.3%	14.9%	9.5%	9.0%
End of Maintenance	16.5%	14.4%	10.6%	9.6%
End of Maintenance	14.2%	16.2%	9.1%	10.9%

Dr. Doi believes that the constellation of events that includes cholesterol changes, weight and blood pressure constitute a metabolic syndrome and requires that these events should be noted in the Warnings and Precautions section of the label. Dr Yasuda agrees. She, however, notes no obvious cardiovascular signal was observed. I believe that while this should be in the label the seriousness and level of proof does not justify placement in the Warnings and Precautions section placement. Thus the, the magnitude of blood pressure, weight, and cholesterol changes was relatively small and the effect on cardiovascular risk not obvious. I recommend that these be placed in adverse events. It is noteworthy that the team felt that, considering absence of mean changes the very small signal of this outlier analysis and lack of confirmation in shift tables, the blood pressure changes were not reproducible and should not eb included in the label.

Tendon Rupture

Because of the nonclinical signal, Dr. Doi examined the potential for tendon rupture. She could not find a definitive signal in the clinical database (e.g. rates were similar between drug and placebo). She does not recommend labeling, but does recommend post marketing vigilance. Both Dr. Yasuda and I agree.

Hepatobiliary issues

There was a suggestion of chololithiasis based upon a small difference between drug and placebo groups. This was not confirmed in the non epilepsy control trials, but many patients with this problem had risk factors. Dr. Doi and Yasuda believe that this should be a subject of pharmacovigilance, and I agree.

No patients in the total database met Hy's law. There were no discontinuations in the epilepsy database for liver related AEs. There were 4 patients who discontinued because of elevated transaminase in the non-epilepsy pool. Analysis of these patients revealed that they generally had preexisting elevations. In total Drs. Doi and Yasuda do not feel there is a signal for liver toxicity and I agree.

Immunologic reactions

No cases of Stevens Johnson syndrome or Toxic Epidermal Necrolysis were reported in any patients taking perampanel in the complete data pool; one patient on placebo was noted to have Stevens Johnson syndrome. Rash and pruritus was slightly more commonly reported in epilepsy phase 3 controlled trials (e.g. for rash 2.2% for drug and 1.6% for placebo). No such event in the epilepsy pool was classified as serious, but there were 7 patients who were discontinued (with resolution) for rash on drug and none on placebo. The general picture in non-epilepsy studies was similar with the exception of two cases. One of these was described as generalized exanthematous pustolisis (AGEP); Dr. Doi noted that this lacked criteria needed to make a definitive diagnosis. The other was a case of erythema multiforme, which was determined to be a result of viral infection. Both Drs. Yasuda and Doi believe that there is no signal for serious skin reactions. Dr. Yasuda notes that "there were no definitive cases of severe cutaneous adverse reactions associated with perampanel use." I agree with this conclusion. It is possible that there are allergic reactions to the drug, but as these are not serious, the rash information can be provided in the Adverse Reactions section of the label.

Because of the nonclinical results of the potential for perampanel in inducing photosensitivity, the Sponsor provided subject with a questioner on photosensitivity. Dr. Doi examined his and performed an adverse event analysis of. Both Dr. Doi and Yasuda believe that this data does not point to definitive signals. I agree.

Dr. Doi performed an analysis to determine whether there might be a signal for angioedema and anaphylaxis. While there were rare cases angioedema, none appeared to be attributable to

drug. For example one case resolved despite continuing of perampanel, and one occurred after being on drug for nearly a year, There were no cases consistent with anaphylaxis.

There was a search for potential Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) reactions. Dr. Doi concluded that an association could not be made that perampanel can produce DRESS. Some cases did not meet criteria for DRESS and/or symptoms resolved in despite drug being continued. Dr Yasuda and I agree with this conclusion.

Cardiac

Dr Doe performed a carful analysis of cardiac events in the complete database and could not find consistent signal for any cardiac related events including deaths from cardiac events, arrhythmias or syncope.

Off note one non-epilepsy open label study (228) revealed a large magnitude mean change in the mean QTcF of 12.6 msec, and as a result Dr. Doi requested an IRT consult for this observation. The consult noted that this change was not a significant for a number of reasons; two of these being it did not significantly differ from placebo arm in other studies and no dose dependent trend could be appreciated. Perhaps, more importantly, a review by IRT of a formal QT study did not reveal a significant QT prolongation. Thus a double delta change in the QTcF was 3.7 msec (CI: 0.6 to 6.9 msec) at the highest dose of 12 mg. The moxifloxacin control was positive. This probably would not cover full exposures in cases of reduced liver function activity, which will be noted in the label.

Other organ systems

Dr Doe could not identify a significant signal for renal, thyroid, or respiratory disease in the database.

Laboratories

Dr. Doi could not identify signal (base don AE profile and laboratories) for hematologic changes. No other significant laboratory changes were noted.

9. Advisory Committee Meeting

None.

10. Pediatrics

The Sponsor submitted a PPSR, which in part assisted this division in determining the necessary PREA requirements. Representatives from this division along with those from OCP and statistics met with the PERC committee on 8/29/12 and the following regarding PREA requirements was agreed upon:

- Because there are presently an adequate number of patients in 12 years and older, perampanel can be labeled for POS in this age group.
- A waiver will be granted for patient efficacy studies 1 month and younger because there are few patients who can be definitively diagnosed with this condition making such a study highly impractical.
- Adequately controlled, randomized, prospective efficacy studies examining POS would be required, but may deferred, for patients > 1 month to 12 years. This should be accomplished through two studies, one using a diary based endpoint for children older than 2 (or 4) years old and the other EEG based endpoint for younger children. The studies should include a long term extension to collect long term safety data.
- Two PK and tolerability studies in epilepsy patients. One in pateints > 1 month to <24 months of age and the other in pateints 2 years to <12 years of age. Pharmacokinetic data can be obtained and analyzed using either conventional pharmacokinetics methods with intensive sampling or using a population PK approach by collecting sparse samples. Subjects should be balanced among age cohorts. Effort should also be made to balance the gender distributions within each age cohorts.

11. Other Relevant Regulatory Issues

CSS:

Dr. Alicja Lerner performed the review for CSS.

(b) (4)

This information will go to the DEA for final review and scheduling.

Financial Disclosure

Dr Rusinowitz note that Esiai, notes that the Sponsor certified that there have been no financial arrangements with the 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). They also certified that each 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.

DSI

Four study sites were inspected. Dr. A. El Hage reviewed the results. He concluded that, "overall, the data submitted from these four sites are considered reliable in support of the pending application."

12. Labeling

See labeling provided in the approval letter as well as the commentary throughout this document.

13. Recommendations/Risk Benefit Assessment

Fycompa should be approved with the above recommended labeling and the requested PMRs.

[2] I discussed the strength of the NMDA binding with Dr. Freed, the Pharm/Tox team leader. She noted that this was a very week interaction and would not be clinically relevant at therapeutic concentrations.

The following are PMR's excluding the 4 described above, which are relevant to PREA requirements.

Pharmacovigilance:

As noted above pharmacovigilance is requested on the following two issues:1) tendon rupture, 2) chololithiasis.

Clinical PMR:

- A prospective, multiple dose, randomized, controlled, double-blind, efficacy/safety study for Fycompa as adjunctive treatment of partial onset seizures when Fycompa is added to concomitant treatments in adults on CYP34A inducing antiepileptic drugs (phenytoin, carbamazepine, and oxcarbazepine). The study should include a long term safety extension. The primary efficacy endpoint during the controlled phase will examine seizure frequency based upon diary data. Safety will be evaluated during the controlled phase and long term extension. Study dosages must be selected to produce similar exposure to patients as that experienced by patients receiving 8 and 12 mg of Fycompa daily who were on non-inducing concomitant anticonvulsant drugs.

CSS PMR:

- A prospective human physical dependence trial in epilepsy patients. The subjects should be titrated to the approved therapeutic dose of FYCOMPA of 8-12 mg, and maintained at this dose for an appropriate amount of time. At the end of the treatment, the drug should be abruptly withdrawn. The withdrawal questionnaires should be administered pre-treatment, at several specific times post-treatment withdrawal and 21st day post-treatment. Additionally a withdrawal questionnaire should be administered within last 2 days on treatment before treatment withdrawal. Plasma levels of FYCOMPA should be measured and accompany every administration of withdrawal questionnaires.

Clinical Pharmacology PMRs:

- *In vitro* study(ies) to characterize the contributions of CYP1A2, 2B6, 2C8, 2C9, 2C19 and 2D6 to perampanel metabolism.
- *In vitro* study(ies) to characterize the contributions of non-CYP enzymes to perampanel metabolism. The non-CYP enzymes to be evaluated should be justified and agreed upon by the Agency prior to initiating the study. The requirement for this study will depend on the results of the latter PMR.
- An *in vitro* study in human liver microsomes to evaluate the effects of a range of concentrations of perampanel (e.g, up to 30 μM and including clinical relevant

concentration of ~3 μM) on CYP2B6 activity using a recommended CYP2B6 probe substrate per the FDA Guidance for Drug-Drug Interactions.

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/s/

NORMAN HERSHKOWITZ
10/22/2012