CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202834Orig1s000

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 202834
Drug name:	E2007
Indication(s):	Antiepileptic
Applicant:	Eisai Co
Documents Reviewed:	Electronic submission Electronically submitted dataset Dated: 2011-05-25
Review Priority:	
Biometrics Division:	Division of Biometrics 6
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Keywords:	Animal Mouse Rat Carcinogenicity

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Background

In this submission the sponsor included reports of two animal carcinogenicity studies, in mice and rats, to assess the carcinogenic potential of E2007 when administered by gavage, once daily at appropriate drug levels for about 104 weeks. Results of this review have been discussed with the reviewing pharmacologist, Christopher Toscano, PhD.

In this review, the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

Chapter 1

Summary of findings

1.1 Mouse study

Both the male and female experiments are negative studies. In the case of the female mice, the endpoints for which p-values less than 0.05 were returned (uterine tumors and osteomas) did not remain significant after making an adjustment for multiplicity. In addition, the result for osteomas became completely innocuous when osteosarcomas were included in the endpoint. There were no such findings for the male mice at all.

No organs were reported as being unexamined. However, the autolysis levels reported for the gall bladder (both sexes) and the penis were sufficiently high that the study should be viewed as inconclusive regarding tumor effects in these organs, rather than as negative.

Mortality levels were high, especially among the male mice. In fact, the mortality faced by the high dose group clearly exceeded the MTD, and this group had to be excluded from analyses. Nonetheless, sufficient animals in the other groups did survive in order to make this a valid study. The dose levels can therefore be concluded to be appropriate.

1.2 Rat study

Both the female and male rat experiments are negative experiments. The only remotely worrying tumor finding, for keratoacanthomas in male rats, does not retain its significance after an adjustment for multiple testing is made.

There was no autolysis reported, and the rates at which organs were reported as unexamined were sufficiently low that there is no cause for concern.

In both sexes, the mortality rates were low, so there is no concern of excessive dosing. However, the high dose male animals did experience a statistically significant decrease in survival compared to he control, and both male and female treated animals showed signs of diminished weight gain compared with the control animals. We can therefore conclude that the dose levels were appropriate.

Chapter 2

Mouse Study

2.1 Experimental design

This study comprised two experiments, one in male mice and one in female mice. The mice used were CD-1 (ICR) mice. Three hundred mice were used in each experiment, divided into five dose groups of sixty animals each. One group of each sex was the control group; animals in these groups received daily doses, by gavage, of the vehicle (0.5 w/v% methylcellulose solution, 10 mL/kg). The remaining four groups, the low, mid, mid-high, and high dose groups respectively, received various doses of E2007, by gavage. At the commencement of the study, these dose levels were set at 1, 3, 10, and 30 mg/kg per day. However, due to high levels of mortality during the study, dosing was discontinued for male mid-high and high dose animals (at 87 and 85 weeks respetively) and for mid, mid-high, and high dose female animals (101, 101, and 92 weeks respectively). Animals whose dosing was halted went through a withdrawal phase until either death or the scheduled end of the study, whereupon they were sacrificed.

All animals were observed for mortality and clinical signs three times a day (twice a day on weekends and holidays). Palpation examination were conducted once a week, and animals underwent a full necroscopy after death.

2.2 Sponsor's analysis

2.2.1 Survival analysis

For each sex, the sponsor plotted Kaplan-Meier survival curves for each dose group, and conducted Tarone-type tests for a dose reponse in survival and pairwise log-rank tests between each treated group and the control group.

The discussion on mortality in the sponsor's report focuses on death associated with self trauma; it is reported that there an increase in such deaths increased mortality was noted in mid, mid-high, and high dose groups. However, no statistical analyses of these data are included in the report. The sponsor does conclude that the increase on self trauma is caused by the test article.

The sponsor also concludes that with the exception of the high dose male group, all groups had sufficiently good survival to allow statistical analyses of tumor data.

2.2.2 Tumor analysis

The sponsor used Peto's method [6] to test each type of tumor for a dose reaponse, testing across all groups. Also, for each tumor type, Fisher's exact test was used to conduct pairwise comparisons between each treated group and the control group. Whenever the incidence rate was above 5% in al least one group (i.e. at least three animals), Peto's test was again used to conduct a pairwise comparison.

The sponsor concludes that

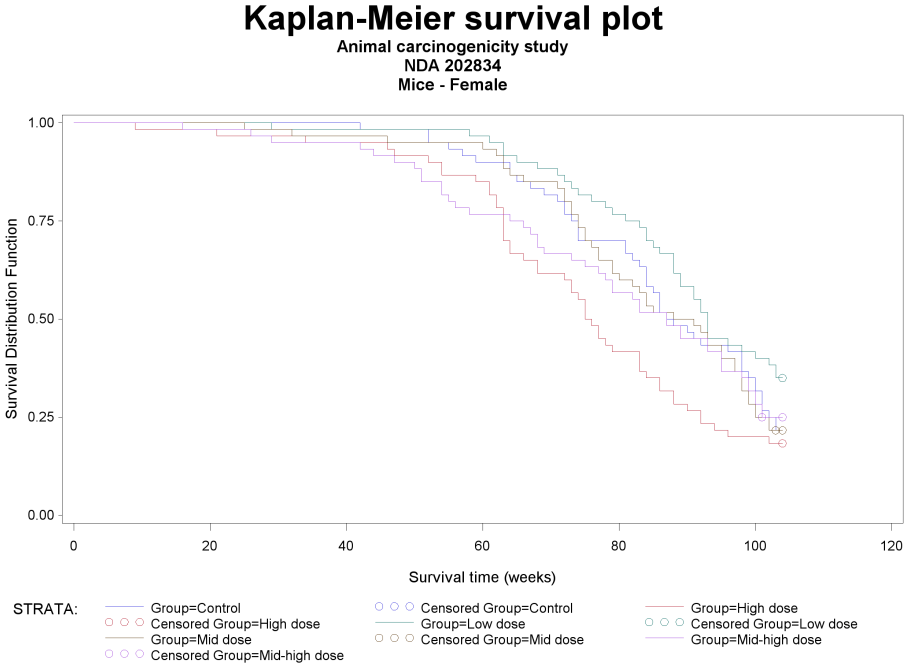
There was no significant increase in the incidence of neoplastic lesions in males or females in any drug-treated group.

2.3 Data analysis

2.3.1 Survival analysis

The Kaplan-Meier survival plots are shown as figures 2.1 and 2.2. The numbers and proportions of animals surviving to various times are presented in table A.1. The results of log-rank tests of heterogeneity of survival and of dose response across the groups are presented in table A.3, and the results of log-rank survival tests comparing the treated groups with the control group are presented in table A.4.

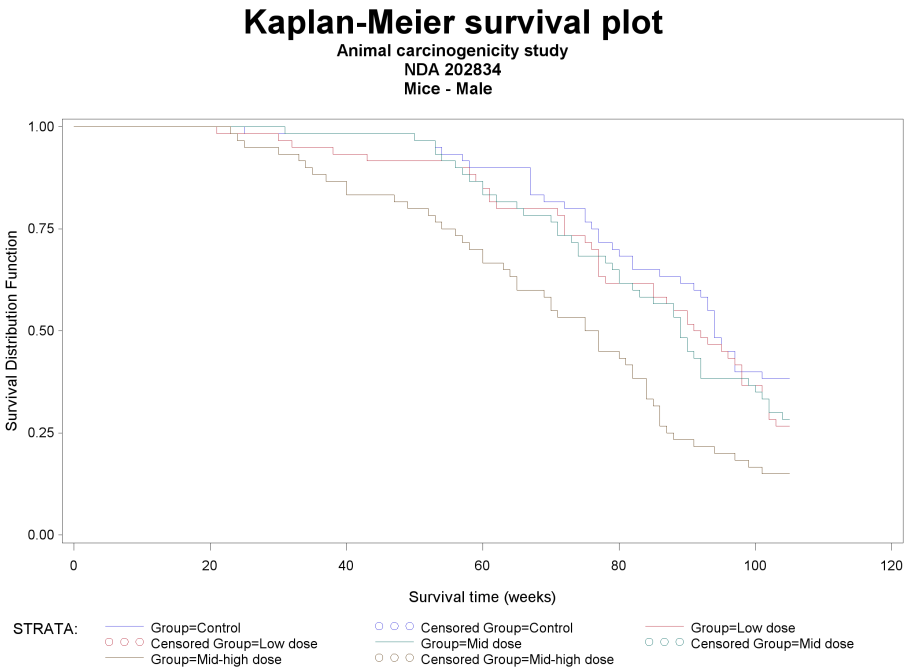
Figure 2.1: Survival curves for female mice



Commentry Among both the female and male mice, there is strong evidence of a dose related increase in mortality; the log-rank test of trend yields p-values of 0.0014 (females) and < 0.0001 (males). The mortality rates for the high dose male group were especially high, with only fifteen animals (25%) surviving to the seventy eighth week, and only ten (17%) surviving to the nintieth week. When this group is excluded from the calculation, the test of trend is still strongly significant ($p < 0.0001$) for an increasing trend in mortality.

No individual groups of treated female mice were found to have a significantly decreased survival rate when compared with the control animals. Among the male groups, however, both the mid-high ($p = 0.0002$) and high dose ($p < 0.0001$) groups experienced significantly higher mortality than the control group.

Figure 2.2: Survival curves for male mice



2.3.2 Tumor analysis

Endpoints

Analyses have been conducted using the sponsor's submitted dataset, and the sponsor's chosen nomenclature. In this dataset, organs or tissue types are described as being either tumorous, examined but found unusable due to autolysis, or unexamined. An organ that has been examined but was not found to be tumorous is not mentioned in the dataset.

From these data, we can infer the numbers of animals for which each organ or tissue type was examined, but only in those cases where at least one anomalous finding (i.e., a tumor was found, or a sample that was planned to be analyzed could not be, either because no sample was taken or becasue the sample was unusable due to autolosys) was reported. Organs which can thus be deduced to have been successfully analyzed in the majority of animals are, for the purposes of this review, considered *primary*. The lists of primary organs in the experiments on female and male mice respectively are presented in tables A.5 and A.6.

Organ or tissue types which were examined in only a few animals are considered *secondary*.

In the mouse study, there are no secondary organs. In fact, there were no organs reported as being unexamined in the mouse study.

Each tumor type found in a primary organ of at least one animal is considered a primary endpoint. In addition, in consultation with Christopher Toscano, PhD, a list of combination endpoints has been drawn up. This list is presented in table A.7.

Statistical procedure

The tumor data were analyzed for dose response relationships and pairwise comparisons of tumor incidence in each of the treated groups versus the control group. Both the dose response relationship tests and pairwise comparisons were performed using the poly-k method described in the paper of Bailer and Portier[1] and developed in the paper of Bieler and Williams[2]. In this method, given a tumor type T, an animal h that lives the full study period (w_m) or dies before the terminal sacrifice

with at least one tumor of type T gets a score of $s_h = 1$. An animal that dies at week w_h before the end of the study without such a tumor gets a score of

$$s_h = \left(\frac{w_h}{w_m}\right)^k < 1.$$

The adjusted group size is defined as $\sum_h s_h$. As an interpretation, an animal with score $s_h = 1$ can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size $\sum s_h$ is equal to N (the original group size) if all animals live up to the end of the study or if each animal develops at least one tumor of type T, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. The test is repeated for each tumor type T.

One critical point to consider in the application of the poly-k test is the choice of the appropriate value of k, which depends on the relationship between tumor onset time and increased dose. For long term 104 week standard rat and mouse studies, a value of $k = 3$ is suggested in the literature, and so has been used in this review. For the calculation of p-values, the exact permutation method was used.

For the adjustment of multiple testing of dose response relationship, the FDA guidance for the carcinogenicity study design and data analysis suggests the use of significance levels $\alpha = 0.005$ for common tumors and $\alpha = 0.025$ for rare tumors for a submission with two species, and a significance level $\alpha = 0.01$ for common tumors and $\alpha = 0.05$ for rare tumors for a submission with one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. For multiple pairwise comparisons of treated group with control, the FDA guidance suggests the use of test levels $\alpha = 0.01$ for common tumors and $\alpha = 0.05$ for rare tumors, for both submissions with one or two species, in order to keep the false-positive rate at the nominal level of approximately 10%.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman [5]. In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin [7] showed that this rule for multiple testing for dose response relationship is also suitable for poly-k tests.

Since this is a study involving two species, it follows that for the comparisons of E2007 with control, we use the thresholds for significance presented in table 2.1.

Table 2.1: Critical p-values used to determine statistical significance

Type of test	Rare tumor	Common tumor
Trend	0.025	0.005
Pairwise test between placebo and high dose	0.05	0.01

Due to the excessive mortality experienced by the high dose male mice, this group has been excluded from the analysis. Results of calculations including these animals are included in appendix B.

An additional problem is caused by the fact that several groups (the mid-high and high dose groups of both sexes and the mid dose female mice) were not dosed uniformly across the entire study; when the number of surviving animals in a group dropped to fifteen, dosing was halted. This raises a question about what the appropriate values of d_i should be. For the following analyses, the value used has been the *average* daily dose level administered to an animal which survived to termination (that is to say, the average of the starting dose and zero, weighted according to the number of weeks that each dosing regimin was applied). This is probably an excessive adjustment, since most animals died prematurely, and so experienced a higher average dose level, and since, from a carcinogenesis perspective, the dose level received during an animal's youth is likely to be more important than dose levels received later in life. Nonetheless, this is not likely to present a significant problem, since the poly-k method used is not, in general, very sensitive to the values of d_i.

The results of the statistical analyses of tumor incidence in primary endpoints are presented in tables A.8 (female mice) and A.9 (male mice). The results of analyses of customized endpoints (see table A.7) are presented in tables A.10 and A.11.

Noteworthy results

Individual tumor types in female mice for which tests yielding p-values below 0.05 were conducted are presented in table A.12, which is excerpted from table A.8. Combination tumor types for which tests yielding p-values below 0.05 were conducted are presented in table A.13, which is excerpted from table A.10. No statistical tests were conducted in the male mouse experiment which resulted in p-values below 0.05.

Uterine tumors The results for endometrial adenomas of the uterus are mildly indicative of a positive effect; the test of trend yields a p-value of 0.0346. However, this result does not remain significant after making an adjustment for multiplicity, Furthermore, none of the pairwise tests yield a significant result; the closest is the comparison between the high dose group and the control group, which has a p-value of 0.1893 (driven by the fact of two cases in the high dose group, and none in the control group). This should therefore be considered a negative finding, despite the consideration of these as rare tumors.

When all endometrial stromal tumors of the uterus are combined, the results are still insufficient to conclude a positive effect. The test of trend yields a p-value of 0.0331, but since these are clearly common tumors, this result does not meet our standards for statistical signficance. Furthermore, none of the treated groups has a significantly higher incidence rate for these tumors than does the control. This is also therefore a negative finding.

Osteomas in female mice The test of trend for all osteomas in female mice, does yield a p-value slightly below 0.05 ($p = 0.0485$), but after discussion with Christopher Toscano, PhD, it has been concluded that these tumors are not sufficiently rare to allow us to relax the our multiplicity adjustments. Furthermore, when osteomas and osteosarcomas are combined, any evidence of a dose related effect goes away; although no cases were reported in the control group, two cases were found in both the low dose group and mid-high groups, one was found in the mid dose group, and none were found in the high dose group. Accordingly, there seems no reason at all to consider this to be a worrying finding.

2.3.3 Analysis of unexamined and autolytic organs

Unexamined animals

No animals have been reported as completely unexamined.

Organs reported autolytic

The numbers of organs found in female mice to be autolytic to the extent that analysis of collected tiussue was not possible are presented in table A.14. The numbers of such organs found in male mice are presented in table A.15.

The only noteworthy autolysis findings in this study are for the gall bladder and the penis. 30% of animals were reported as having their gall bladders unexamined due to autolysis/ These rates were fairly uniform across sexes and across dose groups, except for the high dose male group where the rate was 45%. Autolysis rates for the penis were especially high (38%), and, more worryingly, were concentrated in the higher dose groups. In both cases, the rates are high enough that the study should be considered inconclusive rather than negative.

Organs reported as unexamined

No organs in any animals were reported as being unexamined in this study.

Chapter 3

Rat Study

3.1 Experimental design

This study comprised two experiments, one in male rats and one in female rats. The rats used were Sprague-Dawley rats. Two hundred and forty rats were used in each experiment, divided into four dose groups of sixty animals each. One group of each sex was the control group; animals in these groups received daily doses, by gavage, of the vehicle (0.5 w/v% methylcellulose solution, 10 mL/kg). The remaining three groups, the low, mid, and high dose groups respectively, received doses of E2007, by gavage. These dose levels were 3, 10, and 30 mg/kg per day (females) and 10, 30, and 100mg/day (males).

All animals were observed for mortality and clinical signs once a day. Palpation examination were conducted once a week, and animals underwent a full necroscopy after death.

3.2 Sponsor's analysis

3.2.1 Survival analysis

For each sex, the sponsor plotted Kaplan-Meier survival curves for each dose group, and conducted Tarone-type tests for a dose reponse in survival and pairwise log-rank tests between each treated group and the control group.

Among female rats, no significant survival effects were found. Among male rats, there was no significant evidence of a dose related increase in mortality ($p = 0.1105$), but the high dose group was found to suffer significantly higher mortality than the control group ($p = 0.0245$).

3.2.2 Tumor analysis

The sponsor used Peto's method [6] to test each type of tumor for a dose reaponse, testing across all groups. Also, for each tumor type, Fisher's exact test was used to conduct pairwise comparisons between each treated group and the control group. Whenever the incidence rate was above 5% in al least one group (i.e. at least three animals), Peto's test was again used to conduct a pairwise comparison.

The sponsor concludes that

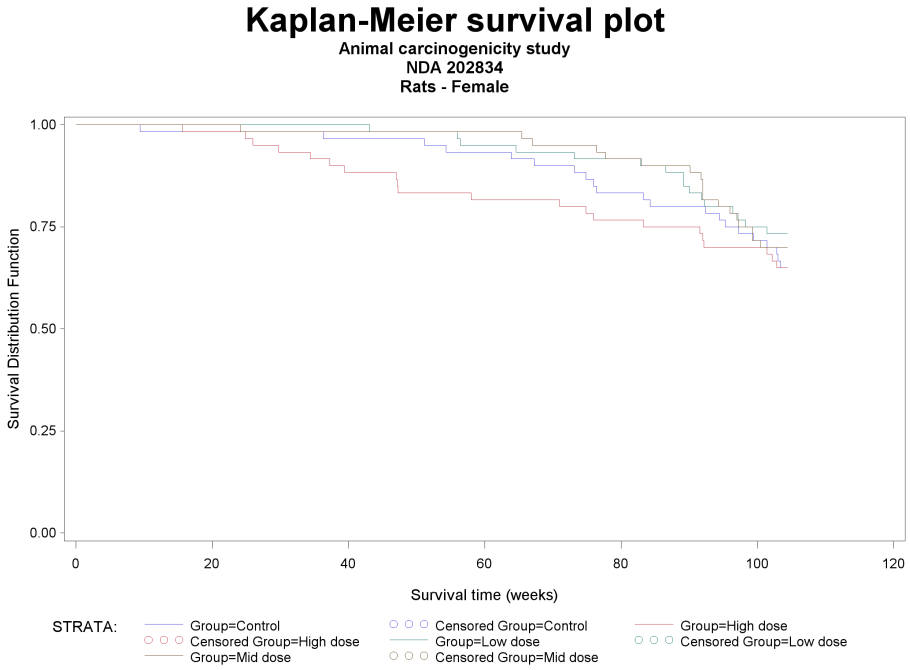
> There were no tumors that showed dose-related positive tendency toward increase in incidence, and pairwise comparison between the control group and each treated group revealed no clear differences.

3.3 Data analysis

3.3.1 Survival analysis

The Kaplan-Meier survival plots are shown as figures 3.1 and 3.2. The numbers and proportions of animals surviving to various times are presented in table C.1. The results of log-rank tests of heterogeneity of survival and of dose response across the groups are presented in table C.2, and the results of log-rank survival tests comparing the treated groups with the control group are presented in table C.3.

Figure 3.1



Commentry In neither sex does the test of trend indicate a dose related increase in mortality. Altghough the Kaplan-Meier plot for female rats does appear to show that the high dose group has experienced higher mortality than the other groups, the pairwise comparison of the high dose group with the control does not yield a significant result ($p = 0.8172$). Conversely, the high dose male group has experienced significantly higher mortality than the control group ($p = 0.0308$), even though this is not apparant from visual inspection of the Kaplan-Meier plot.

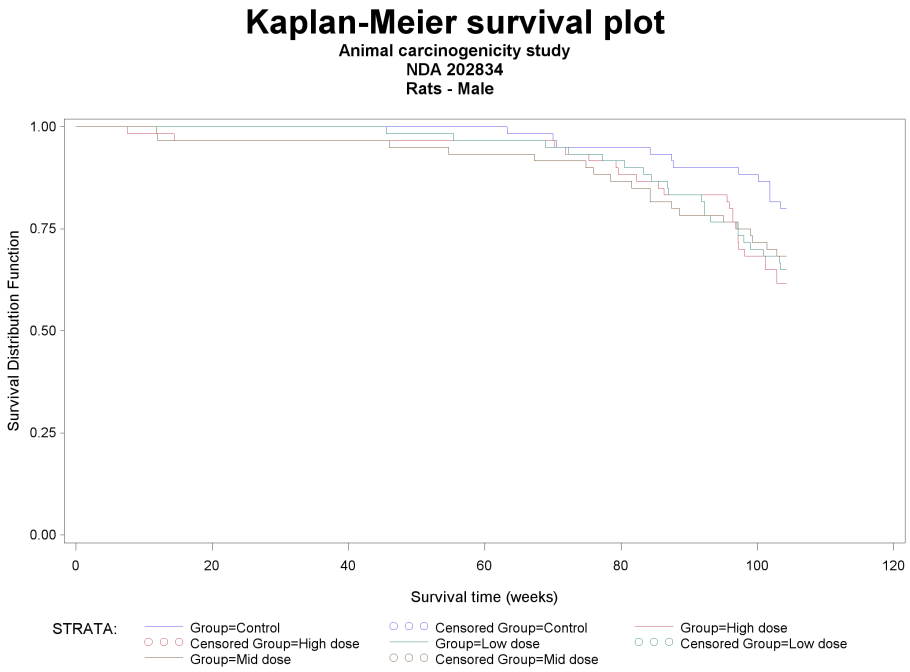
3.3.2 Tumor analysis

Endpoints

As in the mouse study, organs have been classed as either primary or secondary (see Section 2.3.2). The lists of organs adduced to be primary are presented in tables C.4 and C.5. In the rat study, there are no secondary organs.

The same customized endpoints have been analyzed as were considered in the mouse study (see table A.7).

Figure 3.2



Statistical procedure

The same statistical procedures are used to assess tumor incidence in rats are were used in mice (see Section 2.3.2). Note that the critical p-values used to determine significance are presented in table 2.1.

The results of the statistical analyses of tumor incidence in primary endpoints are presented in tables C.6 (female rats) and C.7 (male rats). The results of analyses of customized endpoints (see table A.7) are presented in tables C.8 and C.9.

Noteworthy results

No statistical tests were conducted in the female rat experiment which resulted in p-values below 0.05. Individual tumor types in male rats for which tests yielding p-values below 0.05 were conducted are presented in table C.10, which is excerpted from table C.7. Combination tumor types for which tests yielding p-values below 0.05 were conducted are presented in table C.11, which is excerpted from table C.9.

Keratoacanthimas in male rats The test of trend for keratoacanthomas in male rats yields a p-value below 0.05: $p = 0.0377$. However, since there has been one case reported in the control group, these must be treated as common tumors, and so this result fails to meet the threshold for significance. Furthermore, even though five cases have been reported in the high dose group, this is not sufficient to generate a significant result; the p-value of the pairwise comparison is $p = 0.0828$. Thus this must be considered a negative finding.

3.3.3 Analysis of unexamined and autolytic organs

Unexamined animals

No animals have been reported as completely unexamined.

Organs reported autolytic

No rats were reported as having any organs autolyzed to the extent that a usable sample was not obtainable.

Organs reported as unexamined

The numbers of animals with organs reported as being unexamined are presented in tables C.12 and C.13. No organ was reported as unexamined in enough animals to warrant any concern.

Chapter 4

Assessment of the validity of a negative study

4.1 Issues of concern when selecting the dose levels

The selection of an appropriate dose level for the high dose group is made difficult by the need to satisfy two competing imperatives: on the one hand, if the dose level is insufficiently high, then genuine carcinogenicity effects may not be apparent, but on the other hand, if the dose level is too high, then there is a risk of non-carcinogenic toxic effects killing the animals before they have a chance to demonstrate a carcinogenicity effect.

Haseman [4] suggested that a satisfactory balance between these two imperatives has been found when the following two conditions are both satisfied:

1. Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumors?

2. Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group. The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman [4] has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3Fl mice conducted at the National Toxicology Program (NTP). It was found that, on the average, approximately 50% of the animals in the high dose group survived the two year study period. Also, in a personal communication with Dr. Karl Lin of Division of Biometrics-6, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals or 20 to 30 animals still alive in the high dose group, between weeks 80—90, would be considered as a sufficient number and adequate exposure. In addition Chu, Cueto and Ward [3], suggested that "to be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one year."

It appears, from these three sources that the proportions of survival at 52 weeks, 80–90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the maximum tolerated dose (MTD). In the paper of Chu, Cueto and Ward [3], the following criteria are mentioned for dose adequacy. A high dose is considered as close to MTD if any of the criteria is met:

1. A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls.

2. The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical.

3. In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls.

4.2 Assessment of the validity of the mouse study

The mouse study is a negative study, so it is reasonable to ask whether a sufficient number of animals faced a sufficient tumor challenge to allow us to reach our usual level of confidence in our negative findings.

The mortality levels for the high dose male animals were unacceptably high. However, since four dose groups were included, even once these animals have been excluded, there are three other groups; the survival rates of which were all (just) adequate (with at least twenty seven animals alove at 78 weeks, although the numbers were somewhat lower by 90 weeks). These same mortality data (see table A.1, and the results of the tests of survival (table A.3) however, do allow us to conclude that the dose levels were indeed close to, if not above, then MTD.

The situation with the female mice is similar, except that no group needs to be excluded; survival rates in all groups were (just) acceptable, but provide ample evidence of dose related toxicity (again, see table A.3).

We conclude that the study was indeed adequete.

4.3 Assessment of the validity of the rat study

The rat study is also a negative study, so again it is appropriate to consider whether an adequate tumor challence has been posed to the animals. It is clear from table C.1 that the survival rates were good enough that there is no reason to fear excessive mortality. And in the case of the male rats, the fact that the high dose group experienced significantly higher mortality than the control group means that we can be satisfied with the dose level for this experiment. However, the survival data for the female rat experiment does not show any such effect. Accordingly, we look at the weight changes across the treated groups. Table C.14shows the weight gain across the groups; it is apparent that all treated groups of both male and female rats experienced less weight gain than the corresponding control groups. This in turn suggests that the selected dose levels did indeed pose a reasonable challenge to the animals, and that they were therefore appropriate.

Appendix A

Tables from mouse study

A.1 Survival analysis

Table A.1

Survival rates at key times
NDA 202834
Animal carcinogenicity study
Mice

Species and Sex	*Dose Group*	*Dose (mg per kg)*	*Number at start*	*Number alive after 52 weeks*	*Proportion alive after 52 weeks*	*Number alive after 78 weeks*	*Proportion alive after 78 weeks*	*Number alive after 90 weeks*	*Proportion alive after 90 weeks*	*Number alive at termination*	*Proportion alive at termination*
Mice - Female	Control	0	60	59	98%	42	70%	29	48%	12	20%
	Low dose	1	60	59	98%	48	80%	35	58%	21	35%
	Mid dose	2.94	60	57	95%	39	65%	30	50%	12	20%
	Mid-high dose	9.81	60	51	85%	37	62%	27	45%	13	22%
	High dose	26.8	60	55	92%	27	45%	17	28%	11	18%
Mice - Male	Control	0	60	58	97%	43	72%	37	62%	23	38%
	Low dose	1	60	55	92%	38	63%	33	55%	16	27%
	Mid dose	3	60	58	97%	41	68%	29	48%	18	30%
	Mid-high dose	8.37	60	48	80%	27	45%	14	23%	9	15%
	High dose	24.52	60	37	62%	15	25%	10	17%	5	8.3%

Table A.2

Log-rank tests of survival
NDA 202834
Animal carcinogenicity study
Mice

Sex	*Test of homogeneity: chi squared statistic*	*Test of homogeneity: degrees of freedom*	*Number of groups*	*Test of homogeneity: p-value*	*Test of trend (two tailed): p-value*	*Test of trend (one tailed): p-value*
Female	11.5229	4	5	0.0213	0.0028	0.0014
Male	49.3326	4	5	<.0001	<.0001	<.0001

Table A.3

Log-rank tests of survival
NDA 202834
Animal carcinogenicity study
Mice

Sex	*Test of homogeneity: chi squared statistic*	*Test of homogeneity: degrees of freedom*	*Number of groups*	*Test of homogeneity: p-value*	*Test of trend (two tailed): p-value*	*Test of trend (one tailed): p-value*
Female	11.5229	4	5	0.0213	0.0028	0.0014
Male	17.9674	3	4	0.0004	<.0001	<.0001

Table A.4

Pairwise comparisons (log-rank) of survival between treated groups and controls
NDA 202834
Animal carcinogenicity study
Mice

Species and Sex	*Quantity*	*Low dose*	*Mid dose*	*Mid-high dose*	*High dose*
Mice - Female	Chi squared test statistic	2.0837	0.0211	0.1076	3.3148
	p-value of comparison with control	0.1489	0.8844	0.7429	0.0687
Mice - Male	Chi squared test statistic	1.2010	1.2712	14.1089	32.1526
	p-value of comparison with control	0.2731	0.2595	0.0002	<0.0001

A.2 Tumor analysis

Table A.5

Primary organs in study of female mice
NDA 202834
Animal carcinogenicity study

Organ or tissue name
Adrenal
Aorta,thoracic
Body cavity,abdominal
Body cavity,thoracic
Bone+Bone marrow,femoral
Clitoral gland
Ear
Eye
Forelimb
Gallbladder
Harderian gland
Hemolymphoreticular(all sites)
Hindlimb
Intestine,cecum
Intestine,colon
Intestine,duodenum
Intestine,ileum
Intestine,jejunum
Intestine,rectum
Lacrimal gland,extraorbital
Liver
Lung(bronchus)
Lymph node,mesenteric
Lymph node,nos
Mammary gland
Maxilla
Optic nerve
Ovary
Parathyroid
Pituitary
Rib
Skeletal system(all sites)
Skin
Spleen
Stomach
Submaxilla
Tail
Thymus

Primary organs in study of female mice
NDA 202834
Animal carcinogenicity study

Organ or tissue name
Thyroid
Tongue
Ureter
Urinary bladder
Uterus
Vagina
Vertebra

Table A.6

Primary organs in study of male mice
NDA 202834
Animal carcinogenicity study

Organ or tissue name
Adrenal
Body cavity,abdominal
Body cavity,thoracic
Bulbocavernosus muscle
Cerebrum
Coagulating gland
Ear
Esophagus
Forelimb
Gallbladder
Harderian gland
Hemolymphoreticular(all sites)
Hindlimb
Intestine,cecum
Intestine,colon
Intestine,duodenum
Intestine,ileum
Intestine,jejunum
Intestine,rectum
Kidney
Liver
Lung(bronchus)
Lymph node,mesenteric
Lymph node,nos
Lymph node,submandibular
Maxilla
Orbital cavity
Pancreas
Parathyroid
Penis
Pituitary
Preputial gland
Seminal vesicle
Skeletal system(all sites)
Skin
Skull
Spinal cord
Spleen

Primary organs in study of male mice
NDA 202834
Animal carcinogenicity study

Organ or tissue name
Stomach
Submaxilla
Tail
Testis
Thymus
Thyroid
Tongue
Trachea
Ureter
Urinary bladder
Vertebra

Table A.7

Customized and combination endpoints analyzed
NDA 202834
Animal carcinogenicity study

Composite endpoint
All pheochromoctoymas
Basal cell tumors
Bronchioalveolar adenomas and carcinomas
C-cell tumors
Cortical cell adenomas and carcinomas
Endometrial adenomas and carcinomas (uterine)
Endometrial stromal tumors (uterine)
Fibrosarcomas of the ear, skin, and tail
Folicular cell tumors
Gliomas
Hemangiomas and hemangiosarcomas
Hemangiomas and hemangiosarcomas of the liver
Hemangiomas and hemangiosarcomas of the spleen
Hemangiomas and hemangiosarcomas of the uterus
Hepatocellular tumors
Intestinal adenomas and adenocarcinomas
Islet cell adenomas and carcinomas
Keratoacanthomas and squamous cell carcinomas (ear, skin, tail)
Leiomyomas and leiomyosarcomas of the GI tract
Leiomyomas and leiomyosarcomas of the ovary and uterus
Leiomyomas and leiomyosarcomas of the uterus
Lipomas and liposarcomas
Malignant schwannomas
Mammary adenomas and adenocarcinomas
Mesothelioma
Osteomas
Osteomas and osteosarcomas
Papillomas and squamous cell carcinomas (ear, skin, tail)
Pituitary adenomas and carcinomas
Pituitary pars distalis tumors
Squamous cell carcinomas (ear, skin, tail)
Stromal cell tumors (vaginal)
Subcapsular cell adenomas and carcinomas

Table A.8

Table of reported tumors in Mouse Study
NDA 202834
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*Mid-high dose*	*High dose*
Adrenal	ADENOMA,SUBCAPSULAR CELL	P-value of test of trend or comparison	.3483			.4789	
		Number of animals reported with tumor	0	0	0	1	0
	CARCINOMA,SUBCAPSULAR CELL	P-value of test of trend or comparison	1	1	1	1	1
		Number of animals reported with tumor	1	0	0	0	0
	PHEOCHROMOCYTOMA	P-value of test of trend or comparison	.8539	.2795	.2466		
		Number of animals reported with tumor	0	2	2	0	0
	PHEOCHROMOCYTOMA,MALIGNANT	P-value of test of trend or comparison	.7921	.5316			
		Number of animals reported with tumor	0	1	0	0	0
Bone+Bone marrow,femoral	OSTEOMA	P-value of test of trend or comparison	.3483			.4789	
		Number of animals reported with tumor	0	0	0	1	0
Ear	CARCINOMA,SQUAMOUS CELL	P-value of test of trend or comparison	.7910	.5316			
		Number of animals reported with tumor	0	1	0	0	0
Gallbladder	PAPILLOMA	P-value of test of trend or comparison	.7971	.5410			
		Number of animals reported with tumor	0	1	0	0	0
Harderian gland	ADENOMA	P-value of test of trend or comparison	.5241	.8235	1	.9641	.8265
		Number of animals reported with tumor	4	3	0	1	2
Hemolymphoreticular(all sites)	LYMPHOMA,MALIGNANT	P-value of test of trend or comparison	.8774	.9850	.9675	.9483	.9844
		Number of animals reported with tumor	16	8	8	8	5
	SARCOMA,HISTIOCYTIC	P-value of test of trend or comparison	.7638	.1944	.6825	.2982	.8239
		Number of animals reported with tumor	2	6	2	4	1
Intestine,duodenum	ADENOMA	P-value of test of trend or comparison	.5607		.5068		
		Number of animals reported with tumor	0	0	1	0	0
Intestine,jejunum	ADENOMA	P-value of test of trend or comparison	.5581		.5070		
		Number of animals reported with tumor	0	0	1	0	0
Liver	ADENOMA,HEPATOCELLULAR	P-value of test of trend or comparison	.0867	.3072	1	.3094	.2304
		Number of animals reported with tumor	3	6	0	5	5
	CARCINOMA,HEPATOCELLULAR	P-value of test of trend or comparison	.5766	1	1	.7320	1

Table A.8

Table of reported tumors in Mouse Study
NDA 202834
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*Mid-high dose*	*High dose*
		Number of animals reported with tumor	1	0	0	1	0
	HEMANGIOMA	P-value of test of trend or comparison	.8016	1	.7467	1	1
		Number of animals reported with tumor	1	0	1	0	0
	HEMANGIOSARCOMA	P-value of test of trend or comparison	.8338	.9791	.5000	.9641	.9438
		Number of animals reported with tumor	4	1	5	1	1
Lung(bronchus)	ADENOMA,BRONCHIOLO-ALVEOLAR	P-value of test of trend or comparison	.9249	.1941	.2834	.7977	.8188
		Number of animals reported with tumor	6	11	9	4	3
	CARCINOMA,BRONCHIOLO-ALVEOLAR	P-value of test of trend or comparison	.2560	.5796	.3852	.7366	.3284
		Number of animals reported with tumor	4	5	6	3	5
Mammary gland	ADENOACANTHOMA,MALIGNANT	P-value of test of trend or comparison	.6398	.5316	.2466	.4789	
		Number of animals reported with tumor	0	1	2	1	0
	ADENOCARCINOMA	P-value of test of trend or comparison	.5139	.9562	.9851	.8314	.8865
		Number of animals reported with tumor	5	2	1	3	2
Ovary	CYSTADENOMA	P-value of test of trend or comparison	.2758	.5316	.5000		.4394
		Number of animals reported with tumor	0	1	1	0	1
	LEIOMYOMA	P-value of test of trend or comparison	.3483			.4789	
		Number of animals reported with tumor	0	0	0	1	0
	LEIOMYOSARCOMA	P-value of test of trend or comparison	.1501		.5000		.4308
		Number of animals reported with tumor	0	0	1	0	1
	LUTEOMA	P-value of test of trend or comparison	1	1	1	1	1
		Number of animals reported with tumor	1	0	0	0	0
	SERTOLI CELL TUMOR	P-value of test of trend or comparison	.3483			.4789	
		Number of animals reported with tumor	0	0	0	1	0
	SEX CORD STROMAL TUMOR,MIXED	P-value of test of trend or comparison	1	1	1	1	1
		Number of animals reported with tumor	1	0	0	0	0
Parathyroid	ADENOMA	P-value of test of trend or comparison	.7927	.5278			
		Number of animals reported with tumor	0	1	0	0	0

Table A.8

Table of reported tumors in Mouse Study
NDA 202834
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*Mid-high dose*	*High dose*
Pituitary	ADENOMA,PARS DISTALIS	P-value of test of trend or comparison	.0758	.5380	.7467	.4578	.2121
		Number of animals reported with tumor	1	2	1	2	3
	ADENOMA,PARS INTERMEDIA	P-value of test of trend or comparison	.4401	.7775	.7467	1	.6820
		Number of animals reported with tumor	1	1	1	0	1
Rib	OSTEOMA	P-value of test of trend or comparison	.3483			.4789	
		Number of animals reported with tumor	0	0	0	1	0
Skeletal system(all sites)	OSTEOSARCOMA	P-value of test of trend or comparison	.8591	.2795			
		Number of animals reported with tumor	0	2	0	0	0
Skin	CARCINOMA,SQUAMOUS CELL	P-value of test of trend or comparison	1	1	1	1	1
		Number of animals reported with tumor	1	0	0	0	0
	FIBROSARCOMA	P-value of test of trend or comparison	1	1	1	1	1
		Number of animals reported with tumor	1	0	0	0	0
	KERATOACANTHOMA	P-value of test of trend or comparison	.3483			.4789	
		Number of animals reported with tumor	0	0	0	1	0
	LEIOMYOSARCOMA	P-value of test of trend or comparison	.8016	1	.7467	1	1
		Number of animals reported with tumor	1	0	1	0	0
	LIPOSARCOMA	P-value of test of trend or comparison	.5045	.1452	.5000		.4308
		Number of animals reported with tumor	0	3	1	0	1
	RHABDOMYOSARCOMA	P-value of test of trend or comparison	.5562		.5000		
		Number of animals reported with tumor	0	0	1	0	0
Spleen	HEMANGIOMA	P-value of test of trend or comparison	.7921	.5316			
		Number of animals reported with tumor	0	1	0	0	0
	HEMANGIOSARCOMA	P-value of test of trend or comparison	.2970	1	1	1	.6820
		Number of animals reported with tumor	1	0	0	0	1
Stomach	CARCINOMA,SQUAMOUS CELL	P-value of test of trend or comparison	.8591	.2795			
		Number of animals reported with tumor	0	2	0	0	0
	PAPILLOMA	P-value of test of trend or comparison	.2263	.5316	.5000	.4789	.4394

Table A.8

Table of reported tumors in Mouse Study
NDA 202834
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*Mid-high dose*	*High dose*
		Number of animals reported with tumor	0	1	1	1	1
Uterus	ADENOMA,ENDOMETRIAL	P-value of test of trend or comparison	.0346		.5000		.1893
		Number of animals reported with tumor	0	0	1	0	2
	CARCINOMA,ENDOMETRIAL	P-value of test of trend or comparison	.4778	1	1	.4578	1
		Number of animals reported with tumor	1	0	0	2	0
	HEMANGIOMA	P-value of test of trend or comparison	.5562		.5000		
		Number of animals reported with tumor	0	0	1	0	0
	HEMANGIOSARCOMA	P-value of test of trend or comparison	.7689	.8973	.8751	.6609	1
		Number of animals reported with tumor	2	1	1	2	0
	LEIOMYOMA	P-value of test of trend or comparison	.8575	.8973	.6825	.8586	1
		Number of animals reported with tumor	2	1	2	1	0
	LEIOMYOSARCOMA	P-value of test of trend or comparison	.0679	.7775	.4899	.7250	.2121
		Number of animals reported with tumor	1	1	2	1	3
	POLYP,ENDOMETRIAL STROMAL	P-value of test of trend or comparison	.5112	.9893	.7104	.5273	.8797
		Number of animals reported with tumor	7	2	6	7	3
	SARCOMA,ENDOMETRIAL STROMAL	P-value of test of trend or comparison	.1759	.8907	.6148	.2817	.4767
		Number of animals reported with tumor	5	3	5	7	5
	SCHWANNOMA	P-value of test of trend or comparison	.7921	.5316			
		Number of animals reported with tumor	0	1	0	0	0
Vagina	POLYP,VAGINAL STROMAL	P-value of test of trend or comparison	.7921	.5316			
		Number of animals reported with tumor	0	1	0	0	0
	SARCOMA,VAGINAL STROMAL	P-value of test of trend or comparison	.7921	.5316			
		Number of animals reported with tumor	0	1	0	0	0
Vertebra	OSTEOMA	P-value of test of trend or comparison	.5562		.5000		
		Number of animals reported with tumor	0	0	1	0	0

Table A.9

Table of reported tumors in Mouse Study
NDA 202834
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*Mid-high dose*
Adrenal	ADENOMA,CORTICAL CELL	P-value of test of trend or comparison	.2279	.4744		.3881
		Number of animals reported with tumor	0	1	0	1
	PHEOCHROMOCYTOMA	P-value of test of trend or comparison	.1844			.3881
		Number of animals reported with tumor	0	0	0	1
Cerebrum	ASTROCYTOMA,MALIGNANT	P-value of test of trend or comparison	.7092	.4810		
		Number of animals reported with tumor	0	1	0	0
	MENINGIOMA,MALIGNANT	P-value of test of trend or comparison	.7092	.4810		
		Number of animals reported with tumor	0	1	0	0
Gallbladder	PAPILLOMA	P-value of test of trend or comparison	.9705	.8502	1	1
		Number of animals reported with tumor	2	1	0	0
Harderian gland	ADENOMA	P-value of test of trend or comparison	.9072	.5676	.4209	.9722
		Number of animals reported with tumor	6	6	7	1
Hemolymphoreticular(all sites)	LYMPHOMA,MALIGNANT	P-value of test of trend or comparison	.9720	.4635	1	1
		Number of animals reported with tumor	2	3	0	0
	SARCOMA,HISTIOCYTIC	P-value of test of trend or comparison	.6544	.3139	.2895	.7775
		Number of animals reported with tumor	2	4	4	1
Intestine,ileum	ADENOCARCINOMA	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
Intestine,jejunum	ADENOMA	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
Kidney	NEPHROBLASTOMA	P-value of test of trend or comparison	.1786			.3788
		Number of animals reported with tumor	0	0	0	1
Liver	ADENOMA,HEPATOCELLULAR	P-value of test of trend or comparison	.0877	.2710	.5154	.0960
		Number of animals reported with tumor	13	16	12	15
	CARCINOMA,HEPATOCELLULAR	P-value of test of trend or comparison	.8791	.4370	.8612	.9143
		Number of animals reported with tumor	4	5	2	1
	HEMANGIOMA	P-value of test of trend or comparison	.8381	.8745	1	.9224

Table A.9

Table of reported tumors in Mouse Study
NDA 202834
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*Mid-high dose*
		Number of animals reported with tumor	4	2	0	1
	HEMANGIOSARCOMA	P-value of test of trend or comparison	.9103	.6131	.6131	1
		Number of animals reported with tumor	3	3	3	0
Lung(bronchus)	ADENOMA,BRONCHIOLO-ALVEOLAR	P-value of test of trend or comparison	.1640	.3421	.5813	.2012
		Number of animals reported with tumor	5	7	5	6
	CARCINOMA,BRONCHIOLO-ALVEOLAR	P-value of test of trend or comparison	.7508	.6748	.6930	.8483
		Number of animals reported with tumor	7	6	6	3
Pancreas	ADENOMA,ISLET CELL	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
Pituitary	ADENOMA,PARS DISTALIS	P-value of test of trend or comparison	.1871			.3939
		Number of animals reported with tumor	0	0	0	1
	CARCINOMA,ANTERIOR	P-value of test of trend or comparison	.7101	.4805		
		Number of animals reported with tumor	0	1	0	0
Seminal vesicle	ADENOMA	P-value of test of trend or comparison	.6347	.2282	.4744	
		Number of animals reported with tumor	0	2	1	0
Skeletal system(all sites)	OSTEOSARCOMA	P-value of test of trend or comparison	.7591	.2282		
		Number of animals reported with tumor	0	2	0	0
Skin	CARCINOMA,SQUAMOUS CELL	P-value of test of trend or comparison	.4429		.4744	
		Number of animals reported with tumor	0	0	1	0
	HEMANGIOSARCOMA	P-value of test of trend or comparison	.1786			.3788
		Number of animals reported with tumor	0	0	0	1
Spinal cord	ASTROCYTOMA	P-value of test of trend or comparison	.1844			.3881
		Number of animals reported with tumor	0	0	0	1
Spleen	HEMANGIOMA	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
Tail	HEMANGIOMA	P-value of test of trend or comparison	.1857			.3881
		Number of animals reported with tumor	0	0	0	1

Table A.9

Table of reported tumors in Mouse Study
NDA 202834
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*Mid-high dose*
Testis	LEYDIG CELL TUMOR	P-value of test of trend or comparison	.5355	.4744	.4744	
		Number of animals reported with tumor	0	1	1	0
	SEMINOMA	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
Thyroid	ADENOMA,FOLLICULAR CELL	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
	CARCINOMA,FOLLICULAR CELL	P-value of test of trend or comparison	.7122	.4805		
		Number of animals reported with tumor	0	1	0	0
Urinary bladder	PAPILLOMA	P-value of test of trend or comparison	.4370		.4667	
		Number of animals reported with tumor	0	0	1	0

Table A.10

Table of reported tumors in Mouse Study
NDA 202834
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*Mid-high dose*	*High dose*
All pheochromoctoymas	P-value of test of trend or comparison	.9073	.1502	.2466		
	Number of animals reported with tumor	0	3	2	0	0
Bronchioalveolar adenomas and carcinomas	P-value of test of trend or comparison	.7881	.3275	.1874	.7852	.6395
	Number of animals reported with tumor	10	14	15	7	7
Endometrial adenomas and carcinomas (uterine)	P-value of test of trend or comparison	.0799	1	.7467	.4578	.3983
	Number of animals reported with tumor	1	0	1	2	2
Endometrial stromal tumors (uterine)	P-value of test of trend or comparison	.2083	.9665	.5000	.2111	.5758
	Number of animals reported with tumor	10	5	11	13	8
Fibrosarcomas of the ear, skin, and tail	P-value of test of trend or comparison	1	1	1	1	1
	Number of animals reported with tumor	1	0	0	0	0
Hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.8446	.9893	.6155	.9433	.9595
	Number of animals reported with tumor	7	2	7	3	2
Hemangiomas and hemangiosarcomas of the liver	P-value of test of trend or comparison	.8982	.9908	.5000	.9823	.9696
	Number of animals reported with tumor	5	1	6	1	1
Hemangiomas and hemangiosarcomas of the spleen	P-value of test of trend or comparison	.3965	.7775	1	1	.6820
	Number of animals reported with tumor	1	1	0	0	1
Hemangiomas and hemangiosarcomas of the uterus	P-value of test of trend or comparison	.8064	.8973	.6825	.6609	1
	Number of animals reported with tumor	2	1	2	2	0
Hepatocellular tumors	P-value of test of trend or comparison	.0817	.3072	1	.1997	.2304
	Number of animals reported with tumor	3	6	0	6	5
Intestinal adenomas and adenocarcinomas	P-value of test of trend or comparison	.6182		.2533		
	Number of animals reported with tumor	0	0	2	0	0
Keratoacanthomas and squamous cell carcinomas (ear, skin, tail)	P-value of test of trend or comparison	.6978	.7775	1	.7250	1
	Number of animals reported with tumor	1	1	0	1	0
Leiomyomas and leiomyosarcomas of the ovary and uterus	P-value of test of trend or comparison	.3006	.8427	.4852	.7755	.5125
	Number of animals reported with tumor	3	2	4	2	3
Leiomyomas and leiomyosarcomas of the uterus	P-value of test of trend or comparison	.3006	.8427	.4852	.7755	.5125

Table A.10

Table of reported tumors in Mouse Study
NDA 202834
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*Mid-high dose*	*High dose*
	Number of animals reported with tumor	3	2	4	2	3
Lipomas and liposarcomas	P-value of test of trend or comparison	.5045	.1452	.5000		.4308
	Number of animals reported with tumor	0	3	1	0	1
Mammary adenomas and adenocarcinomas	P-value of test of trend or comparison	.5139	.9562	.9851	.8314	.8865
	Number of animals reported with tumor	5	2	1	3	2
Osteomas	P-value of test of trend or comparison	.4324		.5000	.2258	
	Number of animals reported with tumor	0	0	1	2	0
Osteomas and osteosarcomas	P-value of test of trend or comparison	.6487	.2795	.5000	.2258	
	Number of animals reported with tumor	0	2	1	2	0
Papillomas and squamous cell carcinomas (ear, skin, tail)	P-value of test of trend or comparison	.9559	.7775	1	1	1
	Number of animals reported with tumor	1	1	0	0	0
Pituitary adenomas and carcinomas	P-value of test of trend or comparison	.1026	.5480	.6825	.6495	.2309
	Number of animals reported with tumor	2	3	2	2	4
Pituitary pars distalis tumors	P-value of test of trend or comparison	.0758	.5380	.7467	.4578	.2121
	Number of animals reported with tumor	1	2	1	2	3
Squamous cell carcinomas (ear, skin, tail)	P-value of test of trend or comparison	.9559	.7775	1	1	1
	Number of animals reported with tumor	1	1	0	0	0
Stromal cell tumors (vaginal)	P-value of test of trend or comparison	.8591	.2795			
	Number of animals reported with tumor	0	2	0	0	0
Subcapsular cell adenomas and carcinomas	P-value of test of trend or comparison	.5766	1	1	.7320	1
	Number of animals reported with tumor	1	0	0	1	0

Table A.11

Table of reported tumors in Mouse Study
NDA 202834
Animal carcinogenicity study
Male mice
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*Mid-high dose*	*High dose*
All pheochromoctoymas	P-value of test of trend or comparison	.1844			.3881	
	Number of animals reported with tumor	0	0	0	1	
Bronchioalveolar adenomas and carcinomas	P-value of test of trend or comparison	.4234	.4449	.5455	.4820	
	Number of animals reported with tumor	11	12	11	8	
Cortical cell adenomas and carcinomas	P-value of test of trend or comparison	.2279	.4744		.3881	
	Number of animals reported with tumor	0	1	0	1	
Folicular cell tumors	P-value of test of trend or comparison	.9187	.7334	1	1	
	Number of animals reported with tumor	1	1	0	0	
Hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.7205	.7729	.9384	.8231	
	Number of animals reported with tumor	7	5	3	3	
Hemangiomas and hemangiosarcomas of the liver	P-value of test of trend or comparison	.9429	.6792	.8970	.9722	
	Number of animals reported with tumor	6	5	3	1	
Hemangiomas and hemangiosarcomas of the spleen	P-value of test of trend or comparison	1	1	1	1	
	Number of animals reported with tumor	1	0	0	0	
Hepatocellular tumors	P-value of test of trend or comparison	.1855	.2728	.6872	.1803	
	Number of animals reported with tumor	17	20	13	16	
Intestinal adenomas and adenocarcinomas	P-value of test of trend or comparison	1	1	1	1	
	Number of animals reported with tumor	2	0	0	0	
Islet cell adenomas and carcinomas	P-value of test of trend or comparison	1	1	1	1	
	Number of animals reported with tumor	1	0	0	0	
Keratoacanthomas and squamous cell carcinomas (ear, skin, tail)	P-value of test of trend or comparison	.4429		.4744		
	Number of animals reported with tumor	0	0	1	0	
Osteomas and osteosarcomas	P-value of test of trend or comparison	.7591	.2282			
	Number of animals reported with tumor	0	2	0	0	
Papillomas and squamous cell carcinomas (ear, skin, tail)	P-value of test of trend or comparison	.4429		.4744		
	Number of animals reported with tumor	0	0	1	0	
Pituitary adenomas and carcinomas	P-value of test of trend or comparison	.2318	.4805		.3939	

Table A.11

Table of reported tumors in Mouse Study
NDA 202834
Animal carcinogenicity study
Male mice
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*Mid-high dose*	*High dose*
	Number of animals reported with tumor	0	1	0	1	
Pituitary pars distalis tumors	P-value of test of trend or comparison	.1871			.3939	
	Number of animals reported with tumor	0	0	0	1	
Squamous cell carcinomas (ear, skin, tail)	P-value of test of trend or comparison	.4429		.4744		
	Number of animals reported with tumor	0	0	1	0	

Table A.12

Table of tumors reported significant in at least one arm - Mouse Study
NDA 202834
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*Mid-high dose*	*High dose*
Uterus	ADENOMA,ENDOMETRIAL	P-value of test of trend or comparison	.0346		.5000		.1893
		Number of animals reported with tumor	0	0	1	0	2
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.7%	0.0%	6.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,9.5)	(0,8.4)	(0.07,14.2)	(0,10.3)	(0.82,22.8)
		Poly-3 adjusted number of animals at risk	38.0	42.2	37.2	34.1	29.3

Table A.13

Table of tumors reported significant in at least one arm - Mouse Study
NDA 202834
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*Mid-high dose*
Endometrial stromal tumors (uterine)	P-value of test of trend or comparison	.0331	.9665	.5000	.2111
	Number of animals reported with tumor	10	5	11	13
	Poly-3 adjusted incidence rate	25%	12%	27%	36%
	95% CI for poly-3 adjusted incidence rate (%)	(12.4,41.2)	(3.89,25.6)	(14.2,43.9)	(20.2,53.8)
	Poly-3 adjusted number of animals at risk	40.5	43.0	40.5	36.6
Osteomas	P-value of test of trend or comparison	.0485		.5000	.2258
	Number of animals reported with tumor	0	0	1	2
	Poly-3 adjusted incidence rate	0.0%	0.0%	2.7%	5.8%
	95% CI for poly-3 adjusted incidence rate (%)	(0,9.5)	(0,8.4)	(0.07,14.2)	(0.7,19.7)
	Poly-3 adjusted number of animals at risk	38.0	42.2	37.6	34.3

A.3 Unexamined and autolytic organs

Table A.14

Organs reported as autolytic
NDA 202834
Animal carcinogenicity study
Female Mice

Organ or tissue name	Control(count)	Control(%)	Low dose(count)	Low dose(%)	Mid dose(count)	Mid dose(%)	Mid-high dose(count)	Mid-high dose(%)	High dose(count)	High dose(%)	Total(count)	Total(%)
Aorta,thoracic	.	.	.	.	.	.	1	1.7%	.	.	1	0.3%
Body cavity,abdominal	1	1.7%	2	3.3%	1	1.7%	1	1.7%	.	.	5	1.7%
Body cavity,thoracic	.	.	1	1.7%	.	.	1	1.7%	.	.	2	0.7%
Clitoral gland	2	3.3%	2	3.3%	.	.	1	1.7%	.	.	5	1.7%
Ear	1	1.7%	.	.	1	1.7%	.	.	.	.	2	0.7%
Eye	.	.	.	.	.	.	1	1.7%	.	.	1	0.3%
Forelimb	.	.	.	.	2	3.3%	6	10%	5	8.3%	13	4.3%
Gallbladder	16	27%	16	27%	19	32%	13	22%	16	27%	80	27%
Hindlimb	2	3.3%	1	1.7%	3	5.0%	.	.	1	1.7%	7	2.3%
Intestine,cecum	9	15%	6	10%	4	6.7%	5	8.3%	2	3.3%	26	8.7%
Intestine,colon	1	1.7%	.	.	.	.	.	.	.	.	1	0.3%
Intestine,duodenum	2	3.3%	4	6.7%	.	.	3	5.0%	1	1.7%	10	3.3%
Intestine,ileum	2	3.3%	3	5.0%	.	.	2	3.3%	1	1.7%	8	2.7%
Intestine,jejunum	3	5.0%	1	1.7%	1	1.7%	3	5.0%	4	6.7%	12	4.0%
Intestine,rectum	.	.	.	.	.	.	.	.	1	1.7%	1	0.3%
Lacrimal gland,extraorbital	.	.	.	.	.	.	1	1.7%	.	.	1	0.3%
Lymph node,mesenteric	2	3.3%	2	3.3%	.	.	2	3.3%	2	3.3%	8	2.7%
Lymph node,nos	14	23%	7	12%	8	13%	6	10%	3	5.0%	38	13%
Mammary gland	.	.	1	1.7%	.	.	.	.	.	.	1	0.3%
Maxilla	.	.	.	.	.	.	.	.	1	1.7%	1	0.3%
Optic nerve	.	.	1	1.7%	3	5.0%	1	1.7%	4	6.7%	9	3.0%
Ovary	.	.	.	.	.	.	1	1.7%	.	.	1	0.3%
Parathyroid	4	6.7%	7	12%	1	1.7%	2	3.3%	11	18%	25	8.3%
Spleen	1	1.7%	.	.	.	.	.	.	.	.	1	0.3%
Submaxilla	.	.	.	.	.	.	3	5.0%	1	1.7%	4	1.3%
Tail	.	.	1	1.7%	.	.	1	1.7%	2	3.3%	4	1.3%
Thymus	2	3.3%	3	5.0%	3	5.0%	4	6.7%	4	6.7%	16	5.3%

Table A.14

Organs reported as autolytic
NDA 202834
Animal carcinogenicity study
Female Mice

Organ or tissue name	*Control(count)*	*Control(%)*	*Low dose(count)*	*Low dose(%)*	*Mid dose(count)*	*Mid dose(%)*	*Mid-high dose(count)*	*Mid-high dose(%)*	*High dose(count)*	*High dose(%)*	*Total(count)*	*Total(%)*
Thyroid	.	.	1	1.7%	.	.	.	.	.	.	1	0.3%
Tongue	.	.	1	1.7%	.	.	.	.	.	.	1	0.3%
Ureter	.	.	.	.	.	.	1	1.7%	.	.	1	0.3%
Urinary bladder	2	3.3%	.	.	.	.	.	.	.	.	2	0.7%

Table A.15

Organs reported as autolytic
NDA 202834
Animal carcinogenicity study
Male Mice

Organ or tissue name	*Control(count)*	*Control(%)*	*Low dose(count)*	*Low dose(%)*	*Mid dose(count)*	*Mid dose(%)*	*Mid-high dose(count)*	*Mid-high dose(%)*	*High dose(count)*	*High dose(%)*	*Total(count)*	*Total(%)*
Adrenal	.	.	1	1.7%	.	.	.	.	.	.	1	0.3%
Body cavity,abdominal	.	.	2	3.3%	.	.	.	.	1	1.7%	3	1.0%
Body cavity,thoracic	1	1.7%	.	.	1	1.7%	.	.	.	.	2	0.7%
Bulbocavernosus muscle	1	1.7%	.	.	.	.	.	.	.	.	1	0.3%
Coagulating gland	1	1.7%	1	1.7%	1	1.7%	.	.	.	.	3	1.0%
Ear	1	1.7%	1	1.7%	1	1.7%	.	.	.	.	3	1.0%
Esophagus	1	1.7%	.	.	.	.	.	.	.	.	1	0.3%
Forelimb	.	.	1	1.7%	.	.	3	5.0%	5	8.3%	9	3.0%
Gallbladder	13	22%	15	25%	22	37%	18	30%	29	48%	97	32%
Hindlimb	3	5.0%	1	1.7%	2	3.3%	1	1.7%	3	5.0%	10	3.3%
Intestine,cecum	6	10%	8	13%	9	15%	9	15%	8	13%	40	13%
Intestine,colon	2	3.3%	1	1.7%	1	1.7%	.	.	.	.	4	1.3%
Intestine,duodenum	3	5.0%	4	6.7%	3	5.0%	4	6.7%	7	12%	21	7.0%
Intestine,ileum	3	5.0%	2	3.3%	5	8.3%	1	1.7%	3	5.0%	14	4.7%
Intestine,jejunum	4	6.7%	3	5.0%	6	10%	9	15%	2	3.3%	24	8.0%
Intestine,rectum	.	.	1	1.7%	.	.	.	.	1	1.7%	2	0.7%
Lymph node,mesenteric	4	6.7%	.	.	.	.	7	12%	2	3.3%	13	4.3%
Lymph node,nos	5	8.3%	5	8.3%	2	3.3%	.	.	1	1.7%	13	4.3%
Lymph node,submandibular	.	.	.	.	.	.	1	1.7%	.	.	1	0.3%
Maxilla	.	.	1	1.7%	.	.	.	.	.	.	1	0.3%
Orbital cavity	.	.	.	.	.	.	2	3.3%	.	.	2	0.7%
Parathyroid	9	15%	9	15%	11	18%	5	8.3%	7	12%	41	14%
Penis	20	33%	18	30%	27	45%	27	45%	37	62%	129	43%
Pituitary	1	1.7%	.	.	1	1.7%	.	.	.	.	2	0.7%
Preputial gland	1	1.7%	1	1.7%	4	6.7%	.	.	1	1.7%	7	2.3%
Skull	1	1.7%	.	.	.	.	.	.	1	1.7%	2	0.7%
Stomach	.	.	1	1.7%	.	.	.	.	.	.	1	0.3%

Table A.15

Organs reported as autolytic
NDA 202834
Animal carcinogenicity study
Male Mice

Organ or tissue name	*Control(count)*	*Control(%)*	*Low dose(count)*	*Low dose(%)*	*Mid dose(count)*	*Mid dose(%)*	*Mid-high dose(count)*	*Mid-high dose(%)*	*High dose(count)*	*High dose(%)*	*Total(count)*	*Total(%)*
Submaxilla	1	1.7%	.	.	2	3.3%	.	.	1	1.7%	4	1.3%
Tail	.	.	2	3.3%	2	3.3%	1	1.7%	2	3.3%	7	2.3%
Thymus	9	15%	6	10%	12	20%	15	25%	9	15%	51	17%
Thyroid	2	3.3%	.	.	.	.	.	.	.	.	2	0.7%
Tongue	2	3.3%	.	.	.	.	.	.	.	.	2	0.7%
Trachea	1	1.7%	.	.	.	.	.	.	.	.	1	0.3%
Ureter	3	5.0%	4	6.7%	3	5.0%	8	13%	6	10%	24	8.0%
Urinary bladder	1	1.7%	3	5.0%	4	6.7%	1	1.7%	1	1.7%	10	3.3%
Vertebra	.	.	1	1.7%	.	.	.	.	.	.	1	0.3%

Appendix B

Tumor tables from mouse male mouse experiment with high dose animals included

Table of reported tumors in Mouse Study
NDA 202834
Animal carcinogenicity study
Male mice

Table B.1

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*Mid-high dose*	*High dose*
Adrenal	ADENOMA,CORTICAL CELL	P-value of test of trend or comparison	.3933	.4744		.3881	
		Number of animals reported with tumor	0	1	0	1	0
	PHEOCHROMOCYTOMA	P-value of test of trend or comparison	.2767			.3881	
		Number of animals reported with tumor	0	0	0	1	0
Cerebrum	ASTROCYTOMA,MALIGNANT	P-value of test of trend or comparison	.7421	.4810			
		Number of animals reported with tumor	0	1	0	0	0
	MENINGIOMA,MALIGNANT	P-value of test of trend or comparison	.7421	.4810			
		Number of animals reported with tumor	0	1	0	0	0
Ear	FIBROSARCOMA	P-value of test of trend or comparison	.1210				.3220
		Number of animals reported with tumor	0	0	0	0	1
Gallbladder	PAPILLOMA	P-value of test of trend or comparison	.2954	.8502	1	1	.5388
		Number of animals reported with tumor	2	1	0	0	1
Harderian gland	ADENOMA	P-value of test of trend or comparison	.9924	.5676	.4209	.9722	1
		Number of animals reported with tumor	6	6	7	1	0
Hemolymphoreticular(all sites)	LYMPHOMA,MALIGNANT	P-value of test of trend or comparison	.9848	.4635	1	1	1
		Number of animals reported with tumor	2	3	0	0	0
	SARCOMA,HISTIOCYTIC	P-value of test of trend or comparison	.9103	.3139	.2895	.7775	1
		Number of animals reported with tumor	2	4	4	1	0
Intestine,ileum	ADENOCARCINOMA	P-value of test of trend or comparison	1	1	1	1	1
		Number of animals reported with tumor	1	0	0	0	0
Intestine,jejunum	ADENOMA	P-value of test of trend or comparison	1	1	1	1	1
		Number of animals reported with tumor	1	0	0	0	0
Kidney	NEPHROBLASTOMA	P-value of test of trend or comparison	.2722			.3788	
		Number of animals reported with tumor	0	0	0	1	0
Liver	ADENOMA,HEPATOCELLULAR	P-value of test of trend or comparison	.2896	.2710	.5154	.0960	.3858
		Number of animals reported with tumor	13	16	12	15	8
	CARCINOMA,HEPATOCELLULAR	P-value of test of trend or comparison	.7962	.4370	.8612	.9143	.8512

Table of reported tumors in Mouse Study
NDA 202834
Animal carcinogenicity study
Male mice

Table B.1

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*Mid-high dose*	*High dose*
		Number of animals reported with tumor	4	5	2	1	1
	HEMANGIOMA	P-value of test of trend or comparison	.5991	.8745	1	.9224	.8628
		Number of animals reported with tumor	4	2	0	1	1
	HEMANGIOSARCOMA	P-value of test of trend or comparison	.9700	.6131	.6131	1	1
		Number of animals reported with tumor	3	3	3	0	0
Lung(bronchus)	ADENOMA,BRONCHIOLO-ALVEOLAR	P-value of test of trend or comparison	.2167	.3421	.5813	.2012	.3277
		Number of animals reported with tumor	5	7	5	6	4
	CARCINOMA,BRONCHIOLO-ALVEOLAR	P-value of test of trend or comparison	.9069	.6748	.6930	.8483	.9569
		Number of animals reported with tumor	7	6	6	3	1
Pancreas	ADENOMA,ISLET CELL	P-value of test of trend or comparison	1	1	1	1	1
		Number of animals reported with tumor	1	0	0	0	0
Pituitary	ADENOMA,PARS DISTALIS	P-value of test of trend or comparison	.2803			.3939	
		Number of animals reported with tumor	0	0	0	1	0
	CARCINOMA,ANTERIOR	P-value of test of trend or comparison	.7436	.4805			
		Number of animals reported with tumor	0	1	0	0	0
Seminal vesicle	ADENOMA	P-value of test of trend or comparison	.7459	.2282	.4744		
		Number of animals reported with tumor	0	2	1	0	0
Skeletal system(all sites)	OSTEOSARCOMA	P-value of test of trend or comparison	.8107	.2282			
		Number of animals reported with tumor	0	2	0	0	0
Skin	CARCINOMA,SQUAMOUS CELL	P-value of test of trend or comparison	.5063		.4744		
		Number of animals reported with tumor	0	0	1	0	0
	HEMANGIOSARCOMA	P-value of test of trend or comparison	.2722			.3788	
		Number of animals reported with tumor	0	0	0	1	0
Spinal cord	ASTROCYTOMA	P-value of test of trend or comparison	.2767			.3881	
		Number of animals reported with tumor	0	0	0	1	0
Spleen	HEMANGIOMA	P-value of test of trend or comparison	1	1	1	1	1
		Number of animals reported with tumor	1	0	0	0	0

Table of reported tumors in Mouse Study
NDA 202834
Animal carcinogenicity study
Male mice

Table B.1

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*Mid-high dose*	*High dose*
Tail	HEMANGIOMA	P-value of test of trend or comparison	.2739			.3881	
		Number of animals reported with tumor	0	0	0	1	0
Testis	ADENOMA,RETE TESTIS	P-value of test of trend or comparison	.1139				.3051
		Number of animals reported with tumor	0	0	0	0	1
	LEYDIG CELL TUMOR	P-value of test of trend or comparison	.6356	.4744	.4744		
		Number of animals reported with tumor	0	1	1	0	0
	SEMINOMA	P-value of test of trend or comparison	1	1	1	1	1
		Number of animals reported with tumor	1	0	0	0	0
Thyroid	ADENOMA,FOLLICULAR CELL	P-value of test of trend or comparison	1	1	1	1	1
		Number of animals reported with tumor	1	0	0	0	0
	CARCINOMA,FOLLICULAR CELL	P-value of test of trend or comparison	.7452	.4805			
		Number of animals reported with tumor	0	1	0	0	0
Urinary bladder	PAPILLOMA	P-value of test of trend or comparison	.5033		.4667		
		Number of animals reported with tumor	0	0	1	0	0

Table of reported tumors in Mouse Study
NDA 202834
Animal carcinogenicity study
Male mice
Composite endpoints

Table E2

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*Mid-high dose*	*High dose*
All pheochromoctoymas	P-value of test of trend or comparison	.2767			.3881	
	Number of animals reported with tumor	0	0	0	1	0
Bronchioalveolar adenomas and carcinomas	P-value of test of trend or comparison	.5735	.4449	.5455	.4820	.6530
	Number of animals reported with tumor	11	12	11	8	5
Cortical cell adenomas and carcinomas	P-value of test of trend or comparison	.3933	.4744		.3881	
	Number of animals reported with tumor	0	1	0	1	0
Fibrosarcomas of the ear, skin, and tail	P-value of test of trend or comparison	.1195				.3167
	Number of animals reported with tumor	0	0	0	0	1
Folicular cell tumors	P-value of test of trend or comparison	.9363	.7334	1	1	1
	Number of animals reported with tumor	1	1	0	0	0
Hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.8618	.7729	.9384	.8231	.9599
	Number of animals reported with tumor	7	5	3	3	1
Hemangiomas and hemangiosarcomas of the liver	P-value of test of trend or comparison	.8959	.6792	.8970	.9722	.9382
	Number of animals reported with tumor	6	5	3	1	1
Hemangiomas and hemangiosarcomas of the spleen	P-value of test of trend or comparison	1	1	1	1	1
	Number of animals reported with tumor	1	0	0	0	0
Hepatocellular tumors	P-value of test of trend or comparison	.3775	.2728	.6872	.1803	.4783
	Number of animals reported with tumor	17	20	13	16	9
Intestinal adenomas and adenocarcinomas	P-value of test of trend or comparison	1	1	1	1	1
	Number of animals reported with tumor	2	0	0	0	0
Islet cell adenomas and carcinomas	P-value of test of trend or comparison	1	1	1	1	1
	Number of animals reported with tumor	1	0	0	0	0
Keratoacanthomas and squamous cell carcinomas (ear, skin, tail)	P-value of test of trend or comparison	.5063		.4744		
	Number of animals reported with tumor	0	0	1	0	0
Osteomas and osteosarcomas	P-value of test of trend or comparison	.8107	.2282			
	Number of animals reported with tumor	0	2	0	0	0
Papillomas and squamous cell carcinomas (ear, skin, tail)	P-value of test of trend or comparison	.5063		.4744		

Table of reported tumors in Mouse Study
NDA 202834
Animal carcinogenicity study
Male mice
Composite endpoints

Table E2

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*Mid-high dose*	*High dose*
	Number of animals reported with tumor	0	0	1	0	0
Pituitary adenomas and carcinomas	P-value of test of trend or comparison	.3983	.4805		.3939	
	Number of animals reported with tumor	0	1	0	1	0
Pituitary pars distalis tumors	P-value of test of trend or comparison	.2803			.3939	
	Number of animals reported with tumor	0	0	0	1	0
Squamous cell carcinomas (ear, skin, tail)	P-value of test of trend or comparison	.5063		.4744		
	Number of animals reported with tumor	0	0	1	0	0

Appendix C

Tables from rat study

C.1 Survival analysis

Table C.1

Survival rates at key times
NDA 202834
Animal carcinogenicity study
Rats

Species and Sex	*Dose Group*	*Dose (mg per kg)*	*Number at start*	*Number alive after 52 weeks*	*Proportion alive after 52 weeks*	*Number alive after 78 weeks*	*Proportion alive after 78 weeks*	*Number alive after 90 weeks*	*Proportion alive after 90 weeks*	*Number alive at termination*	*Proportion alive at termination*
Rats - Female	Control	0	60	57	95%	50	83%	48	80%	39	65%
	Low dose	3	60	59	98%	55	92%	51	85%	44	73%
	Mid dose	10	60	59	98%	55	92%	54	90%	42	70%
	High dose	30	60	50	83%	46	77%	45	75%	39	65%
Rats - Male	Control	0	60	60	100%	57	95%	54	90%	48	80%
	Low dose	10	60	59	98%	55	92%	50	83%	39	65%
	Mid dose	30	60	57	95%	53	88%	47	78%	41	68%
	High dose	100	60	58	97%	55	92%	50	83%	37	62%

Table C.2

Log-rank tests of survival
NDA 202834
Animal carcinogenicity study
Rats

Sex	*Test of homogeneity: chi squared statistic*	*Test of homogeneity: degrees of freedom*	*Number of groups*	*Test of homogeneity: p-value*	*Test of trend (two tailed): p-value*	*Test of trend (one tailed): p-value*
Female	1.7871	3	4	0.6177	0.4518	0.2259
Male	5.2945	3	4	0.1515	0.1058	0.0529

Table C.3

Pairwise comparisons (log-rank) of survival between treated groups and controls
NDA 202834
Animal carcinogenicity study
Rats

Species and Sex	*Quantity*	*Low dose*	*Mid dose*	*High dose*
Rats - Female	Chi squared test statistic	0.8699	0.3941	0.0535
	p-value of comparison with control	0.3510	0.5301	0.8172
Rats - Male	Chi squared test statistic	3.2253	2.2971	4.6652
	p-value of comparison with control	0.0725	0.1296	0.0308

C.2 Tumor analysis

Table C.4

Primary organs in study of female rats
NDA 202834
Animal carcinogenicity study

Organ or tissue name
Adrenals
Bone
Brain
Cecum
Diaphragm
Hematopoietic and lymphatic organs
Jejunum
Kidneys
Liver
Lung
Mammary gland
Mesenteric lymph node
Optic nerves
Other peripheral nerve
Ovaries
Pancreas
Parathyroids
Pituitary
Preputial/Clitoral glands
Sciatic nerve
Skin
Spleen
Subcutis
Thymus
Thyroids
Urinary bladder
Uterus
Vagina
Zymbal glands

Table C.5

Primary organs in study of male rats
NDA 202834
Animal carcinogenicity study

Organ or tissue name
Adrenals
Bone
Brain
Cecum
Duodenum
Eyes
Heart
Hematopoietic and lymphatic organs
Kidneys
Limb
Liver
Lung
Mammary gland
Mesenteric lymph node
Optic nerves
Pancreas
Parathyroids
Pituitary
Pleura
Preputial/Clitoral glands
Skin
Spinal cord
Stomach
Subcutis
Sublingual glands
Submaxillary glands
Submaxillary lymph node
Testes
Thymus
Thyroids
Zymbal glands

Table C.6

Table of reported tumors in Rat Study
NDA 202834
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Adrenals	Cortical adenoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
	Cortical carcinoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
	Malignant pheochromocytoma	P-value of test of trend or comparison	.9811	.7060	1	1
		Number of animals reported with tumor	2	2	0	0
	Pheochromocytoma	P-value of test of trend or comparison	.1556	.5149	.5221	.2776
		Number of animals reported with tumor	1	2	2	3
Bone	Osteosarcoma	P-value of test of trend or comparison	.2289			.4792
		Number of animals reported with tumor	0	0	0	1
Brain	Glioma	P-value of test of trend or comparison	.7512	.5098		
		Number of animals reported with tumor	0	1	0	0
	Meningeal sarcoma	P-value of test of trend or comparison	.2289			.4792
		Number of animals reported with tumor	0	0	0	1
Cecum	Hamartoma, malignant	P-value of test of trend or comparison	.7512	.5098		
		Number of animals reported with tumor	0	1	0	0
	Leiomyosarcoma	P-value of test of trend or comparison	.6119	.5098	.5146	
		Number of animals reported with tumor	0	1	1	0
Diaphragm	Lipoma	P-value of test of trend or comparison	.7512	.5098		
		Number of animals reported with tumor	0	1	0	0
Hematopoietic and lymphatic organs	Histiocytic sarcoma	P-value of test of trend or comparison	.2303	.7668	.5221	.4684
		Number of animals reported with tumor	1	1	2	2
	Malignant lymphoma	P-value of test of trend or comparison	.2327			.4845
		Number of animals reported with tumor	0	0	0	1
Jejunum	Leiomyosarcoma	P-value of test of trend or comparison	.7512	.5098		
		Number of animals reported with tumor	0	1	0	0
Kidneys	Liposarcoma	P-value of test of trend or comparison	1	1	1	1

Table C.6

Table of reported tumors in Rat Study
NDA 202834
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	1	0	0	0
Liver	Hepatocellular adenoma	P-value of test of trend or comparison	.3658	1	.7668	.7314
		Number of animals reported with tumor	1	0	1	1
	Hepatocellular carcinoma	P-value of test of trend or comparison	.2289			.4792
		Number of animals reported with tumor	0	0	0	1
Lung	Paraganglioma	P-value of test of trend or comparison	.2289			.4792
		Number of animals reported with tumor	0	0	0	1
Mammary gland	Adenocarcinoma	P-value of test of trend or comparison	.7425	.9831	.9846	.9362
		Number of animals reported with tumor	10	4	4	5
	Adenoma	P-value of test of trend or comparison	.2990	.5188	1	.4601
		Number of animals reported with tumor	2	3	0	3
	Carcinosarcoma	P-value of test of trend or comparison	.2327			.4845
		Number of animals reported with tumor	0	0	0	1
	Fibroadenoma	P-value of test of trend or comparison	.9558	.7525	.9444	.9716
		Number of animals reported with tumor	20	18	14	11
Other peripheral nerve	Schwannoma	P-value of test of trend or comparison	.4925		.5146	
		Number of animals reported with tumor	0	0	1	0
Ovaries	Sertoli's cell tumor	P-value of test of trend or comparison	.7512	.5098		
		Number of animals reported with tumor	0	1	0	0
Pancreas	Islet-cell adenoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
	Islet-cell carcinoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
Parathyroids	Adenoma	P-value of test of trend or comparison	.4922		.5253	
		Number of animals reported with tumor	0	0	1	0
Pituitary	Adenocarcinoma, pars distalis	P-value of test of trend or comparison	.6866	.9696	.9873	.9015
		Number of animals reported with tumor	12	6	5	7

Table C.6

Table of reported tumors in Rat Study
NDA 202834
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Adenoma, pars distalis	P-value of test of trend or comparison	.9928	.5654	.2490	.9929
		Number of animals reported with tumor	23	24	28	10
Preputial/Clitoral glands	Squamous cell papilloma	P-value of test of trend or comparison	.4925		.5149	
		Number of animals reported with tumor	0	0	1	0
Skin	Basal cell tumor	P-value of test of trend or comparison	.2289			.4792
		Number of animals reported with tumor	0	0	0	1
	Squamous cell carcinoma	P-value of test of trend or comparison	.2289			.4792
		Number of animals reported with tumor	0	0	0	1
	Squamous cell papilloma	P-value of test of trend or comparison	.4925		.5146	
		Number of animals reported with tumor	0	0	1	0
Spleen	Fibrosarcoma	P-value of test of trend or comparison	.2289			.4792
		Number of animals reported with tumor	0	0	0	1
	Hemangioma	P-value of test of trend or comparison	.2289			.4792
		Number of animals reported with tumor	0	0	0	1
Subcutis	Fibrosarcoma	P-value of test of trend or comparison	.8214	.7668	.7668	1
		Number of animals reported with tumor	1	1	1	0
	Lipoma	P-value of test of trend or comparison	.6119	.5098	.5146	
		Number of animals reported with tumor	0	1	1	0
Thymus	Thymoma	P-value of test of trend or comparison	.5000		.5102	
		Number of animals reported with tumor	0	0	1	0
Thyroids	C-cell adenoma	P-value of test of trend or comparison	.9107	.7130	.7130	1
		Number of animals reported with tumor	2	2	2	0
	C-cell carcinoma	P-value of test of trend or comparison	.4925		.5146	
		Number of animals reported with tumor	0	0	1	0
Urinary bladder	Transitional cell carcinoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
Uterus	Endometrial stromal polyp	P-value of test of trend or comparison	.4439	.6796	.5328	.6206

Table C.6

Table of reported tumors in Rat Study
NDA 202834
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	3	3	4	3
	Endometrial stromal sarcoma	P-value of test of trend or comparison	.9966	.9479	1	1
		Number of animals reported with tumor	3	1	0	0
	Hemangiosarcoma	P-value of test of trend or comparison	.2289			.4792
		Number of animals reported with tumor	0	0	0	1
	Leiomyoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
	Leiomyosarcoma	P-value of test of trend or comparison	.1317	1	1	.4684
		Number of animals reported with tumor	1	0	0	2
Vagina	Squamous cell papilloma	P-value of test of trend or comparison	.4925		.5146	
		Number of animals reported with tumor	0	0	1	0
Zymbal glands	Carcinoma	P-value of test of trend or comparison	.9397	.7668	1	1
		Number of animals reported with tumor	1	1	0	0

Table C.7

Table of reported tumors in Rat Study
NDA 202834
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Adrenals	Cortical adenoma	P-value of test of trend or comparison	.7321	.4815		
		Number of animals reported with tumor	0	1	0	0
	Malignant pheochromocytoma	P-value of test of trend or comparison	.9239	.1457	.8690	.8742
		Number of animals reported with tumor	4	8	2	2
	Pheochromocytoma	P-value of test of trend or comparison	.6528	.8986	.6475	.8291
		Number of animals reported with tumor	13	8	11	9
Bone	Osteosarcoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
Brain	Glioma	P-value of test of trend or comparison	.1535	1	1	.4720
		Number of animals reported with tumor	1	0	0	2
	Granular cell tumor	P-value of test of trend or comparison	.1777		.4717	.4766
		Number of animals reported with tumor	0	0	1	1
Cecum	Hemangioma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
Duodenum	Leiomyosarcoma	P-value of test of trend or comparison	.2452			.4766
		Number of animals reported with tumor	0	0	0	1
Eyes	Malignant schwannoma	P-value of test of trend or comparison	.7321	.4815		
		Number of animals reported with tumor	0	1	0	0
Heart	Malignant mesothelioma	P-value of test of trend or comparison	.4880		.4766	
		Number of animals reported with tumor	0	0	1	0
	Malignant schwannoma	P-value of test of trend or comparison	.7321	.4815		
		Number of animals reported with tumor	0	1	0	0
Hematopoietic and lymphatic organs	Histiocytic sarcoma	P-value of test of trend or comparison	.1613	1	.7233	.4720
		Number of animals reported with tumor	1	0	1	2
	Malignant lymphoma	P-value of test of trend or comparison	.7321	.4815		
		Number of animals reported with tumor	0	1	0	0
Kidneys	Adenoma	P-value of test of trend or comparison	.4312	1	1	.7284

Table C.7

Table of reported tumors in Rat Study
NDA 202834
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	1	0	0	1
Limb	Rhabdomyosarcoma	P-value of test of trend or comparison	.4880		.4766	
		Number of animals reported with tumor	0	0	1	0
Liver	Cholangioma	P-value of test of trend or comparison	.2452			.4766
		Number of animals reported with tumor	0	0	0	1
	Hepatocellular adenoma	P-value of test of trend or comparison	.9285	.7284	1	1
		Number of animals reported with tumor	1	1	0	0
	Hepatocellular carcinoma	P-value of test of trend or comparison	.6100	.4646	1	.7284
		Number of animals reported with tumor	1	2	0	1
Lung	Carcinoma, bronchiolo-alveolar	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
Mammary gland	Adenoma	P-value of test of trend or comparison	.2390			.4667
		Number of animals reported with tumor	0	0	0	1
	Fibroadenoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
Mesenteric lymph node	Hemangiosarcoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
Pancreas	Islet-cell adenoma	P-value of test of trend or comparison	.7521	.3127	.3008	.7408
		Number of animals reported with tumor	4	6	6	3
	Islet-cell carcinoma	P-value of test of trend or comparison	.1924	.4646	.6471	.2957
		Number of animals reported with tumor	2	3	2	4
Parathyroids	Adenoma	P-value of test of trend or comparison	.2500			.4950
		Number of animals reported with tumor	0	0	0	1
Pituitary	Adenocarcinoma, pars distalis	P-value of test of trend or comparison	.2347	.4880	.8788	.3589
		Number of animals reported with tumor	4	5	2	6
	Adenoma, pars distalis	P-value of test of trend or comparison	.9930	.4244	.3095	.9837
		Number of animals reported with tumor	27	29	29	16

Table C.7

Table of reported tumors in Rat Study
NDA 202834
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Adenoma, pars intermedia	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	2	0	0	0
Pleura	Malignant mesothelioma	P-value of test of trend or comparison	.2488			.4815
		Number of animals reported with tumor	0	0	0	1
Skin	Basal cell carcinoma	P-value of test of trend or comparison	.7321	.4815		
		Number of animals reported with tumor	0	1	0	0
	Keratoacanthoma	P-value of test of trend or comparison	.0377	.2815	1	.0828
		Number of animals reported with tumor	1	3	0	5
	Sebaceous cell adenoma	P-value of test of trend or comparison	.7952	.2295		
		Number of animals reported with tumor	0	2	0	0
	Squamous cell papilloma	P-value of test of trend or comparison	.7937	.7284	.2673	1
		Number of animals reported with tumor	1	1	3	0
Spinal cord	Glioma	P-value of test of trend or comparison	.7321	.4815		
		Number of animals reported with tumor	0	1	0	0
Stomach	Leiomyosarcoma	P-value of test of trend or comparison	.7308	.4766		
		Number of animals reported with tumor	0	1	0	0
Subcutis	Fibroma	P-value of test of trend or comparison	.8246	.2957	.4460	.8603
		Number of animals reported with tumor	2	4	3	1
	Fibrosarcoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
	Lipoma	P-value of test of trend or comparison	.9812	.8603	1	1
		Number of animals reported with tumor	2	1	0	0
	Liposarcoma	P-value of test of trend or comparison	.7321	.4815		
		Number of animals reported with tumor	0	1	0	0
	Malignant Schwannoma	P-value of test of trend or comparison	.4856		.4717	
		Number of animals reported with tumor	0	0	1	0
Testes	Interstitial cell adenoma	P-value of test of trend or comparison	.0622	.8603	1	.2957

Table C.7

Table of reported tumors in Rat Study
NDA 202834
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	2	1	0	4
Thyroids	C-cell adenoma	P-value of test of trend or comparison	.7560	.7408	.8690	.8742
		Number of animals reported with tumor	4	3	2	2
	C-cell carcinoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
	Follicular cell adenoma	P-value of test of trend or comparison	.5189	.7284	1	.7284
		Number of animals reported with tumor	1	1	0	1
Zymbal glands	Carcinoma	P-value of test of trend or comparison	.7321	.4815		
		Number of animals reported with tumor	0	1	0	0

Table C.8

Table of reported tumors in Rat Study
NDA 202834
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
All pheochromoctoymas	P-value of test of trend or comparison	.5112	.5221	.8364	.6206
	Number of animals reported with tumor	3	4	2	3
Basal cell tumors	P-value of test of trend or comparison	.2289			.4792
	Number of animals reported with tumor	0	0	0	1
C-cell tumors	P-value of test of trend or comparison	.8973	.7130	.5278	1
	Number of animals reported with tumor	2	2	3	0
Cortical cell adenomas and carcinomas	P-value of test of trend or comparison	1	1	1	1
	Number of animals reported with tumor	2	0	0	0
Endometrial stromal tumors (uterine)	P-value of test of trend or comparison	.7613	.8634	.8634	.8993
	Number of animals reported with tumor	6	4	4	3
Gliomas	P-value of test of trend or comparison	.7512	.5098		
	Number of animals reported with tumor	0	1	0	0
Hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.0515			.2270
	Number of animals reported with tumor	0	0	0	2
Hemangiomas and hemangiosarcomas of the spleen	P-value of test of trend or comparison	.2289			.4792
	Number of animals reported with tumor	0	0	0	1
Hemangiomas and hemangiosarcomas of the uterus	P-value of test of trend or comparison	.2289			.4792
	Number of animals reported with tumor	0	0	0	1
Hepatocellular tumors	P-value of test of trend or comparison	.1445	1	.7668	.4684
	Number of animals reported with tumor	1	0	1	2
Islet cell adenomas and carcinomas	P-value of test of trend or comparison	1	1	1	1
	Number of animals reported with tumor	2	0	0	0
Keratoacanthomas and squamous cell carcinomas (ear, skin, tail)	P-value of test of trend or comparison	.2289			.4792
	Number of animals reported with tumor	0	0	0	1
Leiomyomas and leiomyosarcomas of the GI tract	P-value of test of trend or comparison	.7192	.2574	.5146	
	Number of animals reported with tumor	0	2	1	0
Leiomyomas and leiomyosarcomas of the ovary and uterus	P-value of test of trend or comparison	.2416	1	1	.6593

Table C.8

Table of reported tumors in Rat Study
NDA 202834
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Number of animals reported with tumor	2	0	0	2
Leiomyomas and leiomyosarcomas of the uterus	P-value of test of trend or comparison	.2416	1	1	.6593
	Number of animals reported with tumor	2	0	0	2
Lipomas and liposarcomas	P-value of test of trend or comparison	.8225	.7622	.7668	1
	Number of animals reported with tumor	1	1	1	0
Mammary adenomas and adenocarcinomas	P-value of test of trend or comparison	.3712	.9618	.9846	.7210
	Number of animals reported with tumor	10	5	4	8
Osteomas and osteosarcomas	P-value of test of trend or comparison	.2289			.4792
	Number of animals reported with tumor	0	0	0	1
Papillomas and squamous cell carcinomas (ear, skin, tail)	P-value of test of trend or comparison	.1728		.5146	.4792
	Number of animals reported with tumor	0	0	1	1
Pituitary adenomas and carcinomas	P-value of test of trend or comparison	.9935	.8747	.6790	.9973
	Number of animals reported with tumor	35	30	33	17
Pituitary pars distalis tumors	P-value of test of trend or comparison	.9935	.8747	.6790	.9973
	Number of animals reported with tumor	35	30	33	17
Squamous cell carcinomas (ear, skin, tail)	P-value of test of trend or comparison	.2289			.4792
	Number of animals reported with tumor	0	0	0	1

Table C.9

Table of reported tumors in Rat Study
NDA 202834
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
All pheochromoctoymas	P-value of test of trend or comparison	.7359	.6662	.6217	.8032
	Number of animals reported with tumor	15	13	13	11
Basal cell tumors	P-value of test of trend or comparison	.7321	.4815		
	Number of animals reported with tumor	0	1	0	0
Bronchioalveolar adenomas and carcinomas	P-value of test of trend or comparison	1	1	1	1
	Number of animals reported with tumor	1	0	0	0
C-cell tumors	P-value of test of trend or comparison	.8267	.8323	.9239	.9276
	Number of animals reported with tumor	5	3	2	2
Cortical cell adenomas and carcinomas	P-value of test of trend or comparison	.7321	.4815		
	Number of animals reported with tumor	0	1	0	0
Folicular cell tumors	P-value of test of trend or comparison	.5189	.7284	1	.7284
	Number of animals reported with tumor	1	1	0	1
Gliomas	P-value of test of trend or comparison	.2307	.7335	1	.4720
	Number of animals reported with tumor	1	1	0	2
Hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	1	1	1	1
	Number of animals reported with tumor	2	0	0	0
Hepatocellular tumors	P-value of test of trend or comparison	.8026	.4554	1	.8603
	Number of animals reported with tumor	2	3	0	1
Islet cell adenomas and carcinomas	P-value of test of trend or comparison	.4852	.2385	.3029	.4276
	Number of animals reported with tumor	6	9	8	7
Keratoacanthomas and squamous cell carcinomas (ear, skin, tail)	P-value of test of trend or comparison	.0377	.2815	1	.0828
	Number of animals reported with tumor	1	3	0	5
Leiomyomas and leiomyosarcomas of the GI tract	P-value of test of trend or comparison	.2985	.4766		.4766
	Number of animals reported with tumor	0	1	0	1
Lipomas and liposarcomas	P-value of test of trend or comparison	.9766	.6625	1	1
	Number of animals reported with tumor	2	2	0	0
Malignant schwannomas	P-value of test of trend or comparison	.7139	.2341	.4717	

Table C.9

Table of reported tumors in Rat Study
NDA 202834
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Number of animals reported with tumor	0	2	1	0
Mammary adenomas and adenocarcinomas	P-value of test of trend or comparison	.2390			.4667
	Number of animals reported with tumor	0	0	0	1
Mesothelioma	P-value of test of trend or comparison	.1813		.4766	.4815
	Number of animals reported with tumor	0	0	1	1
Osteomas and osteosarcomas	P-value of test of trend or comparison	1	1	1	1
	Number of animals reported with tumor	1	0	0	0
Papillomas and squamous cell carcinomas (ear, skin, tail)	P-value of test of trend or comparison	.7937	.7284	.2673	1
	Number of animals reported with tumor	1	1	3	0
Pituitary adenomas and carcinomas	P-value of test of trend or comparison	.9875	.5910	.6388	.9830
	Number of animals reported with tumor	33	34	31	22
Pituitary pars distalis tumors	P-value of test of trend or comparison	.9772	.4361	.4886	.9590
	Number of animals reported with tumor	31	34	31	22

Table C.10

Table of tumors reported significant in at least one arm - Rat Study
NDA 202834
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Skin	Keratoacanthoma	P-value of test of trend or comparison	.0377	.2815	1	.0828
		Number of animals reported with tumor	1	3	0	5
		Poly-3 adjusted incidence rate	1.8%	5.7%	0.0%	9.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,9.6)	(1.18,15.9)	(0,7.1)	(3.2,21.4)
		Poly-3 adjusted number of animals at risk	56.1	52.4	50.7	51.7

Table C.11

Table of tumors reported significant in at least one arm - Rat Study
NDA 202834
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Keratoacanthomas and squamous cell carcinomas (ear, skin, tail)	P-value of test of trend or comparison	.0377	.2815	1	.0828
	Number of animals reported with tumor	1	3	0	5
	Poly-3 adjusted incidence rate	1.8%	5.7%	0.0%	9.7%
	95% CI for poly-3 adjusted incidence rate (%)	(0.04,9.6)	(1.18,15.9)	(0,7.1)	(3.2,21.4)
	Poly-3 adjusted number of animals at risk	56.1	52.4	50.7	51.7

C.3 Unexamined and autolytic organs

Table C.12

Organs reported as unexamined
NDA 202834
Animal carcinogenicity study
Female Rats

Organ or tissue name	*Control(count)*	*Control(%)*	*Low dose(count)*	*Low dose(%)*	*Mid dose(count)*	*Mid dose(%)*	*High dose(count)*	*High dose(%)*	*Total(count)*	*Total(%)*
Mesenteric lymph node	1	1.7%	1	1.7%	.	.	.	.	2	0.8%
Optic nerves	.	.	.	.	.	.	2	3.3%	2	0.8%
Parathyroids	4	6.7%	2	3.3%	1	1.7%	3	5.0%	10	4.2%
Preputial/Clitoral glands	1	1.7%	.	.	1	1.7%	2	3.3%	4	1.7%
Sciatic nerve	.	.	.	.	1	1.7%	.	.	1	0.4%
Thymus	3	5.0%	7	12%	4	6.7%	2	3.3%	16	6.7%

Table C.13

Organs reported as unexamined
NDA 202834
Animal carcinogenicity study
Male Rats

Organ or tissue name	*Control(count)*	*Control(%)*	*Low dose(count)*	*Low dose(%)*	*Mid dose(count)*	*Mid dose(%)*	*High dose(count)*	*High dose(%)*	*Total(count)*	*Total(%)*
Mammary gland	.	.	2	3.3%	.	.	4	6.7%	6	2.5%
Mesenteric lymph node	.	.	.	.	1	1.7%	.	.	1	0.4%
Optic nerves	1	1.7%	1	1.7%	.	.	.	.	2	0.8%
Parathyroids	5	8.3%	1	1.7%	2	3.3%	2	3.3%	10	4.2%
Pituitary	2	3.3%	.	.	1	1.7%	.	.	3	1.3%
Preputial/Clitoral glands	1	1.7%	2	3.3%	1	1.7%	1	1.7%	5	2.1%
Sublingual glands	.	.	1	1.7%	.	.	.	.	1	0.4%
Submaxillary glands	.	.	1	1.7%	.	.	.	.	1	0.4%
Submaxillary lymph node	2	3.3%	1	1.7%	2	3.3%	.	.	5	2.1%
Thymus	3	5.0%	6	10%	5	8.3%	7	12%	21	8.8%

C.4 Weight changes

Table C.14: Weight changes by group (rats)

Sex	Control	E2007					
	Δ_{C_P}	Δ_L	$\frac{\Delta_L}{\Delta_{C_P}} - 1$	Δ_M	$\frac{\Delta_M}{\Delta_{C_P}} - 1$	Δ_H	$\frac{\Delta_H}{\Delta_{C_P}} - 1$
Female	139.7	125.7	-10%	120.8	-14%	129.7	-7%
Male	346.6	334.7	-3%	312	-10%	305.1	-12%

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/s/

MATTHEW T JACKSON
10/23/2012

KARL K LIN
10/24/2012
Concur with review

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	202-834
Drug Name:	Perampanel (E2007)
Indication:	Adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalized seizures in patients with epilepsy aged 12 years and older
Study number:	E2007-A001-024
Applicant:	Eisai Inc.
Date(s):	Filing Mtg: January 26, 2012 PDUFA date: October 22, 2012 Completion date: September 5, 2012
Review Priority:	S
Biometrics Division:	DB VI
Statistical Reviewer:	Ling Chen, Ph.D., Mathematical Statistician, Special Project Team.
Concurring Reviewers:	Stella Machado, Ph.D., Division Director, and Acting Team Leader,
Medical Division:	Controlled Substance Staff
The CSS Team:	Alicja Lerner, M.D., Ph.D., Medical Officer, OD/CSS Lori A. Love, M.D., Ph.D., Lead Medical Officer, OD/CSS
Project Manager:	Corinne P. Moody, OD/CSS

Keywords: Crossover design; Drug abuse potential study; Self-reported endpoint; Multiple endpoints

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1. Executive Summary

Study E2007-A001-0024 was a randomized, double-blind, double-dummy, placebo- and positive-controlled 10-sequence, 7-period, single-dose, crossover study in healthy, nondependent, recreational polydrug users.

There were seven treatments in the study. These treatments were perampanel 8 mg, perampanel 24 mg, perampanel 36 mg, alprazolam 1.5 mg, alprazolam 3 mg, oral ketamine 100 mg, and placebo.

The primary objective was to evaluate the abuse potential of single doses of perampanel (8 mg, 24 mg, and 36 mg) compared to alprazolam (1.5 mg and 3 mg), oral ketamine (100 mg), and placebo in recreational polydrug users.

Forty subjects were enrolled into the Randomization Phase, and 34 subjects provided valid data for the pharmacodynamic analyses.

In the review, the reviewer found that severe missing data occurred during treatment periods at early hours after dosing for alprazolam 3 mg, and perampanel 24 mg and 36 mg. The missing data were due to AEs (somnolence, drowsiness, confusion, decreased concentration, etc) based on the Sponsor's explanation. The missing data were not imputed by the reviewer. The detailed reasons for not imputing missing data can be found in Section 2.3.1.

The primary measures in the study were Drug Liking VAS, Subjective Drug Value (SDV) ($), ARCI Morphine Benzedrine Group (MBG), and ARCI Pentobarbitol Chlorpromazine Alcoho Group (PCAG). This study showed that perampanel 8 mg had statistically lower effects compared to alprazolam and ketamine for three out of four primary measures. No significant difference in means was found between perampanel 8 mg and two doses of alprazolam for Drug Liking VAS, and between perampanel 8 mg and ketamine 100 mg for ARCI PCAG. Perampanel 24 mg and 36 mg were not statistically different in means (or medians) from alprazolam 3 mg for all primary measures. But both high doses of perampanel had significantly larger means than alprazolam 1.5 mg for ARCI MBG. Perampanel 36 mg also had significantly larger medians than alprazolam 1.5 mg for ARCI PCAG. Comparing ketamine 100 mg to two high doses of perampanel, no significant difference in means (or medians) was found for ARCI MBG, and SDV($). Ketamine 100 mg had significantly larger mean response than two high doses of perampanel for Drug Liking VAS, and significantly lower mean response than these doses of perampanel for ARCI PCAG.

The reviewer examined subject responses to the secondary measures High VAS, Overall Drug Liking VAS, and Take Drug Again. For High VAS, perampanel 24 mg and 36 mg had significantly larger median responses than both doses of alprazolam. On the average, perampanel 36 mg had long acting effects for ARCI PCAG and High VAS. These effects would last for at least 22 hours. The time course profiles (both mean and individual) of ketamine 100 mg demonstrated rapid peak effects followed by a relatively rapid decline for the measures used in the reviewer's analysis. Even though for High VAS there was no significant difference in medians between ketamine 100 mg and perampanel 36 mg, from heat map displays for individual time course response profiles, as well as the mean time course profiles, the difference between ketamine and perampanel were evident. Even though there was no significant difference in medians among two doses of alprazolam, ketamine 100 mg, and two high doses of perampanel for Overall Drug Liking VAS, alprazolam 1.5 mg and ketamine 100 mg had significantly larger medians than the two high doses of perampanel for Take Drug Again VAS.

The reviewer also evaluated data for Emax of Good Effects VAS and Emax of Bad Effects VAS for perampanel 24 mg and 36 mg, and alprazolam 3 mg. The results showed that most subjects had Emax of Good Effects VAS larger than that of Bad Effects VAS for perampanel 24 mg. On the other hand, many subjects experienced larger bad effects than good effects for perampanel 36 mg and alprazolam 3 mg. Because there was no significant difference in means (or medians) between two high doses of perampanel for all measures studied by the reviewer, and there were also no significant differences in mean (or medians) between perampanel 24 mg and alprazolam 3 mg except High VAS, perampanel 24 mg may have more abuse potential than both perampanel 36 mg and alprazolam 3 mg.

In conclusion, high doses of perampanel have large and long acting sedative and High VAS effects. In addition, most subjects had good effects much larger than bad effects for perampanel 24 mg. Even though perampanel is more similar to alprazolam than to ketamine, perampanel may have more potential to be abused than alprazolam.

Disclaimer: All conclusions made by the reviewer were based on observed data without imputing the missing because there is a reason to believe that the participants whose data were missing were different from others. Thus, they might be biased.

2. Review Report on Study E2007-A001-024

2.1 Overview

2.1.1 Objectives of the study

Primary objective

The primary objective of this study was to evaluate the abuse potential of single doses of perampanel (8 mg, 24 mg, and 36 mg) compared to alprazolam (1.5 mg and 3 mg), oral ketamine (100 mg), and placebo in healthy recreational polydrug users.

Secondary objectives

The secondary objective of this study was to confirm the safety and tolerability following single oral doses of perampanel (8 mg, 24 mg, and 36 mg) and to assess the pharmacokinetics of perampanel in healthy recreational polydrug users.

Reviewer's comment: This review report is only for the primary objective of the study.

2.1.2 Study design

This was a randomized, double-blind, double-dummy, 10-sequence, 7-period, single-dose, crossover study in healthy, nondependent, recreational polydrug users. Each subject participated in a Prerandomization, and a Randomization phases.

The Prerandomization Phase included a Screening Period and a 5-days (4 nights) inpatient Run-in Period. The Run-in Period was conducted to ensure that subjects were able to distinguish the positive comparators from placebo in a laboratory setting. A washout of at least 5 days separated last drug administration in the Run-in Period and the first drug administration in the Randomization Phase. The washout period between two treatments in the treatment phase was at least 72 hours.

During the Randomization Phase, subjects were randomized to 1 of 10 treatment sequences, according to two 7×7 Williams squares. To reduce the potential for accumulation of perampanel, the 4 random sequences where 3 perampanel doses would have been given in succession were removed, and additional placebo doses were fixed to follow each dose of perampanel, such that each subject participated in a total of 10 Treatment Periods (6 active treatments, 1 fully randomized placebo dose, and 3 "washout" placebo doses). Thus, the Randomization Phase included 10 inpatient Treatment Periods, each lasting 4 days (3 nights). Treatment Periods were separated by a 7-day washout (maximum 14 days).

Subjects underwent end-of-study procedures during their final outpatient safety visit (Follow-Up Period) or upon early termination/discontinuation from the study.

The treatments administered in the Run-in Period of the study are presented below:

- Placebo: 240 mL oral placebo solution

2 alprazolam placebo capsules

- Ketamine 100 mg: 240 mL oral solution containing 100 mg ketamine
  2 alprazolam placebo capsules
- Alprazolam 1.5 mg: 240 mL oral placebo solution
  1, 1.0 mg alprazolam capsule
  1, 0.5 mg alprazolam capsule

The treatments administered in the Randomization Phase are presented below:

- Placebo*: 240 mL oral placebo solution
  3 alprazolam placebo capsules
  9 perampanel placebo capsules
- Ketamine 100 mg: 240 mL oral solution containing
  100 mg ketamine
  3 alprazolam placebo capsules
  9 perampanel placebo capsules
- Alprazolam 1.5 mg: 240 mL oral placebo solution
  3, 0.5 mg alprazolam capsules
  9 perampanel placebo capsules
- Alprazolam 3 mg: 240 mL oral placebo solution
  3, 1 mg alprazolam capsules
  9 perampanel placebo capsules
- Perampanel 8 mg: 240 mL oral placebo solution
  3 alprazolam placebo capsules
  2, 4 mg perampanel capsules

- 7 perampanel placebo capsules

- Perampanel 24 mg: 240 mL oral placebo solution
  3 alprazolam placebo capsules
  6, 4 mg perampanel capsules
  3 perampanel placebo capsules
- Perampanel 36 mg: 240 mL oral placebo solution
  3 alprazolam placebo capsules
  9, 4 mg perampanel capsules

The treatment sequences in the Randomization Phase were presented in the Sponsor's Table 4.

Reviewer's comments: Because the Sponsor eliminated 4 sequences where the 3 perampanel doses would be in succession, the design is no longer a Willliams square design.

2.1.3 Abuse potential measure and data collection times

The following pharmacodynamic assessments were administered to evaluate the subjective and objective effects of perampanel.

Primary subjective variables included:

* Placebo was given on 4 occasions in the study: once in a fully randomized manner and once following each of the 3 perampanel doses.

Balance of effects:

- Drug Liking VAS ("at this moment")
- SDV

Positive effects:

- ARCI MBG scale

Sedative effects:

- ARCI PCAG scale

Secondary subjective variables included:

Balance of effects:

- Overall Drug Liking VAS
- Take Drug Again VAS

Positive effects:

- High VAS
- Good Drug Effects VAS

Negative effects:

- Bad Drug Effects VAS
- ARCI LSD

NMDA-antagonist specific effects VASs:

- Floating; Spaced Out; Vision Clear, Crisp; Detached; Slowed Down; Confused; In Control; Nauseous, Colors Brighter, Sounds Louder; Attention Span Good; Feeling Happy, Euphoric; and Feeling Grounded, Aware

The following pharmacodynamic assessments were administered as supportive variables:

Sedative and stimulant effects:

- Drowsiness VAS
- ARCI Amphetamine scale
- ARCI Benzedrine Group (BG) scale

Other drug effects:

- Any Drug Effects VAS
- Dizziness VAS
- Drug Similarity VAS

Cognitive and psychomotor effects:

- Digit Symbol Substitution Test (DSST)
- Divided Attention (DA) test
- Choice Reaction Time (CRT) test

The following listed the time points of the data collections for various abuse potential measures:

- Drug Liking VAS, Good Drug Effects VAS, Bad Drug Effects VAS, and Any Effects VAS: Data were collected at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours postdose at each Treatment Period.
- Other Subjects Effects VASs (High VAS, Drowsiness VAS, and Dizziness VAS): Data were collected at predose and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours postdose during each Treatment Period.

- ARCI and NMDA-specific VASs: Data were collected at predose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours postdose during each Treatment Period.
- Overall Drug Liking VAS, Take Drug Again VAS, and SDV: Data were collected at 12, 24, and 48 hours postdose at each Treatment Period.
- Drug Similarity VASs: Data were collected at 8 hours postdose at each Treatment Period.
- CRT, DA, and DSST: Data were collected at predose, 1, 2, 3, 4, 8, 12, 24, and 48 hours postdose at each Treatment Period.

Reviewer's Comments: There were too many abuse potential measures in this study. The reviewer is wondering how a subject could respond such many questions within even 1 hour, and how reliable answers from the subjects to the questionnaires are.

Perampanel has a long half-life 70 hours to 120 hours. Probably, the data should have been collected at more time points between 8 and 12 hours and between 12 and 24 hours as well as between 24 and 48 hours.

2.1.4 Number of subjects

Forty subjects were planned for enrollment into the Randomization Phase, to ensure valid pharmacodynamic data from a minimum of 20 subjects.

Forty (31.7%) subjects, who met the Run-in Period criteria, were dosed in the Randomization Phase of the study. Overall, 33 (82.5%) subjects completed the Randomization Phase as planned, and 7 (17.5%) subjects discontinued early. Subject disposition by treatment sequence is provided in Sponsor's Table 14.1.4.1. Reasons for discontinuation by treatment prior to discontinuation are summarized in Sponsor's Table 14.1.4.2. Four subjects were withdrawn from the study because of treatment-emergent adverse events (2 subjects after dosing with perampanel 36 mg, 1 subject after ketamine 100 mg, and 1 subject after placebo following perampanel 24 mg, 1 subject withdrew consent (i.e., could no longer commit to study dates), 1 subject was withdrawn for non-compliance (i.e., positive drug screen at Treatment Period 2), and 1 subject was discontinued for having prolonged QTcF (>450 ms) at admission to Treatment Period 3.

Reviewer's Comments: There was a total of 33 completers. One subject (9197) who was discontinued from the study prior to dosing at Treatment Period 10 (placebo arm fixed to follow perampanel 36 mg) had sufficient data for the analyses. Thus, 34 subjects were included in the analyses.

2.1.5 Statistical methodologies used in the Sponsor's analyses

Pharmacodynamic data at each time point were summarized by descriptive statistics and presented graphically. Derived endpoints were summarized using descriptive statistics, boxplots, and dose-response curves. Pharmacodynamic endpoints (Emax, Emin, and/or TWmean, as appropriate) were analyzed using a mixed-effect model having treatment, period, and sequence as fixed effects and subject nested within sequence as a random effect. First-order carryover effect was tested at the 25% level, and if the test was not significant, the first-order carryover effect term was dropped from the model. From each model, means and 95% confidence intervals for treatments and treatment differences were computed and p-values provided where appropriate. The contrasts included each dose of alprazolam and ketamine compared to placebo, and each dose of perampanel compared to placebo, each dose of alprazolam, and 100 mg ketamine.

All analyses were investigated against the statistical assumptions implicit within that analysis; serious violation of those assumptions (for example, distributional violations) resulted in a changed analysis to account for the true apparent features of the data. The residuals from the mixed-effect model were investigated for centrality of distribution (centrality was sufficient, but the SD may not be accurately estimated if the distribution is not normal). Parameters were analyzed as having a normal distribution if

- probability value for the test of normality of the residuals from the model described above ≥0.05, or
- skewness within (-0.5, 0.5) and the stem & leaf plot was approximately normal (e.g., not bimodal).

Parameters that did not meet these criteria were analyzed non-parametrically. Overall treatment effects were assessed using the Kruskal-Wallis test. Pairwise treatment comparisons were assessed using the Wilcoxon sign-rank test on the within-subject differences.

In Section 9.8.2.2 "Changes in the planned analyses from the statistical analysis plan", the Sponsor stated that although study validity was to be determined based on comparisons between alprazolam and placebo using the 95% CIs of differences in Emax, because some of the endpoints did not meet normality assumptions, for these endpoints the comparison was based on the non-parametric statistic (interquartile range).

Reviewer's Comments: It is not clear to this reviewer what statistical analysis procedure was used for the comparison between alprazolam and placebo based on the interquartile range.

Kruskal-Wallis test is for the comparison among three or more independent samples. In a crossover study, a sequence is a complete block. The Sponsor chose a wrong non-parametric test for assessing the overall treatment effects.

The reviewer sent the comments and gave an instruction for correct analysis methodology to the sponsor before the filing meeting. The Sponsor re-submitted their analysis.

2.1.5 Sponsor's conclusion

The Sponsor stated that the following results:

- Compared to placebo, 1.5 mg and 3 mg alprazolam and the mid-range oral ketamine dose (100 mg) were associated with statistically significant positive and balance effects, including greater effects on the primary measures. In addition, statistically significant negative (alprazolam), sedative, NMDA antagonist-related and other subjective effects were also observed, as expected for both comparators. Based on these results, the study was considered valid and the subject population of prequalified CNS depressant and psychedelic drug users was appropriately sensitive for evaluating abuse-related sedative and perceptual effects.
- Although the design was modified from a traditional full crossover design due to the long half-life of perampanel, the study showed significant and appropriate effects of the positive controls, with no evidence of systematic carryover, period, or sequence effects that would affect the study validity or pharmacodynamic conclusions.

- All perampanel doses were associated with statistically significant subjective positive and balance effects, including greater effects on all 4 primary measures compared to placebo. At the 24 mg and 36 mg doses, perampanel was also associated with statistically significant disliking and other negative effects compared to placebo. Statistically significant sedative, NMDA-antagonist related and other subjective effects were also observed.
- The therapeutic dose of perampanel (8 mg) was associated with statistically lower effects on 3 of 4 primary measures compared to 1.5 mg and 3 mg alprazolam, as well as on most secondary measures of sedative, NMD-Aantagonist related, negative, and other subjective effects.
- Perampanel 8 mg was associated with statistically lower peak subjective effects compared to 100 mg ketamine, other than for some measures of sedative or negative effects, where responses to 100 mg ketamine were relatively low.
- The 24 mg and 36 mg perampanel doses were not statistically different from either alprazolam dose on the majority of subjective measures, including the primary pharmacodynamic endpoints (Emax of Drug Liking VAS, SDV, ARCI MBG, and ARCI PCAG). These perampanel doses were associated with statistically greater negative effects compared to alprazolam and generally lower Take Drug Again and Overall Drug Liking effects. On other secondary and supportive subjective measures, 24 mg and 36 mg perampanel showed similar or greater effects compared to alprazolam.
- Compared to 100 mg ketamine, perampanel 24 mg and 36 mg doses showed lower peak effects on most measures, although statistical differences were observed on some (Drug Liking, Overall Drug Liking, and Take Drug Again) but not all measures (SDV, ARCI MBG, some NMDA-antagonist related effects). In addition, 24 mg and 36 mg perampanel showed statistically greater negative and sedative effects compared to 100 mg ketamine.
- The time course profiles on subjective measures demonstrated strong and rapid peak effects of 100 mg ketamine followed by a relatively rapid decline. In contrast, slightly lower peak effects of perampanel and alprazolam were observed on most measures; onset was also later and effects lasted for a longer duration of time, in particular at the 36 mg dose of perampanel.
- Dose-effect relationships for the primary pharmacodynamic measures were relatively flat for the 2 higher perampanel doses, with some increasing effect between 8 mg and 24 mg perampanel, but little increase from 24 mg to 36 mg perampanel. Alprazolam also showed relatively small increases between the 1.5 mg and 3 mg doses.
- Alprazolam exhibited the expected impairments on DSST, DA, and CRT measures at both dose levels. Perampanel, particularly at the 24 mg and 36 mg doses, also impaired performance on DSST, DA, and CRT measures; however, the effects were generally weaker than those observed with 3 mg alprazolam.

Combined results from the pharmacokinetic and safety evaluations, the Sponsor concluded that

In conclusion, the study was valid as demonstrated by the statistically significant effects of alprazolam and ketamine compared to placebo on relevant abuse potential measures. Perampanel was associated with statistically significant differences compared to placebo on the majority of primary and secondary measures, especially at the 2 higher doses. While 8 mg perampanel showed statistically lower effects compared to alprazolam and ketamine on most measures, the abuse potential profile of perampanel at 24 mg and 36 mg doses was not statistically different from alprazolam on the primary measures or the majority of secondary measures. At 24 mg and 36 mg doses, perampanel had statistically

greater negative effects compared to alprazolam, and particularly at 36 mg, perampanel also had statistically greater other effects compared to alprazolam, such as floating, spaced out, visual clarity, and attention span. In contrast, the subjective effects profile of perampanel differed from that of ketamine, with perampanel demonstrating statistically lower peak effects on a number of key abuse potential measures. Perampanel also had statistically greater negative and sedative effects compared to 100 mg ketamine and demonstrated a different time course profile.

2.2 Data Location

The analysis dataset is located

\\cdsesub1\EVSPROD\NDA202834\\0014\m5\datasets\e2007-a001-024\analyses\datasets\adpdtm.xpt

2.3 Reviewer's Assessment

In the reviewer's report P, A1.5, A3, K100, Per8, Per24, and Per36 denote placebo, alprazolam 1.5 mg and 3 mg, ketamine 100 mg, perampanel 8 mg, 24 mg and 36 mg, respectively. P8, P24, and P36 denote the washout placebo followed by Per8, Per24 and Per36, respectively. Responses to the washout placebos were eliminated in both the sponsor's and the reviewer's analyses.

2.3.1 Missing data issue

The reviewer examined the data for abuse potential measures using heat map displays proposed by Chen and Wang (2012).

Appendix I – VI show the heat maps for time course individual response profiles by treatment for Drug Liking VAS, ARCI MBG, ARCI PCAG and High VAS, respectively. From these figures, one may see that a lot of subjects had missing data at early hours for A3, Per24, and Per36. For example (See Figure 23), for Per36 23.5% (8/34), 38.2% (13/34), 32.3% (11/34), and 26.5% (9/34) of subjects had missing data at hours 1, 2, 3, and 4, respectively. Subject #9112 had missing data from hour 1 to hour 8. The missing data situation in this study was severe. The reviewer requested an explanation from the Sponsor for the missing data issue. The sponsor reported that many subjects experienced somnolence and other AEs in the treatment periods. The following table summarizes the AEs in Sponsor's Table 1 in the document saf-info-amend.pdf submitted to FDA on August 3, 2012. The detailed information may be found at \\Cdsesub1\evsprod\NDA202834\0039\m1\us\111-info-amend\1112-safe-info-amend

Table 1: Summary of AEs in Treatment Periods

AE	A3	A1.5	Per24	Per36
Somnolence	14	2	10	15
Drowsiness			1	3
Confusion				1
Decreased concentration			1	
Multiple AE			1	2

The missing data in this study are informative missing. These missing data can not be imputed for the following reasons:

- When the data were collected at multiple time points. The intention was to collect the information from subjects at the moment. Thus, either the last observation carry forward or the first observation after the missing move backward does not make sense for this study. In addition, the primary analysis is based on Emax. Using existing data of a subject to impute the subject's missing data would not change Emax.

- Another way may be to impute the missing data at a time point by the average of the responses from subjects who had data at the time point. This still does not make sense, because obviously the subjects who were awake were not affected by the sedative effects from A3 or two high doses of perampanel. In other words, the subjects who had missing data and the subjects who did not have missing data were two different subgroups in the study population.

Even though, statistically, missing data can be imputed in many cases, it is definitely not the case for this study. Therefore, missing data were not imputed in the reviewer's analysis.

Note that data for Overall Drug Liking VAS and Take Drug Again VAS were collected at hours 12, 24 and 48. Because the analysis population consisted of completers, every subject in the analysis population should have completed the assessment for these measures. Even though these two measures were secondary measures in the study, they should provide relevant information regarding overall assessment of perampanel from subjects who had missing data due to somnolence or some other AEs. Therefore, besides the primary measures Subjective Drug Value (SDV) ($) which was measured at hours 12, 24, and 48, the reviewer also included Overall Drug Liking VAS in her analyses.

2.3.2 Descriptive Statistics for Primary Abuse Potential Measures

Table 2 summarizes the mean, standard error, minimum, the first quartile (Q_1), median, the third quartile (Q_3), and maximum for the primary measures.

Table 2: Summary Statistics for Emaxs for Primary Measures (N=34)

Abuse Potential Measure	TRT	Mean	StdErr	Min	Q1	Med	Q3	Max
Drug Liking VAS	A1.5	76.62	2.75	50	66	74.5	89.25	100
	A3	77.38	2.70	50	65.75	76.5	92	100
	K100	90.26	2.34	50	85.25	96	100	100
	P	55.50	2.01	50	51	51	52	100
	Per24	82.68	2.91	51	71.25	86	100	100
	Per36	80.29	3.31	50	59.5	85.5	100	100
	Per8	72.62	3.14	50	52.5	69	89.75	100
ARCI MBG	A1.5	5.65	0.74	0	2	4.5	7.5	16
	A3	8.32	0.75	1	4	8.5	11.25	16
	K100	8.47	0.72	0	5.75	9	11.25	16
	P	0.85	0.29	-1	0	0	1	7
	Per24	7.94	0.88	0	3	8	12	16
	Per36	8.44	0.98	0	2.75	7.5	15	16
	Per8	3.94	0.67	0	1	3	5	15
ARCI PCAG	A1.5	8.15	0.66	-9	7	8.5	10	14
	A3	9.09	0.40	5	7.75	9	11	14
	K100	4.94	0.61	-2	2	4.5	8	11
	P	1.59	0.52	-1	0	1	1.25	11
	Per24	8.65	0.54	2	6	9	11.25	14
	Per36	9.59	0.43	3	8	10	11.25	14
	Per8	5.09	0.63	0	1.75	5	8	13
Subjective Drug Value (SDV) ($)	A1.5	23.26	2.89	0.25	9.38	18.50	40.75	48
	A3	25.40	2.90	0.25	10.50	20.75	41.63	48
	K100	27.10	2.96	0.25	11.75	26.75	45.19	48
	P	6.54	2.45	0.25	0.25	0.25	1.06	48
	Per24	23.24	3.14	0.25	5.44	21.25	40.75	48
	Per36	23.85	2.99	0.25	9.56	17.75	40.13	48
	Per8	16.01	2.93	0.25	0.25	10.25	31.31	48

*: Emax was calculated based on change from predose response.

Table 2 shows that both means and medians of Per24 and Per36 were larger than those of A1.5 and A3 for Emax of Drug Liking VAS. Twenty five percent of subjects had maximum liking score 100 to Per24 and Per36. For Emax of ARCI MBG and Emax of ARCI PCAG, the third quartiles of Per24 and Per36 were larger than those of A3 and K100. Overall, the summary statistics of Per24 and Per36 were similar to those of A3, not to those of K100.

Figures 1-3 are the mean time course profiles for Drug Liking VAS, ARCI MBG, and ARCI PCAG, respectively. In the mean time course profiles, because of the missing data issue, the means at early time points were calculated using data from subjects who had responses at these time points. In addition, hour 48 is not shown on the graphs, because there were no data collected

between 24 and 48 hours, and if including the mean response at hour 48, the main pattern of the graph would not be shown clearly in the graph.

From these figures, one may see that the mean time course profile of K100 is very different from alprazolam and perampanel. The profile demonstrated a rapid peak effects at hour 0.5 followed by a relatively rapid decline, except ARCI PCAG, for which K100 still reached the peak at hour 0.5 but had smaller peak mean score than all other treatments except placebo. For ARCI PCAG (See Figure 3), Per36 had the mean response 9.2 at hour 2 on the scale from 1 to 16 when 41.2% (14/34) subjects had missing data at that time, and the peak mean response 9.4 at hour 6 when only two subjects had missing data (See Figure 30 in Appendix III). On the average the sedative effects from Per36 continued for 22 hours (See Figure 3). At hour 24 the mean score to Per36 was still 8.7. Data were not collected between hours 24 and 48. At hour 48, the mean score to Per36 for ARCI PCAG was 4.8 even though it is not shown on the graph. Obviously, Per36 is highly sedative. From Figure 4 one may see that subjects would like pay more for K100. Besides the placebo, Per8 was valued low. The other four treatments, A1.5, A3, Per24 and Per36, were quite similar to each other in terms of SDV ($).

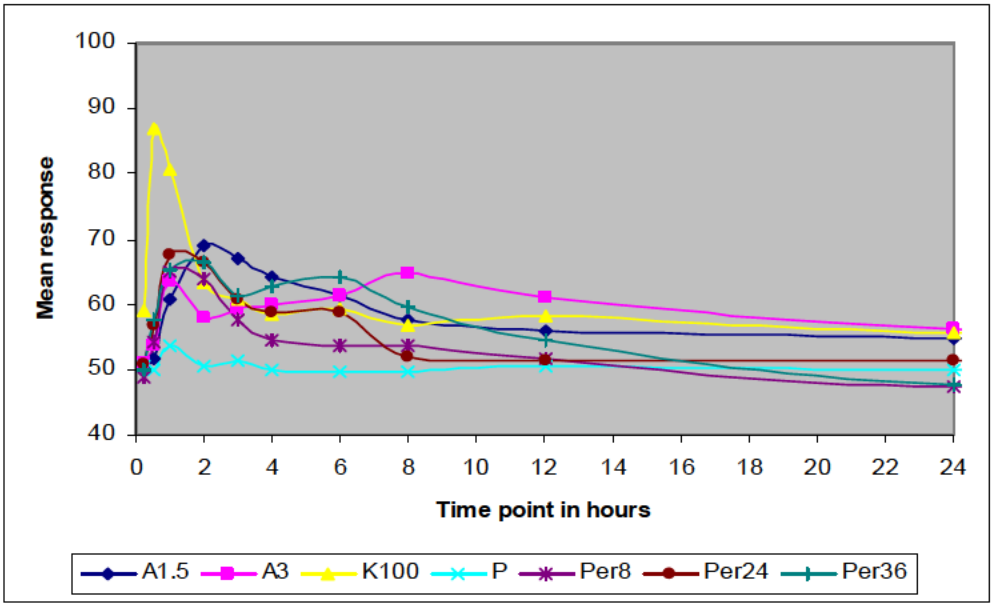

Figure 1: Mean time course profiles for Drug Liking VAS

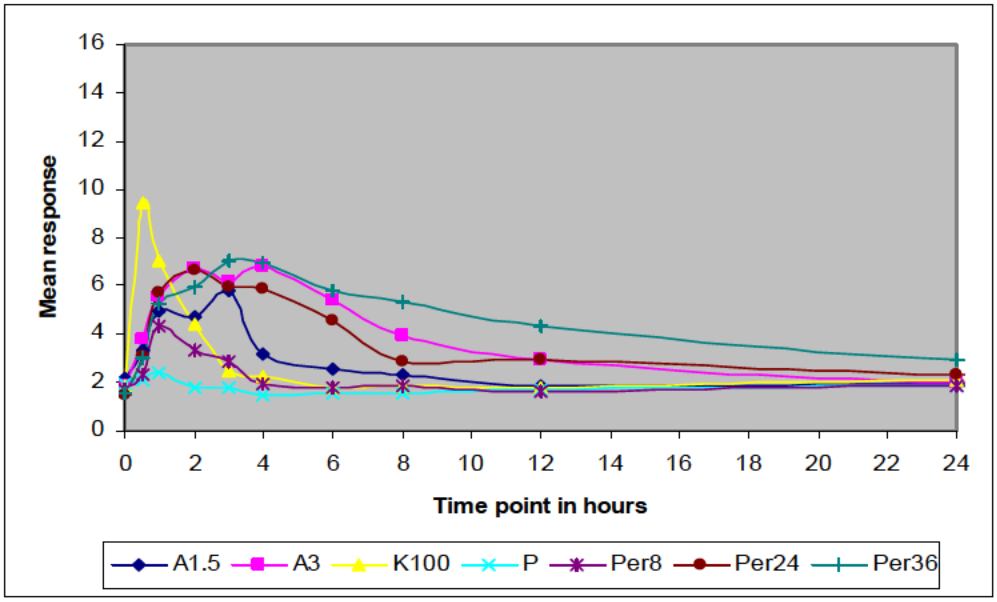

Figure 2: Mean time course profiles for ARCI MBG

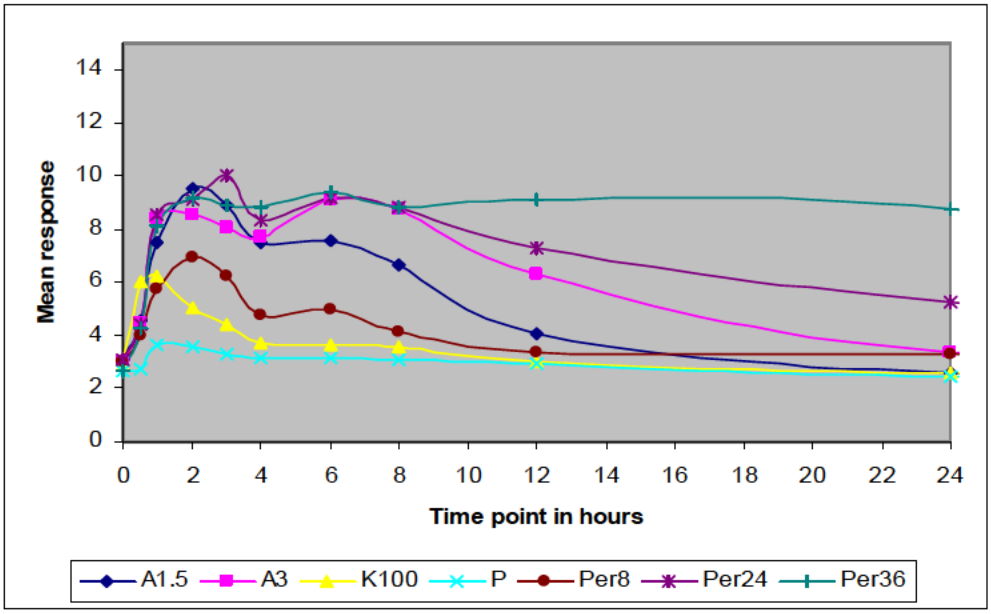

Figure 3: Mean time course profiles for ARCI PCAG

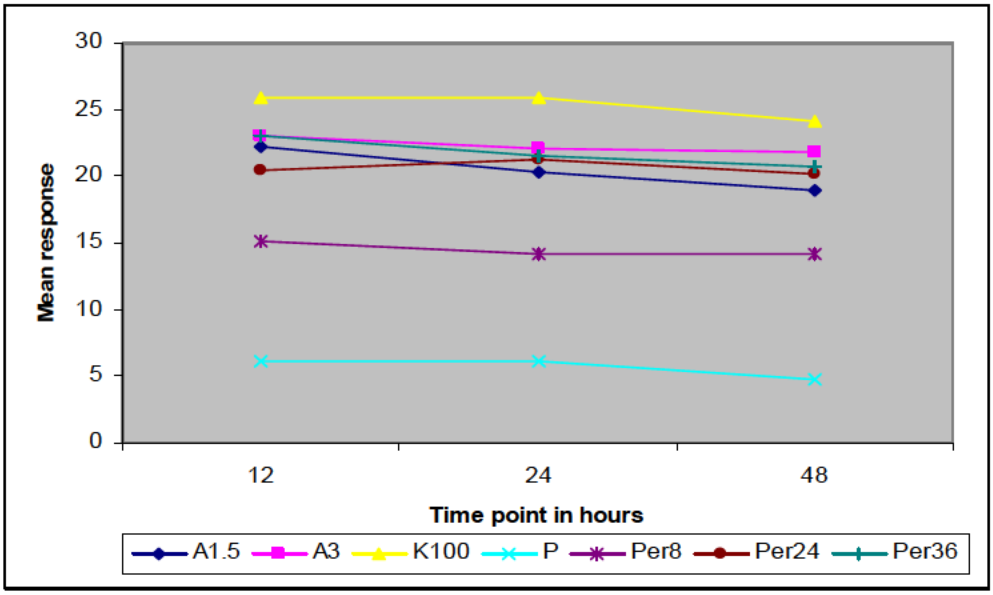

Figure 4: Means at hours 12, 24 and 48 for Subjective Drug Value (SDV) ($)

Table 3 summarizes the mean, standard error, minimum, the first quartile (Q_1), median, the third quartile (Q_3), and maximum for High VAS, Overall Drug Liking VAS, and Take Drug Again VAS.

From Table 3, it can be seen that overall Per24 and Per36 had Emax of High VAS greater than A3, and comparable to K100. Approximately 50% of subjects had Emax of High VAS at least 97.5 and 94 for Per24 and Per36, respectively. Even though the means and medians of Emax of Overall Drug Liking VAS and Take Drug Again VAS to Per24 and Per36 were lower than those to A3 and K100, approximately 25% subjects still had extremely high Emaxs to two high doses of perampanel for both measures.

Table 3: Summary Statistics in Emax for Other Three Measures (N=34)

Abuse Potential Measure	TRT	Mean	StdErr	Min	Q1	Med	Q3	Max
High VAS	A1.5	70.38	4.64	0	59.75	75.5	87.75	100
	A3	76.03	4.06	0	69.25	80.5	94.5	100
	K100	89.62	3.62	0	85.75	100	100	100
	P	10.03	4.42	-50	0	0	2.25	79
	Per24	85.38	3.78	9	76.5	97.5	100	100
	Per36	86.09	3.06	34	80.5	94	100	100
	Per8	56.00	7.02	-51	7.25	68.5	91.5	100
Overall Drug Liking VAS	A1.5	74.47	3.15	42	54	73.5	90.25	100
	A3	77.12	3.41	23	65.25	77.5	97	100
	K100	80.85	3.74	23	67.5	87	100	100
	P	54.06	1.66	50	50	51	51	92
	Per24	67.68	4.82	8	50.75	68	97.5	100
	Per36	67.94	5.39	0	48.25	74	100	100
	Per8	61.65	3.11	0	51	59.5	72	100
Take Drug Again VAS	A1.5	77.82	3.37	31	66.25	77	97	100
	A3	75.41	4.03	14	63.5	78	100	100
	K100	81.88	4.56	0	73.25	96	100	100
	P	42.85	4.69	0	21	50	51	100
	Per24	64.85	5.51	0	48.5	71	93	100
	Per36	64.29	5.72	0	50.75	70.5	95.5	100
	Per8	62.06	4.12	0	50	59	77.5	100

Figure 5 is the mean time course profiles for High VAS. High VAS is measured from 0 to 100 (unipolar). The peak mean response from K100 was approximately 90 reached at hour 0.5, and dropped down within 4 hours. Per24 and Pe36 reached their peak mean responses approximately 69 and 79 at hour 1 and 2, respectively. The means from two high doses of perampanel were larger than those of alprazolam at most time points. The profile from Per36 was quite flat between hour 8 and hour 24. At hour 24, the mean response to High VAS was 39.4. Because the data were not collected between hour 24 and hour 48, it can not be determined how long the high effects from Per36 lasted.

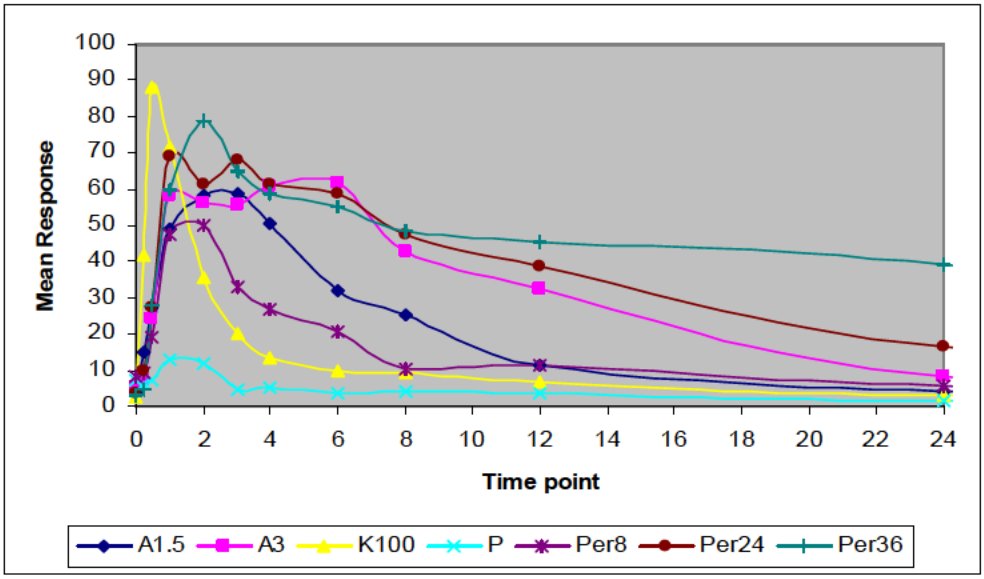

Figure 5: Mean time course profiles for High VAS

Figure 6 and Figure 7 show the mean responses at hours 12, 24, and 48 for Overall Drug Liking VAS, and Take Drug Again VAS, respectively. It can be seen that the mean responses to K100, A1.5, and A3 were larger than those to perampanel. For these measures, the mean was calculated based on the responses from 34 completers. In other words, there were no missing data for these two measures. Heat maps for Emax of Overall Drug Liking VAS and Emax of Take Drug Again VAS by treatment are presented in Figure 39 and Figure 40, respectively (See Appendix V).

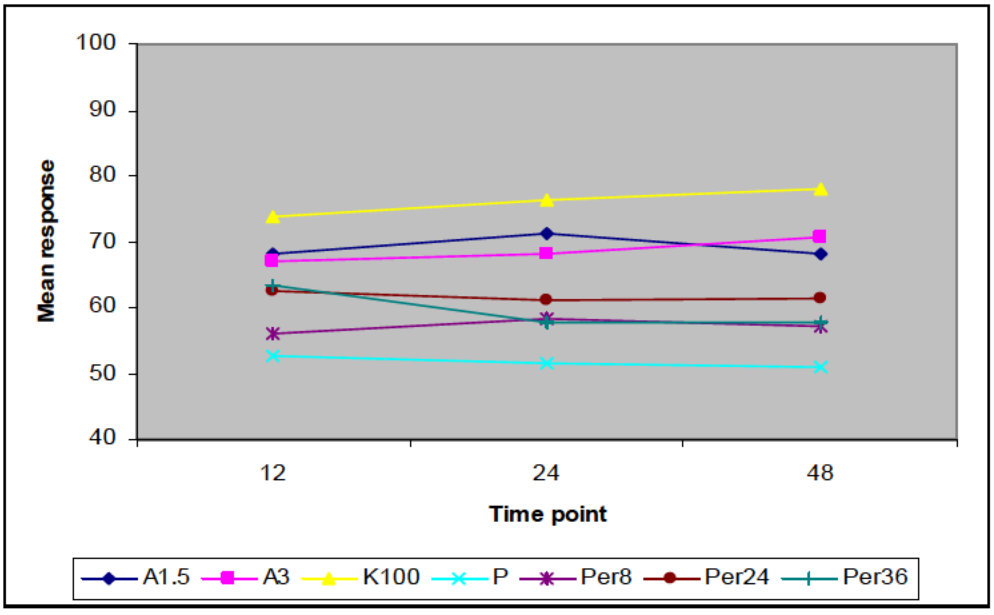

Figure 6: Means at hours 12, 24 and 48 for Overall Drug Liking VAS

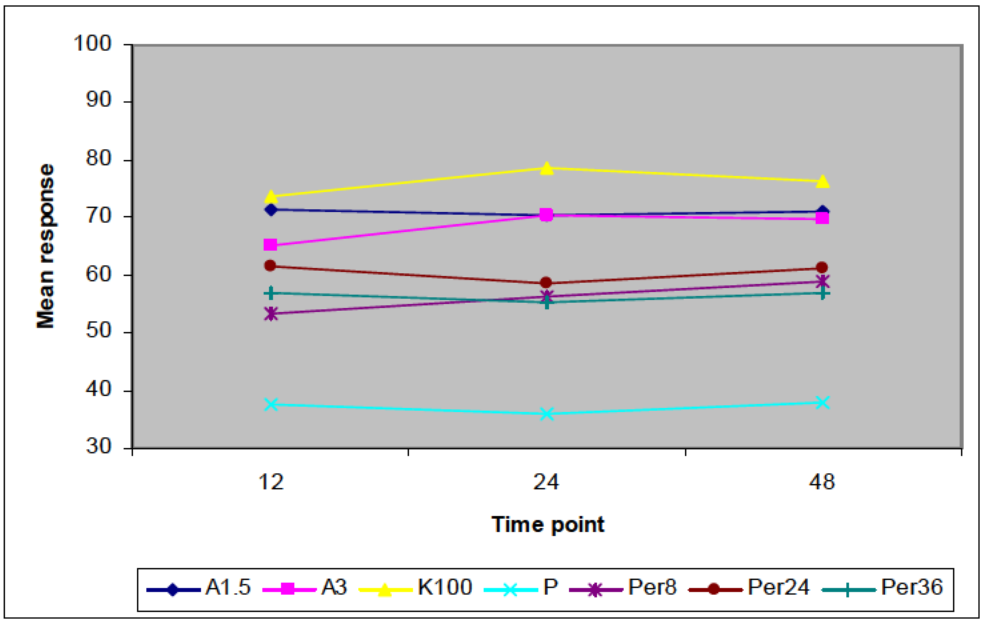

Figure 7: Mean time course profiles for Take Drug Again VAS

2.3.3 Statistical Testing

The statistical model used in the reviewer's analysis was the mixed-effect model with sequence, period, and treatment as fixed effects, and subject nested within sequence as a random effect. If the model assumptions were not satisfied, the Wilcoxon sign-rank test on the within-subject differences was used. The following comparisons were performed in the reviewer's analysis:

Alprazolam 1.5 mg versus placebo
Alprazolam 3 mg versus placebo
Ketamine 100 mg versus placebo
Perampanel 8 mg versus placebo
Perampanel 24 mg versus placebo
Perampanel 36 mg versus placebo
Alprazolam 1.5 mg versus perampanel 8 mg
Alprazolam 1.5 mg versus perampanel 24 mg
Alprazolam 1.5 mg versus perampanel 36 mg
Alprazolam 3 mg versus perampanel 8 mg
Alprazolam 3 mg versus perampanel 24 mg
Alprazolam 3 mg versus perampanel 36 mg
Ketamine 100 mg versus perampanel 8 mg
Ketamine 100 mg versus perampanel 24 mg
Ketamine 100 mg versus perampanel 36 mg
Perampanel 36 mg versus perampanel 8 mg
Perampanel 36 mg versus perampanel 24 mg
Perampanel 24 mg versus perampanel 8 mg

Detailed analysis results can be found in Appendix VI or VII.

Table 4 summarizes the analysis results. Because all treatments had means (or medians) significantly larger than placebo for all measures used in this review, the summaries in Table 4 are only for the comparisons A1.5, A3, and K100 versus three doses of perampanel, as well as the comparison between Per36 and Per24.

Table 4: Summary for Comparison between Positive Control Drugs and perampanel (α=0.05, two-sided)

Study E2007-A001-0024	Abuse Potential Measure	A1.5 vs. Per8	A1.5 vs. Per24	A1.5 vs. Per36	A3 vs. Per8	A3 vs. Per24	A3 vs. Per36	K100 vs. Per8	K100 vs. Per24	K100 vs. Per36	Per36 vs. Per24
Primary	Drug L king VAS	NS	NS(-)	NS(-)	NS	NS(-)	NS(-)	S	S	S	NS(-)
	ARCI MBG	S	S (-)	S (-)	S	NS	NS	S	NS	NS	NS
	ARCI PCAG	S	NS	S (-)	S	NS	NS	NS	S (-)	S (-)	NS
	SDV ($)	S	NS	NS(-)	S	NS	NS	S	NS	NS	NS
Secondary	High VAS	NS	S (-)	S (-)	S	S (-)	S (-)	S	NS	NS	NS
	Overall Drug Liking VAS	S	NS	NS	S	NS	NS	S	S	NS	NS
	Take Drug Again VAS	S	S	S	S	NS	NS	S	S	S	NS

Note: The (-) sign in the table show that in comparison of A versus B, the mean (or median) of B was greater than that of A. Otherwise, the mean (or median) of A was greater than that of B. S notes A had significantly larger mean (or median) response than B, and NS notes A did not have significantly larger mean (or median) response than B.

Table 4 shows that

- Perampanel 8 mg had significantly lower mean (or median) responses than alprazolam and ketamine in most comparisons listed in Table 4. For Drug Liking VAS, no significant difference in means was found between perampanel 8 mg and two doses of alprazolam. There was no significant difference in medians between alprazolam 15 mg and perampanel 8 mg for High VAS.
- Perampanel 24 mg and 36 mg had greater means than both doses of alprazolam for Drug Liking VAS. But these results were not statistically significant.
- Perampanel 24 mg and 36 mg had significantly larger means than alprazolam 1.5, and there was no significant difference in means between alprazolam 3 mg and two high doses of perampanel for ARCI MBG.
- There was no significant difference in means (or medians) between alprazolam 3 mg and two high doses of perampanel for ARCI PCAG and SDV ($) except in comparison between perampanel 36 mg and alprazolam 1.5 mg for ARCI PCAG. In this comparison, perampanel 36 mg had significantly larger median than alprazolam 1.5 mg.
- Perampanel 24 mg and 36 mg had significantly larger medians than both doses of alprazolam for High VAS.
- There was no significant difference in medians between perampanel 24 mg and 36 mg and both doses of alprazolam for Overall Drug Liking VAS.
- For Take Drug Again, there was no difference in medians between perampanel 24 mg and 36 mg and alprazolam 3 mg. However, alprazolam 1.5 mg had significantly larger median than two higher doses of perampanel.
- Compared ketamine 100 mg to two high doses of perampanel, no significant difference in means (or medians) was found for ARCI MBG, SDV($), and High VAS.

- For Drug Liking VAS and Take Drug Again, ketamine 100 mg had significantly larger means (or medians) than both high doses of perampanel.
- Perampanel 24 mg and 36 mg had significantly larger medians than ketamine 100 mg for ARCI PCAG.
- In the comparison for Overall Drug Liking VAS, the median of ketamine 100 mg was significantly larger than that of perampanel 24 mg, but not that of perampanel 36 mg.
- No significant results were found in comparison between perampanel 36 mg and perampanel 24 in all measures studied.

2.3.4 Good Effect VAS and Bad Effects VAS

Before making conclusion, the reviewer examined data from treatments Per24 and Per36 as well as A3 for Good Effect VAS and Bad Effect VAS using bar plots.

The bar plot compares the Emax of Good Effects VAS and Emax of Bad Effects VAS for individual subjects on the same plot. The light blue indicates Emax of Good Effects VAS, and the other color indicates Emax of Bad Effects VAS. Each subject has two bars standing one in front of the other on the graph. If one bar is higher than the other, this bar is put behind the other bar. For example, Subject #21 had 100 and 47 for Emax of Bad Effects VAS and Emax of Good Effects VAS, respectively. The graph shows the bar for Bad Effects VAS behind that for Good Effects VAS. If only one color shows on the bar, it means that either the other Emax is zero or the values of two Emaxs are the same. For identifying the latter case, a star is marked on the bar.

Figure 8 shows the individual response in Emax to Per24 for both Good Effects VAS and Bad Effects VAS.

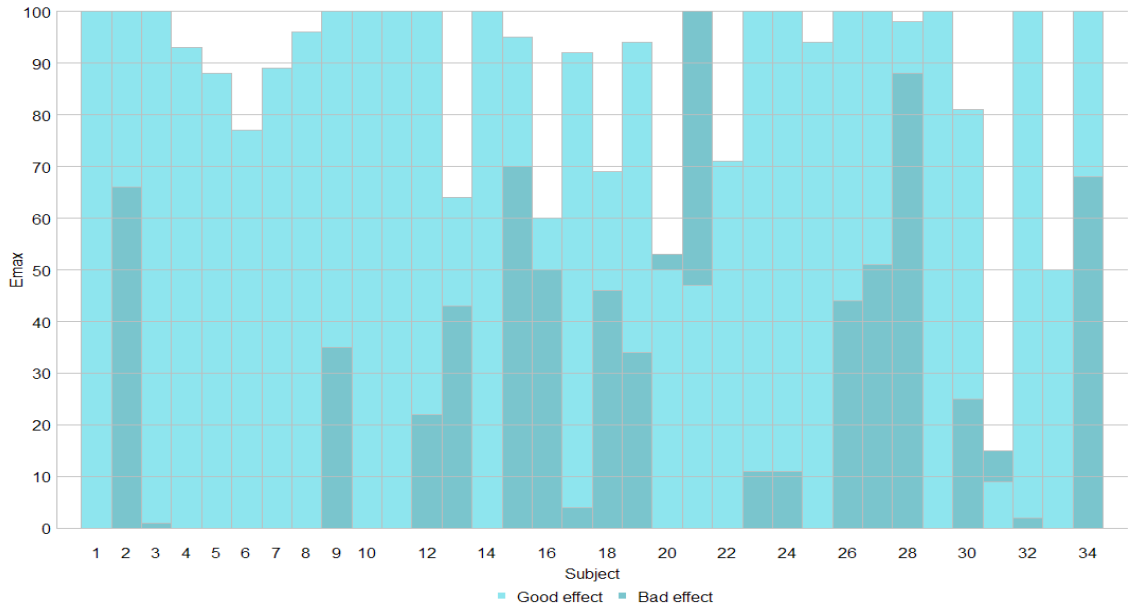

Figure 8: Comparison between Emax of Good Effects VAS and Emax of Bad Effects VAS for Per24

From Figure 8 one may see that approximately 73.5% (25/34) subjects had score 80 or above, and 64.7% (22/34) had at least 90 for Emax of Good Effects VAS. Approximately 38.2% (13/34) subjects did not experience any bad effects from Per24. For those experienced bad effects only 3

of them had larger bad effects than good effects. Fifteen out of 34 subjects had Emax of Good Effects of 100.

Figure 9 is for Per36. Among 34 subjects, 33 subjects experienced some degree of bad effects. Approximately 52.9% (18/34) subjects had Emax of Bad Effect VAS at least 80. Five subjects had the same score in Emax for both measures (See the bars with a star). Subject 29 was the only one subject who had Emax of 100 to Good Effects VAS without any bad effects.

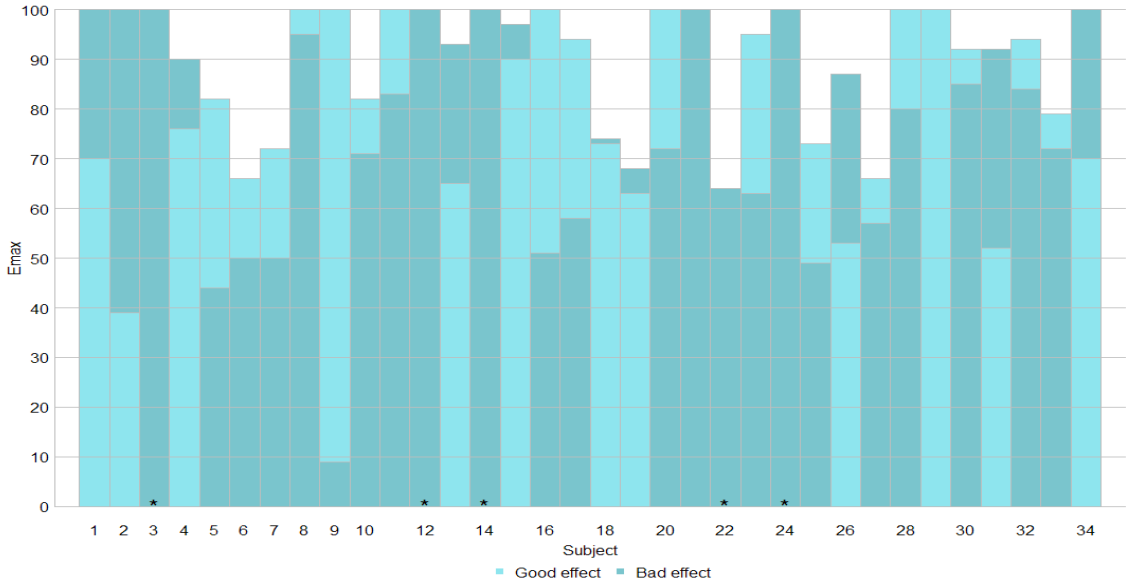

Figure 9: Comparison between Good Effects VAS and Bad Effects VAS for Per36

Figure 10 is for A3. Approximate 29.4% (10/34) subjects had larger Emax of Bad Effects VAS than that of Good Effects VAS. Five subjects had the same Emax for both measures, for which four of the five had Emaxs of 100.

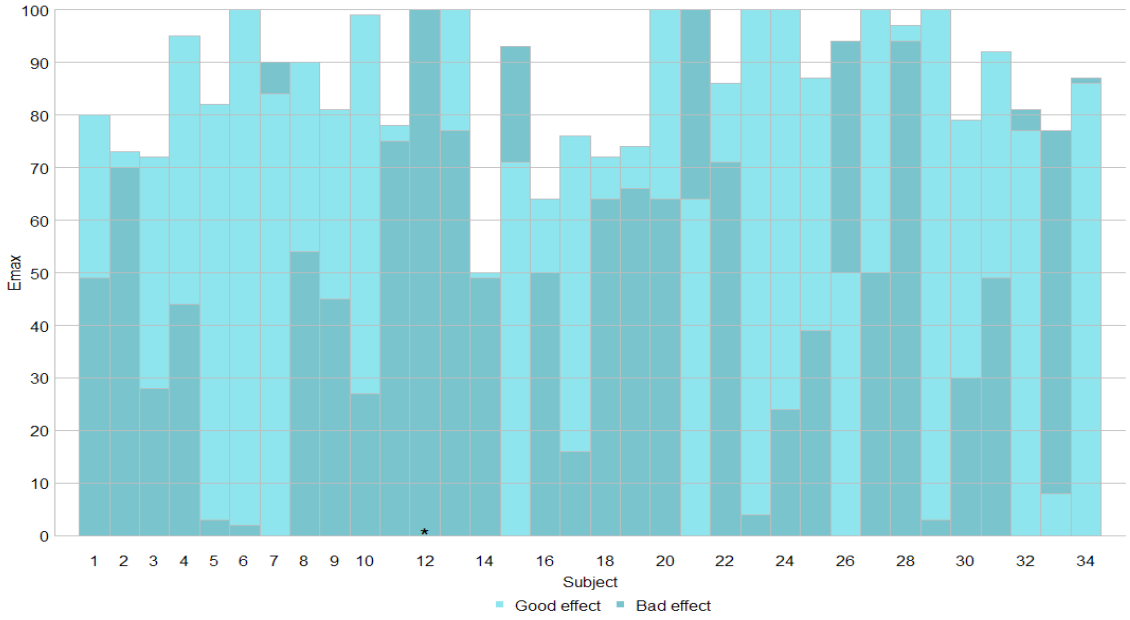

Figure 10: Comparison between Good Effects VAS and Bad Effects VAS for A3

3. Conclusion

This study showed that perampanel 8 mg had statistically lower effects compared to alprazolam and ketamine for three out of four primary measures. No significant difference in means was found between perampanel 8 mg and two doses of alprazolam for Drug Liking VAS, and between perampanel 8 mg and ketamine 100 mg for ARCI PCAG. Perampanel 24 mg and 36 mg were not statistically different in means (or medians) from alprazolam 3 mg for all primary measures. But both high doses of perampanel had significantly larger means than alprazolam 1.5 mg for ARCI MBG. Perampanel 36 mg also had significantly larger medians than alprazolam 1.5 mg for ARCI PCAG. Comparing ketamine 100 mg to two high doses of perampanel, no significant difference in means (or medians) was found for ARCI MBG, and SDV($). Ketamine 100 mg had significantly larger mean response than two high doses of perampanel for Drug Liking VAS, and significantly lower mean response than these doses of perampanel for ARCI PCAG.

The reviewer examined subject responses to the secondary measures High VAS, Overall Drug Liking VAS, and Take Drug Again. For High VAS, perampanel 24 mg and 36 mg had significantly larger median responses than both doses of alprazolam. On the average, perampanel 36 mg had long acting effects for ARCI PCAG and High VAS. These effects would last for at least 22 hours. The time course profiles (both mean and individual) of ketamine 100 mg demonstrated rapid peak effects followed by a relatively rapid decline for the measures used in the reviewer's analysis. Even though for High VAS there was no significant difference in medians between ketamine 100 mg and perampanel 36 mg, from heat map displays for individual time course response profiles, as well as the mean time course profiles, the difference between ketamine and perampanel were evident. Even though there was no significant difference in medians among two doses of alprazolam, ketamine 100 mg, and two high doses of perampanel for Overall Drug Liking VAS, alprazolam 1.5 mg and ketamine 100 mg had significantly larger medians than the two high doses of perampanel for Take Drug Again VAS.

The reviewer also evaluated data for Emax of Good Effects VAS and Emax of Bad Effects VAS for perampanel 24 mg and 36 mg, and alprazolam 3 mg. The results showed that most subjects had Emax of Good Effects VAS larger than that of Bad Effects VAS for perampanel 24 mg. On the other hand, many subjects experienced larger bad effects than good effects for perampanel 36 mg and alprazolam 3 mg. Because there was no significant difference in means (or medians) between two high doses of perampanel for all measures studied by the reviewer, and there were also no significant differences in mean (or medians) between perampanel 24 mg and alprazolam 3 mg except High VAS, perampanel 24 mg may have more abuse potential than both perampanel 36 mg and alprazolam 3 mg.

In conclusion, high doses of perampanel have large and long acting sedative and high effects. In addition, most subjects had good effects much larger than bad effects for perampanel 24 mg. Even though perampanel is more similar to alprazolam than to ketamine, perampanel may have more potential to be abused than alprazolam.

Disclaimer: All conclusions made by the reviewer were based on observed data without imputing the missing because there is a reason to believe that the participants whose data were missing were different from others. Thus, they might be biased.

4. Appendices

4.1 Appendix I: Heat map displays for individual time course response profiles for Drug Liking VAS

Note: The orange line separates females from males. The first six are female subjects. The gray color indicates missing data.

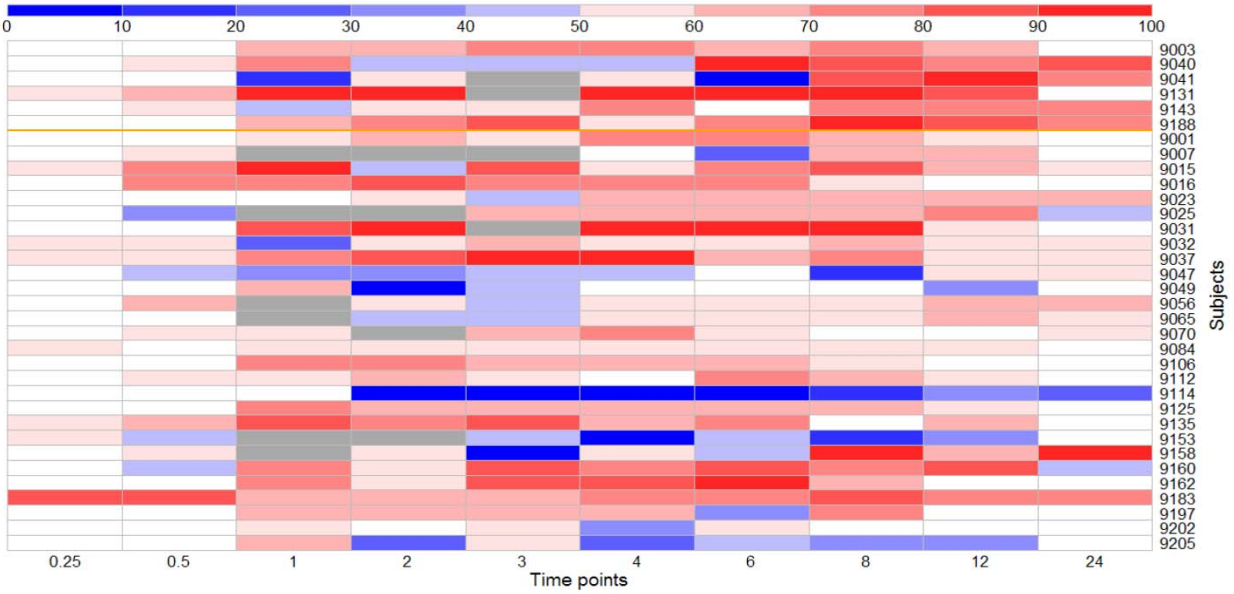

Figure 11: Time course response profiles for individual subjects to alprazolam 3 mg for Drug Liking VAS

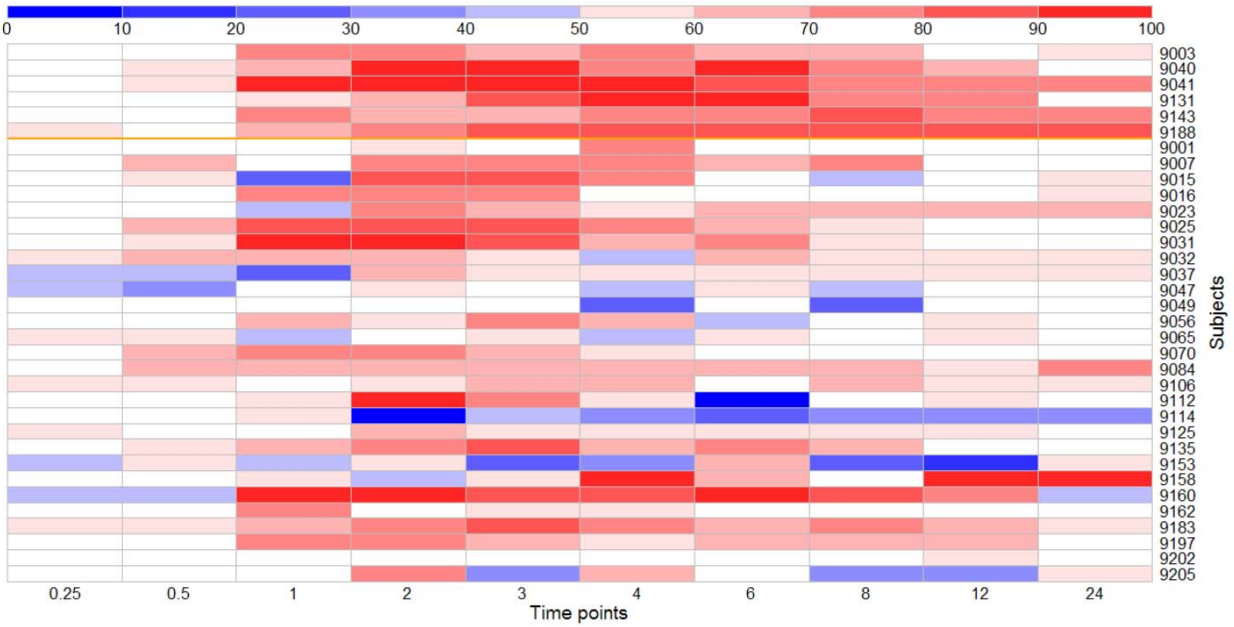

Figure 12: Time course response profiles for individual subjects to alprazolam 1.5 mg for Drug Liking VAS

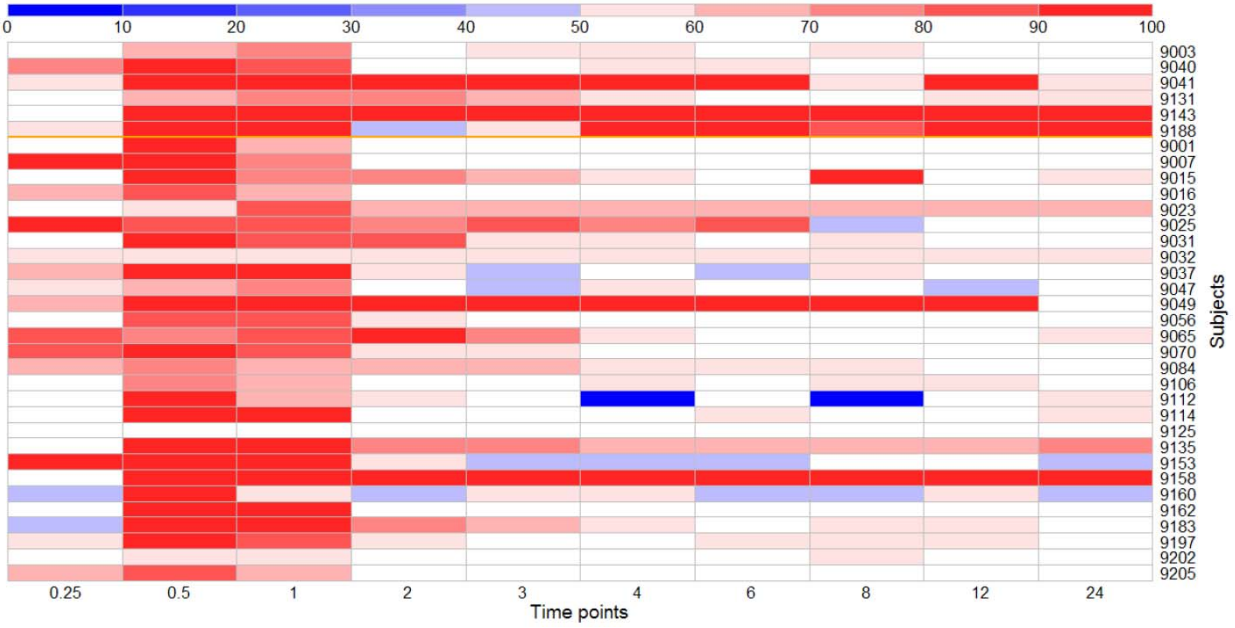

Figure 13: Time course response profiles for individual subjects to ketamine 100 mg for Drug Liking VAS

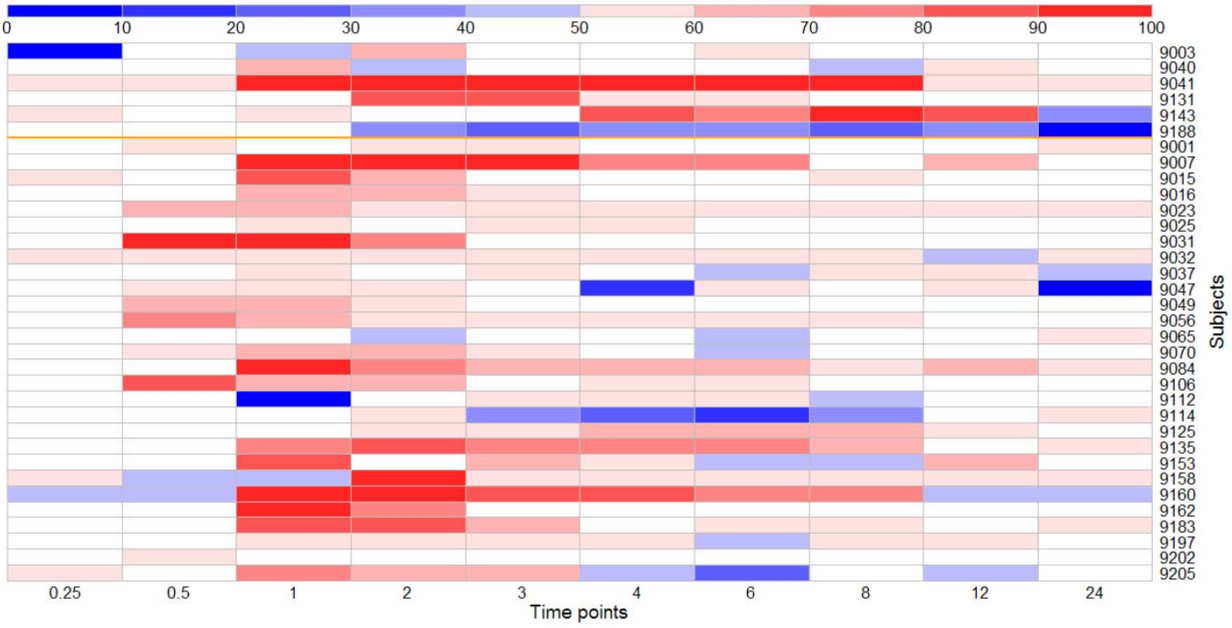

Figure 14: Time course response profiles for individual subjects to perampanel 8 mg for Drug Liking VAS

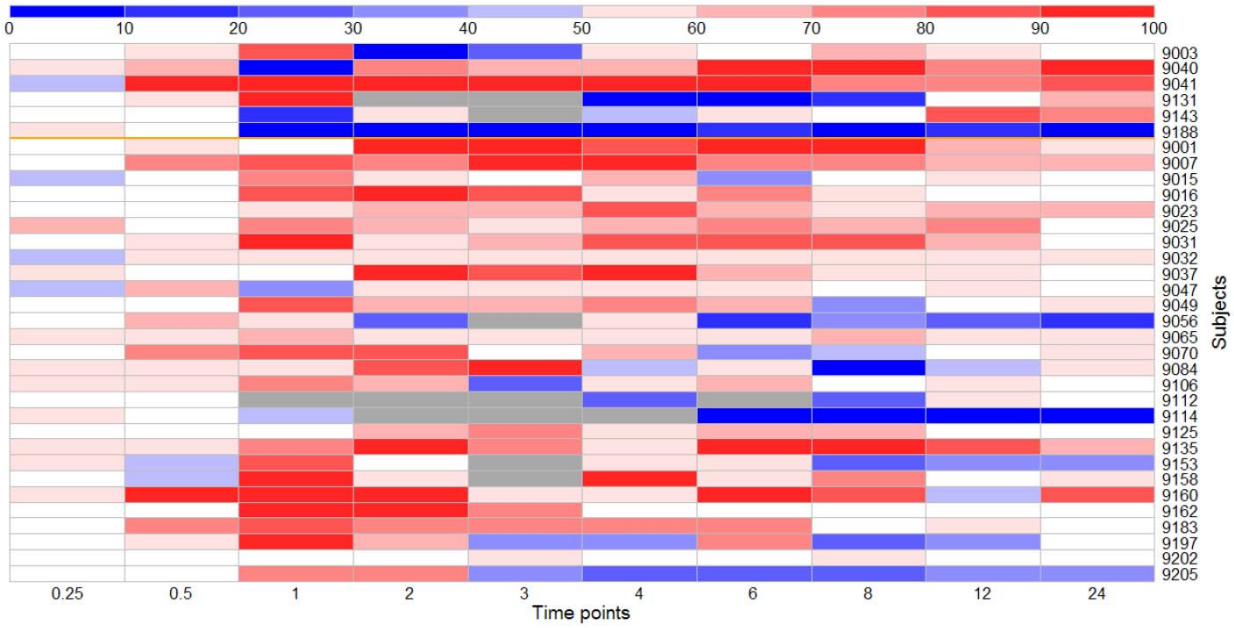

Figure 15: Time course response profiles for individual subjects to perampanel 24 mg for Drug Liking VAS

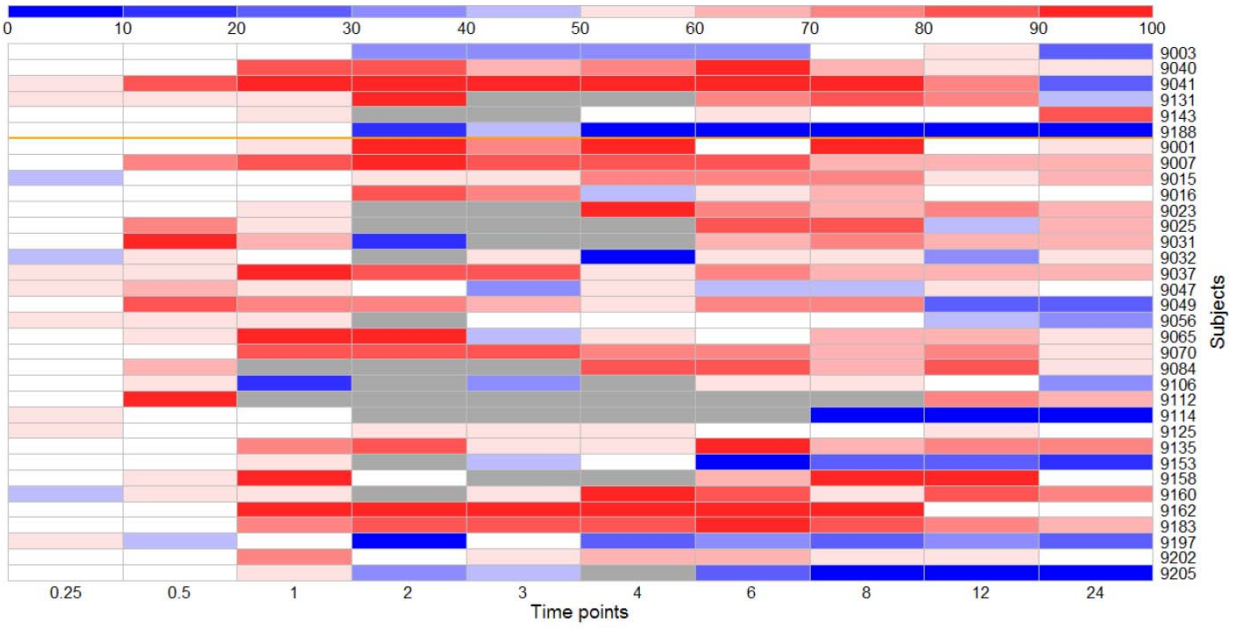

Figure 16: Time course response profiles for individual subjects to perampanel 36 mg for Drug Liking VAS

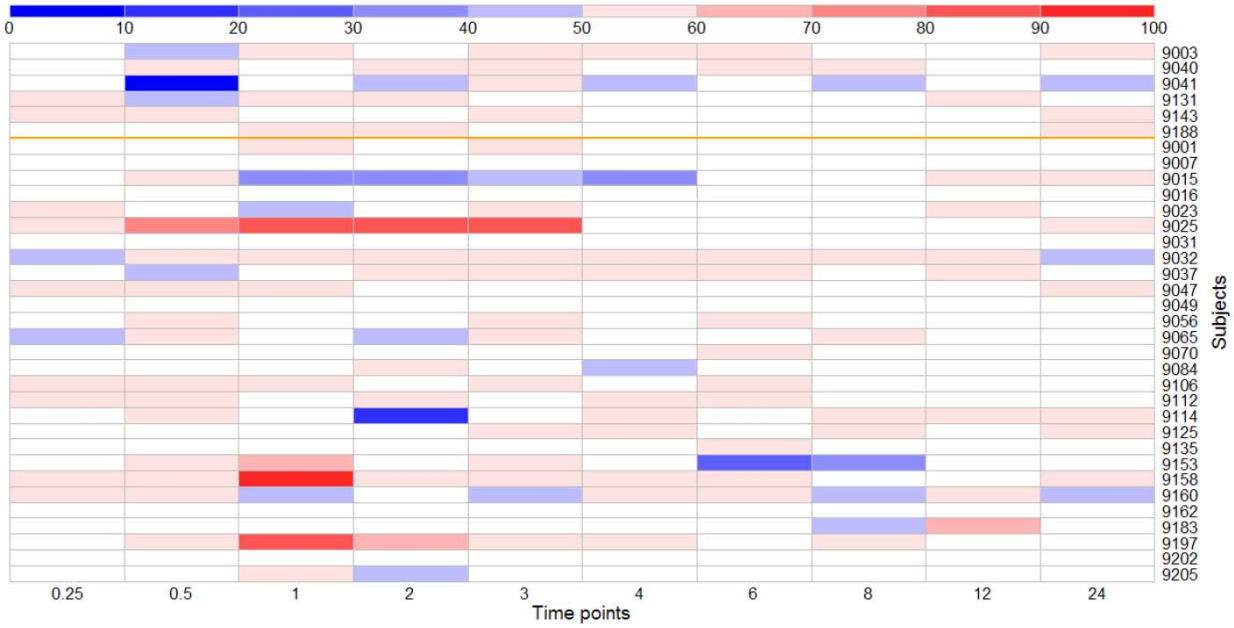

Figure 17: Time course response profiles for individual subjects to placebo for Drug Liking VAS

4.2 Appendix II: Heat map displays for individual time course response profiles for ARCI MBG

Note: The orange line separates females from males. The first six are female subjects. The gray color indicates missing data.

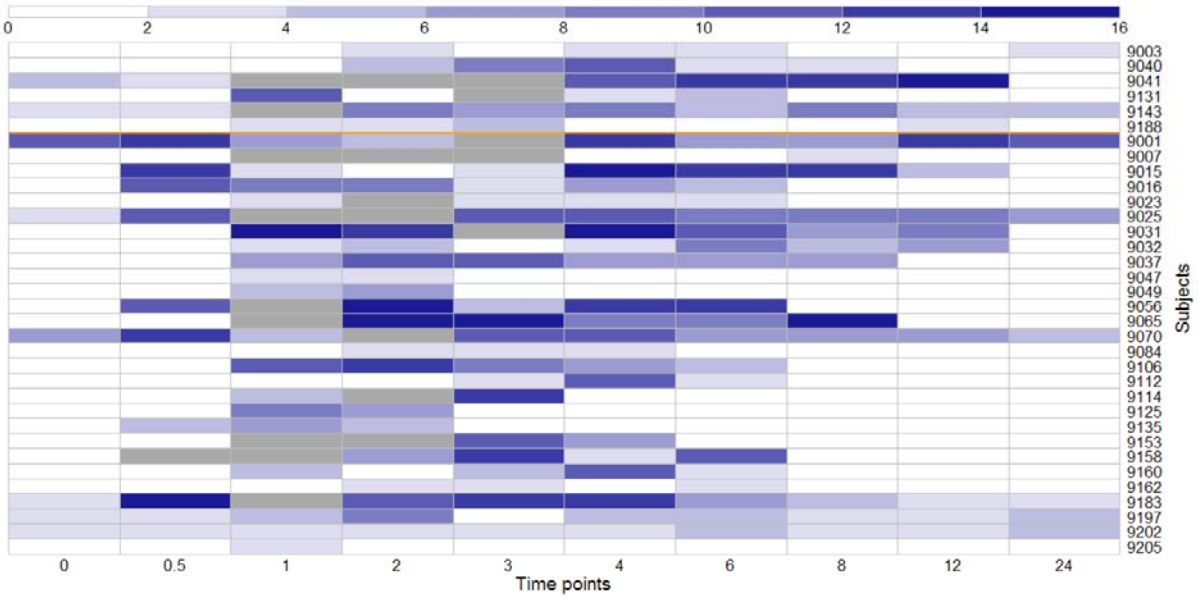

Figure 18: Time course response profiles for individual subjects to alprazolam 3 mg for ARCI MBG

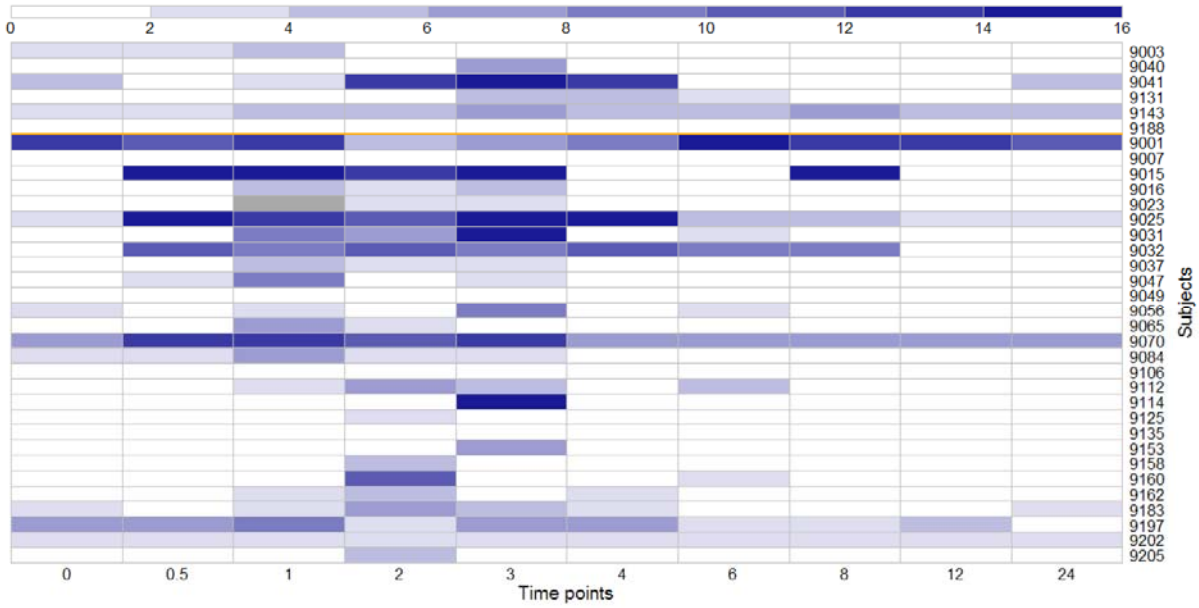

Figure 19: Time course response profiles for individual subjects to alprazolam 1.5 mg for ARCI MBG

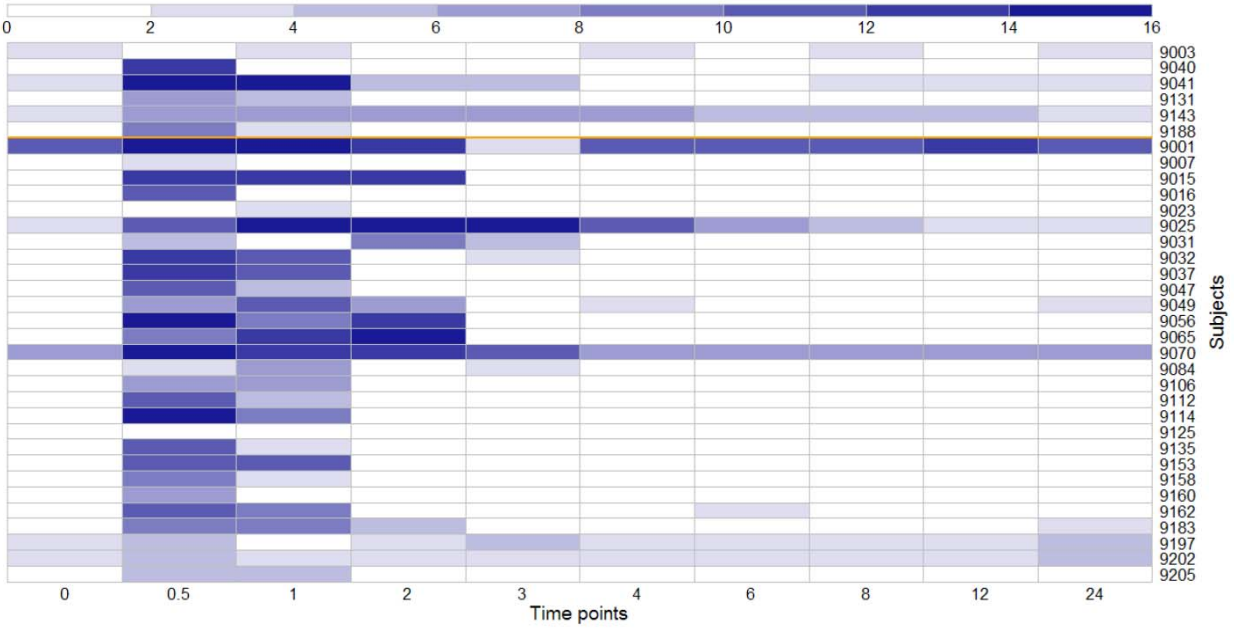

Figure 20: Time course response profiles for individual subjects to ketamine 100 mg for ARCI MBG

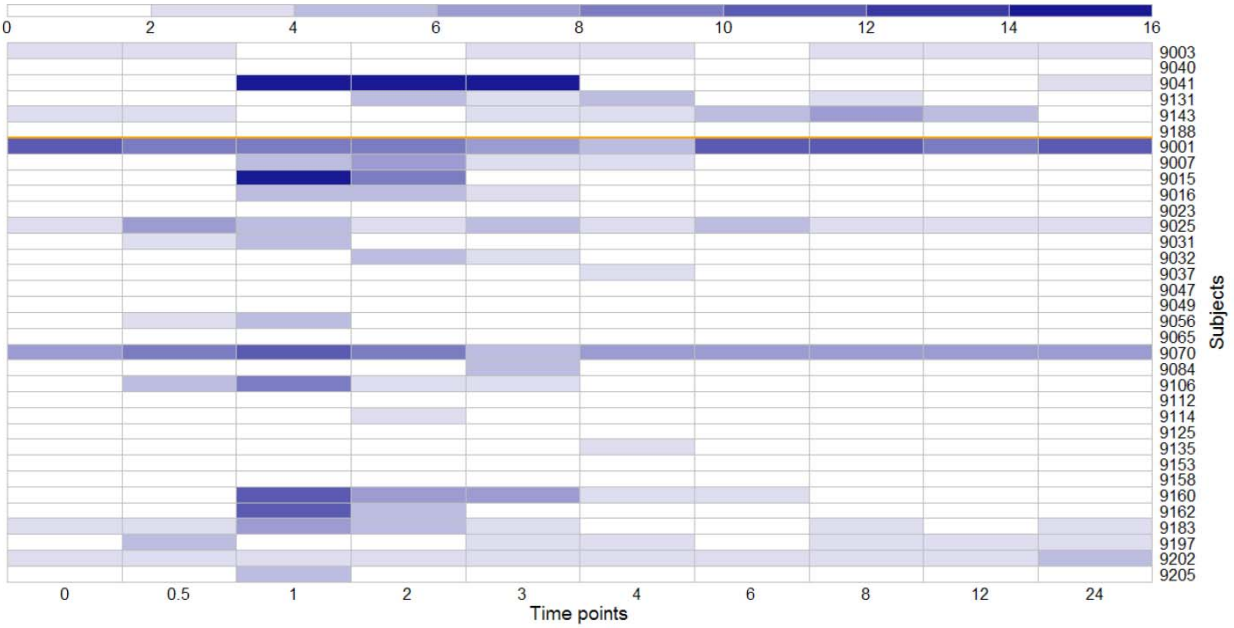

Figure 21: Time course response profiles for individual subjects to perampanel 8 mg for ARCI MBG

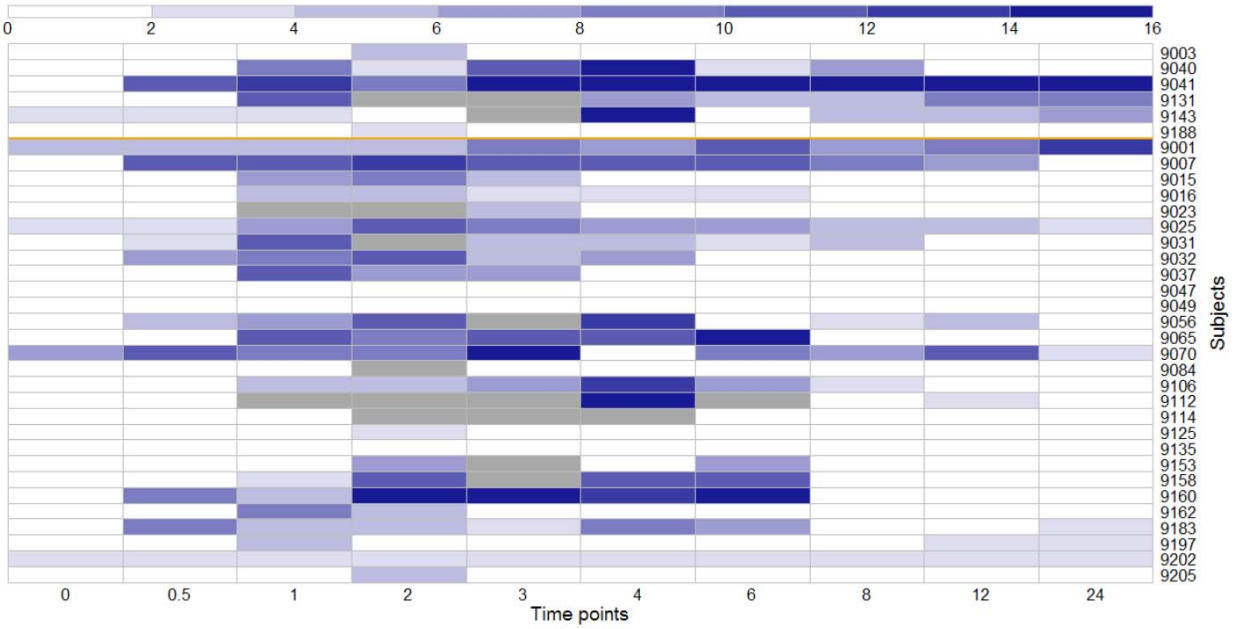

Figure 22: Time course response profiles for individual subjects to perampanel 24 mg for ARCI MBG

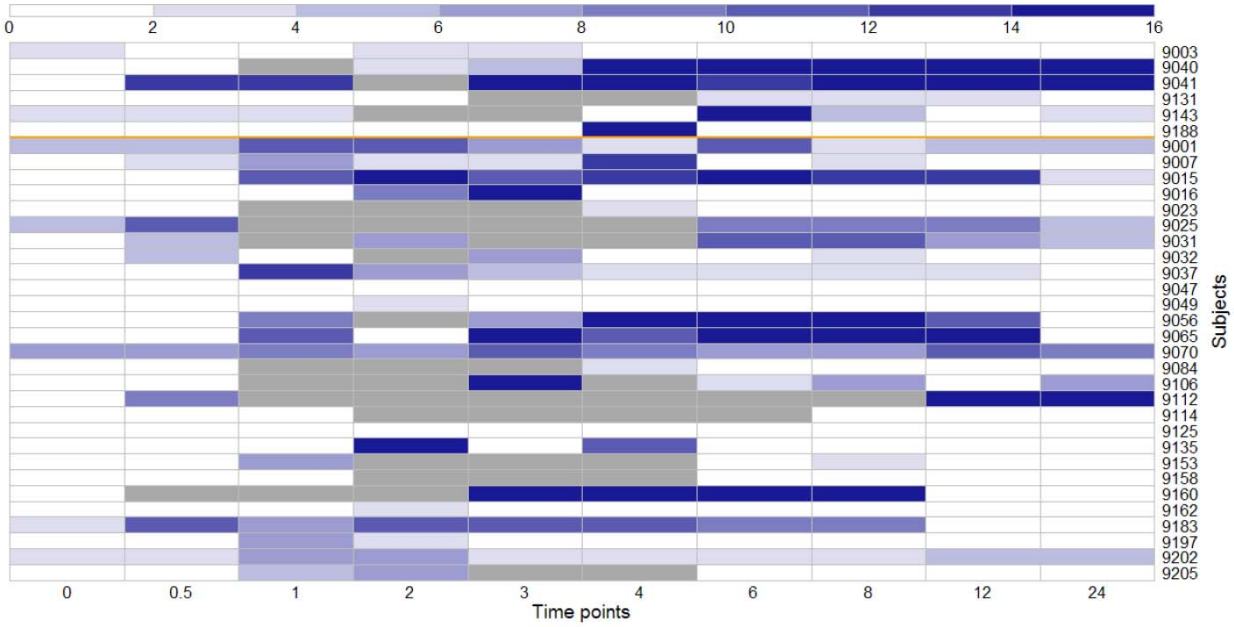

Figure 23: Time course response profiles for individual subjects to perampanel 36 mg for ARCI MBG

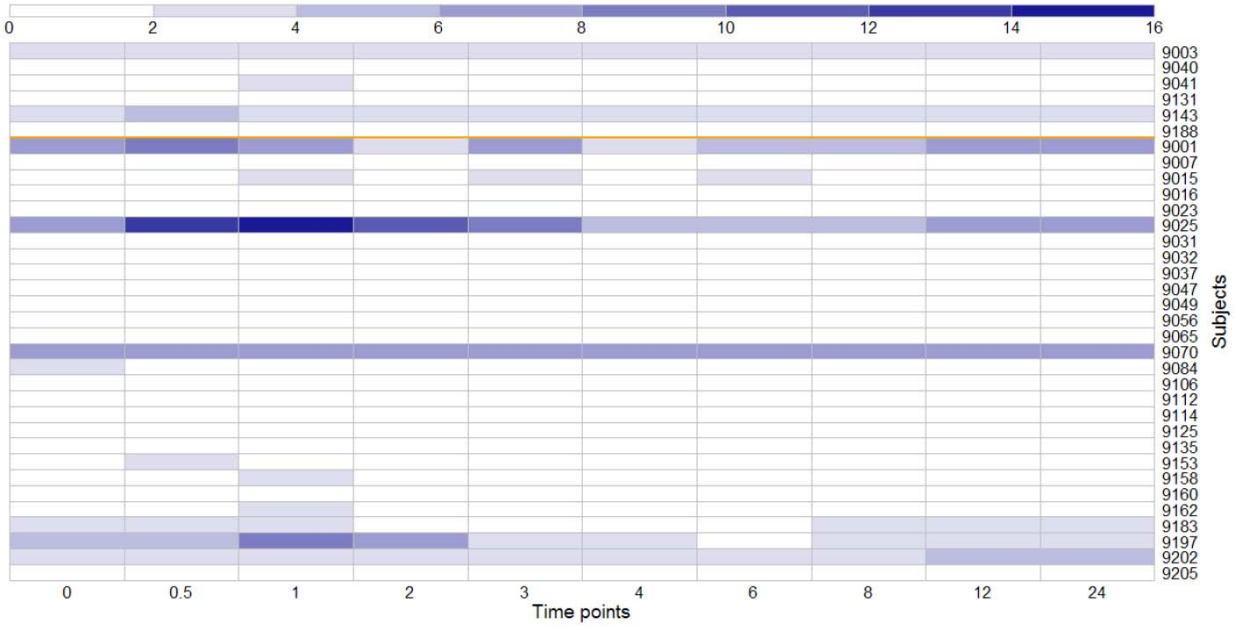

Figure 24: Time course response profiles for individual subjects to placebo for ARCI MBG

4.3 Appendix III: Heat map displays for individual time course response profiles for ARCI PCAG

Note: The orange line separates females from males. The first six are female subjects. The gray color indicates missing data.

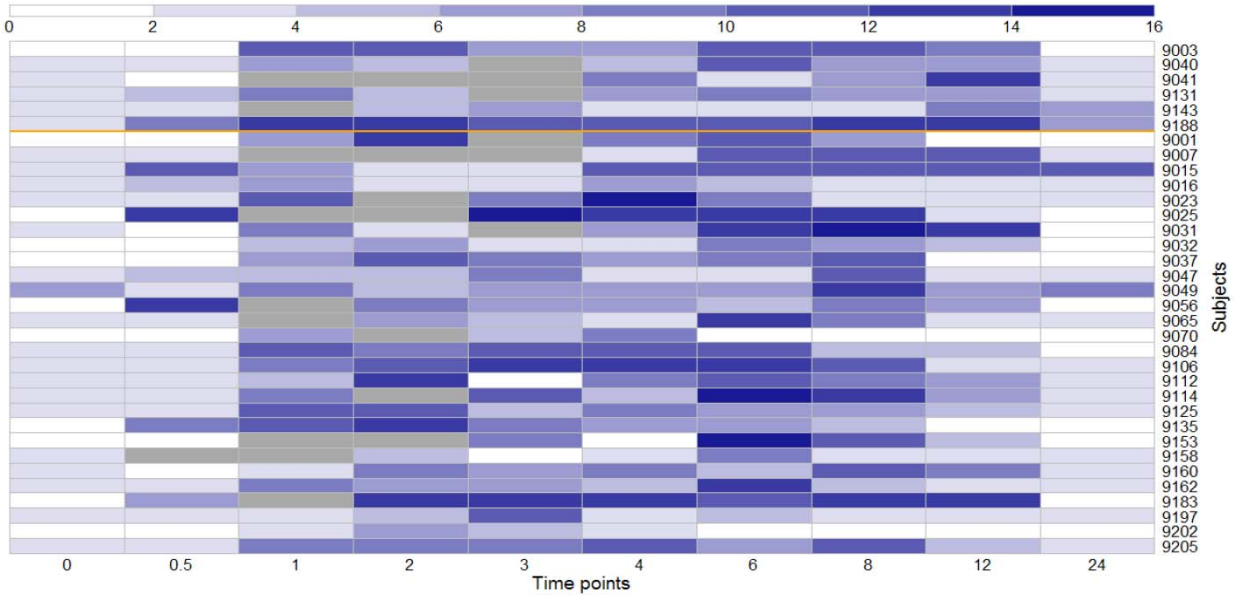

Figure 25: Time course response profiles for individual subjects to alprazolam 3 mg for ARCI PCAG

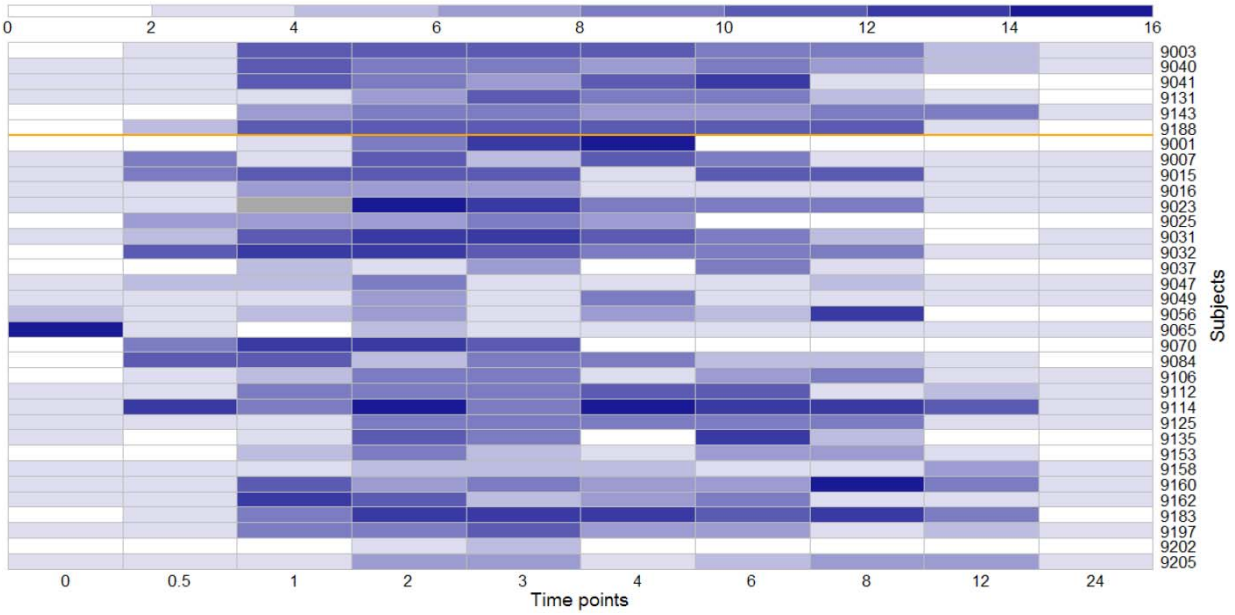

Figure 26: Time course response profiles for individual subjects to alprazolam 1.5 mg for ARCI PCAG

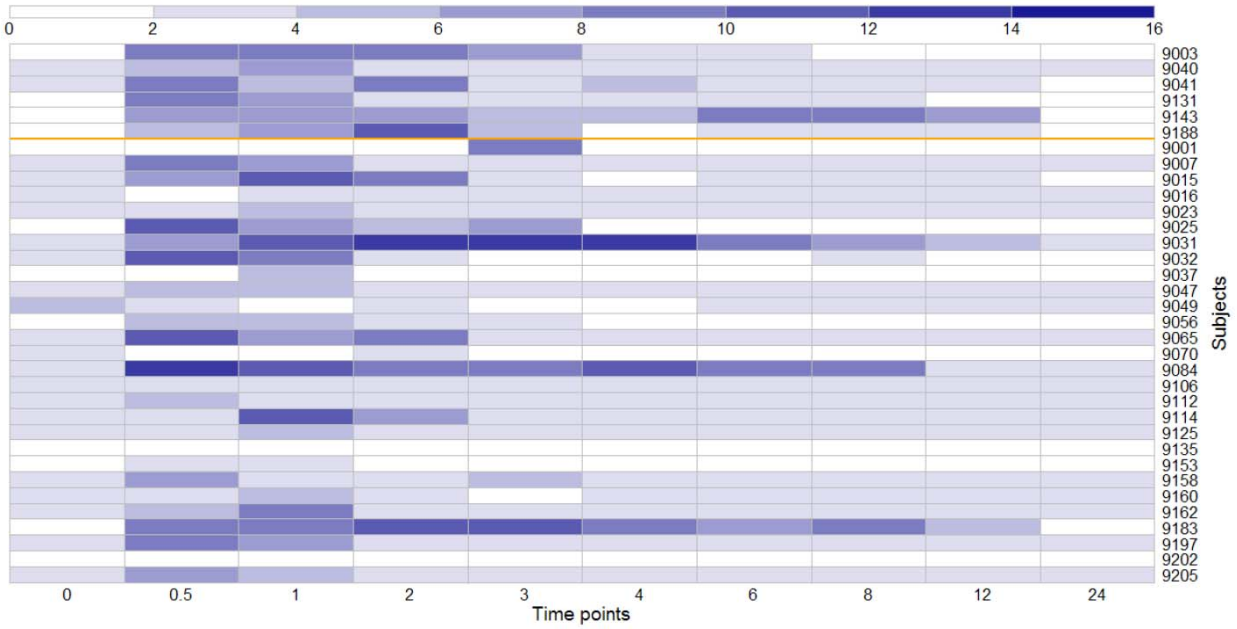

Figure 27: Time course response profiles for individual subjects to ketamine 100 mg for ARCI PCAG

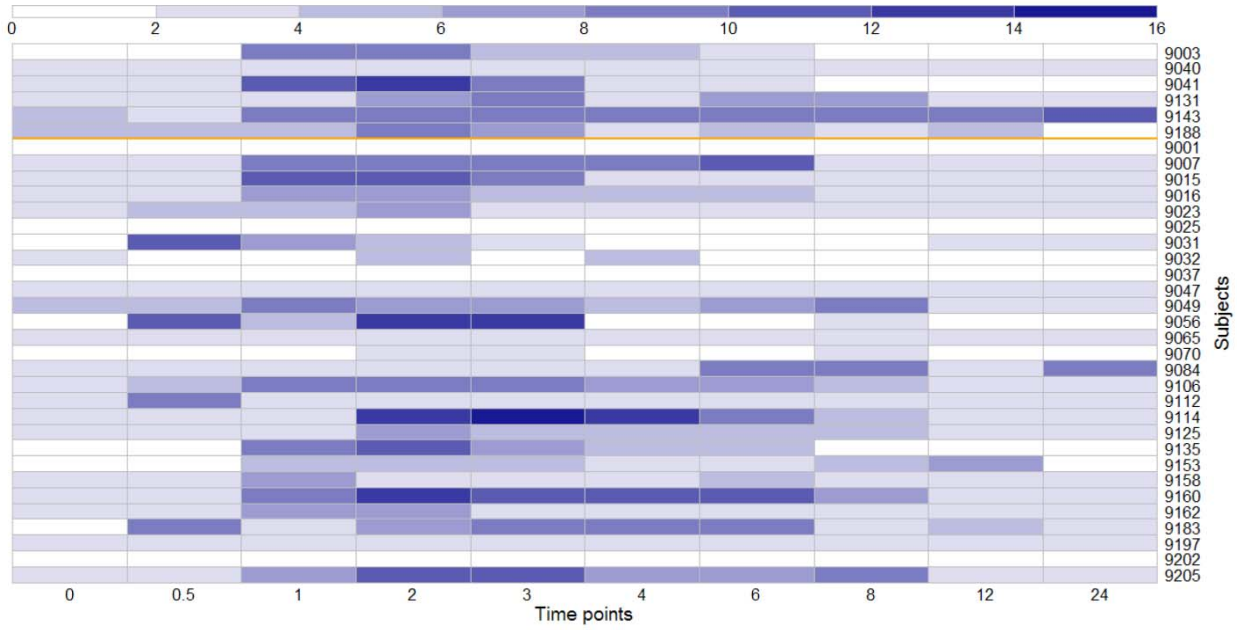

Figure 28: Time course response profiles for individual subjects to perampanel 8 mg for ARCI PCAG

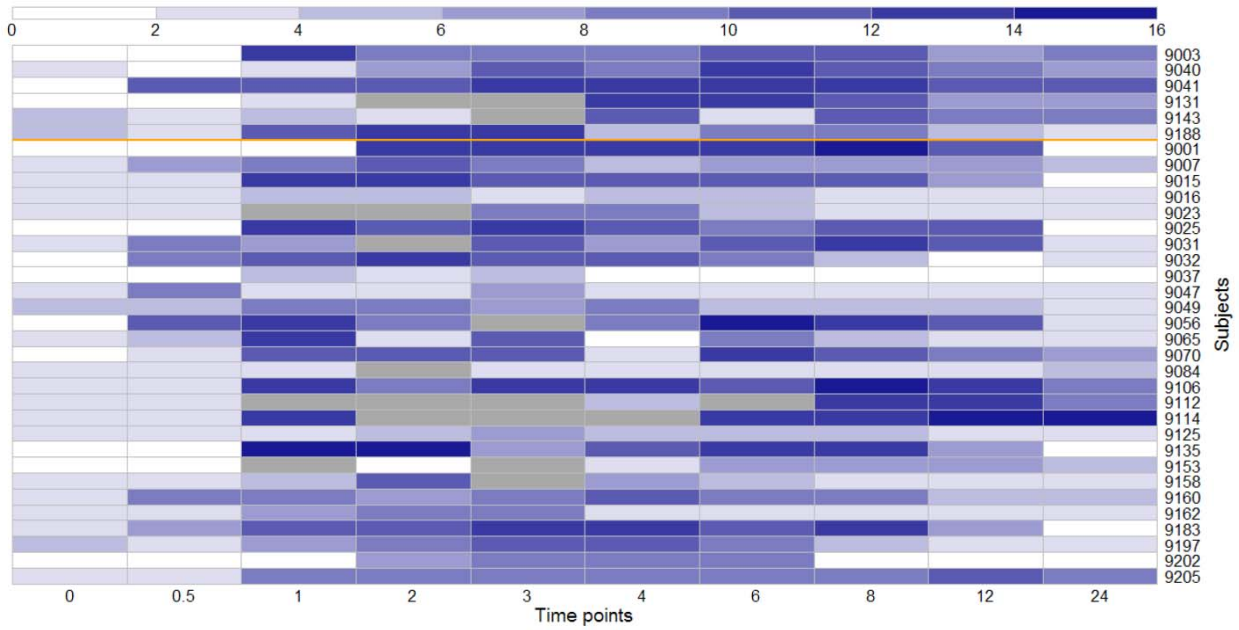

Figure 29: Time course response profiles for individual subjects to perampanel 24 mg for ARCI PCAG

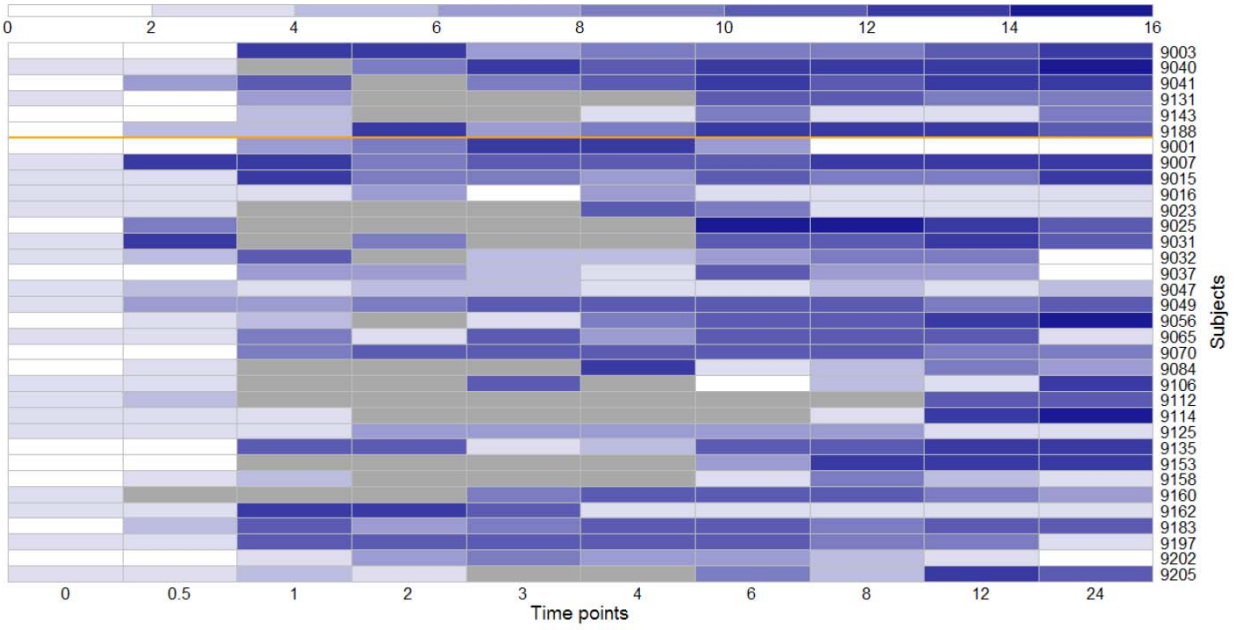

Figure 30: Time course response profiles for individual subjects to perampanel 36 mg for ARCI PCAG

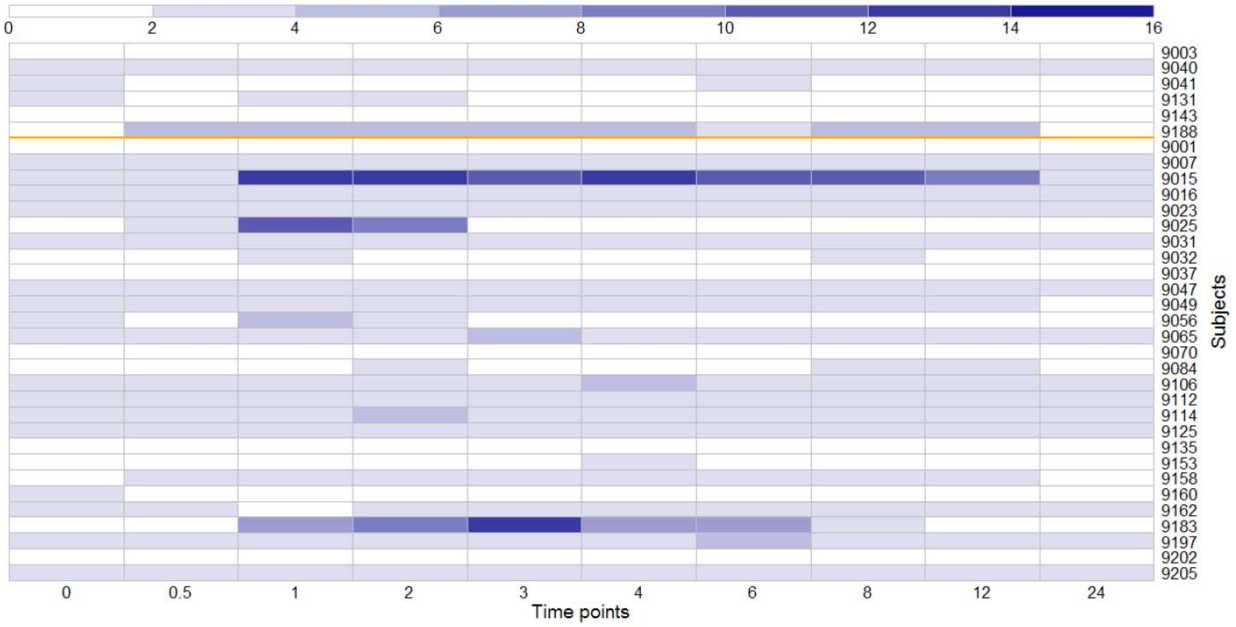

Figure 31: Time course response profiles for individual subjects to placebo for ARCI PCAG

4.4 Appendix IV: Heat map displays for individual time course response profiles for High VAS

Note: The orange line separates females from males. The first six are female subjects. The gray color indicates missing data.

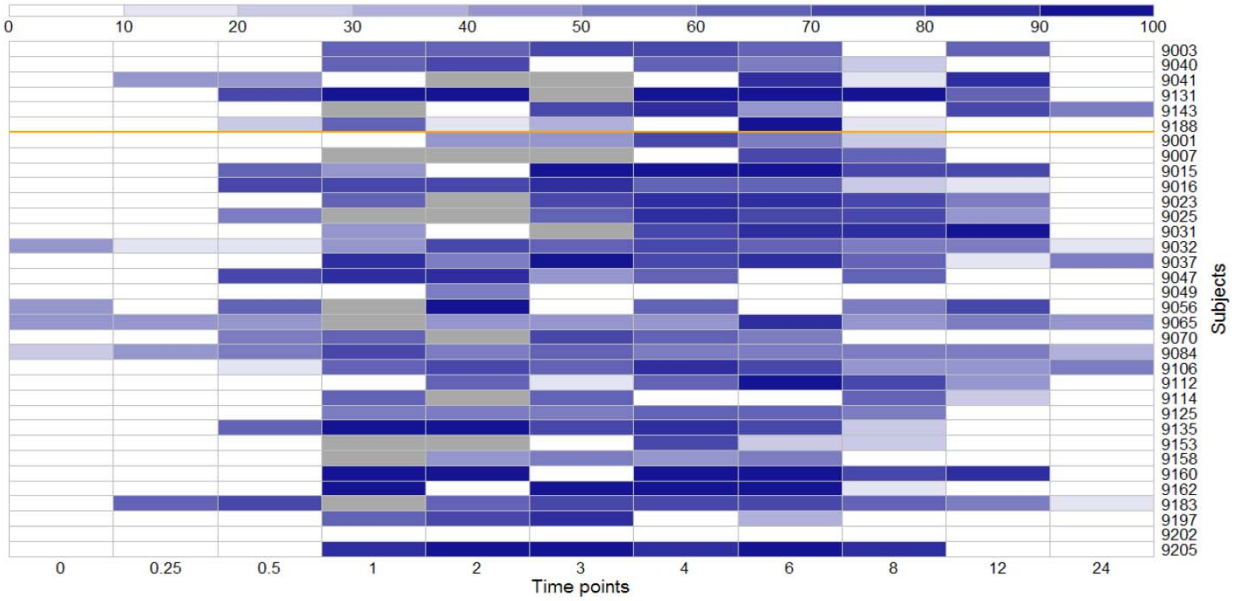

Figure 32: Time course response profiles for individual subjects to alprazolam 3 mg for High VAS

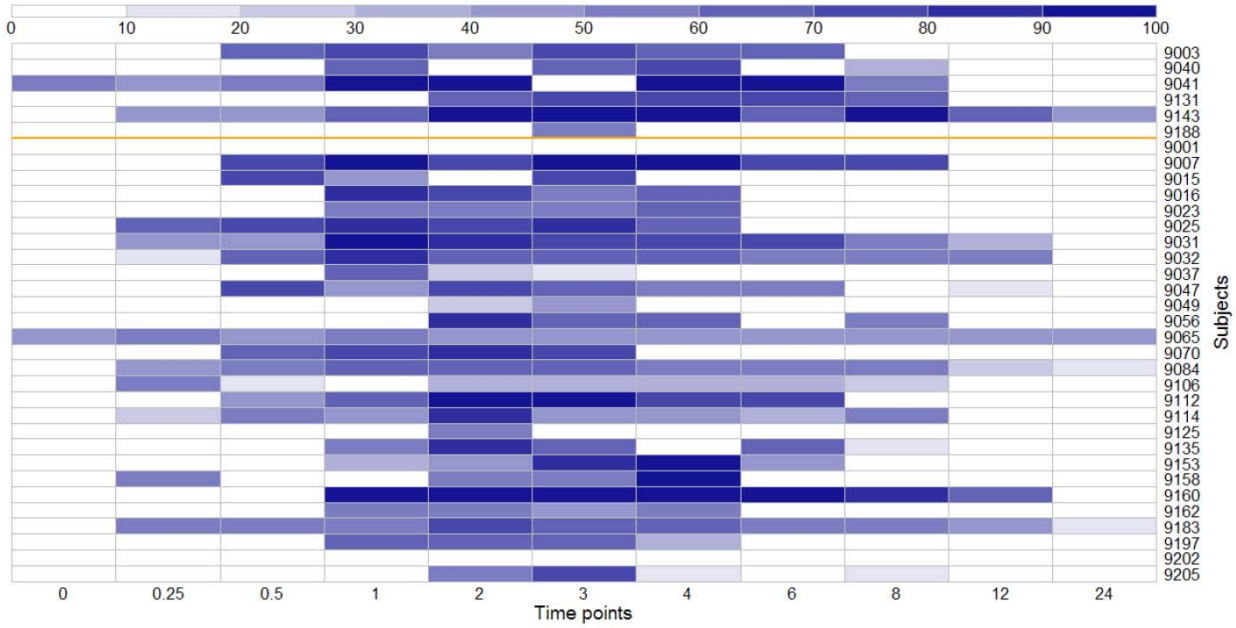

Figure 33: Time course response profiles for individual subjects to alprazolam 1.5 mg for High VAS

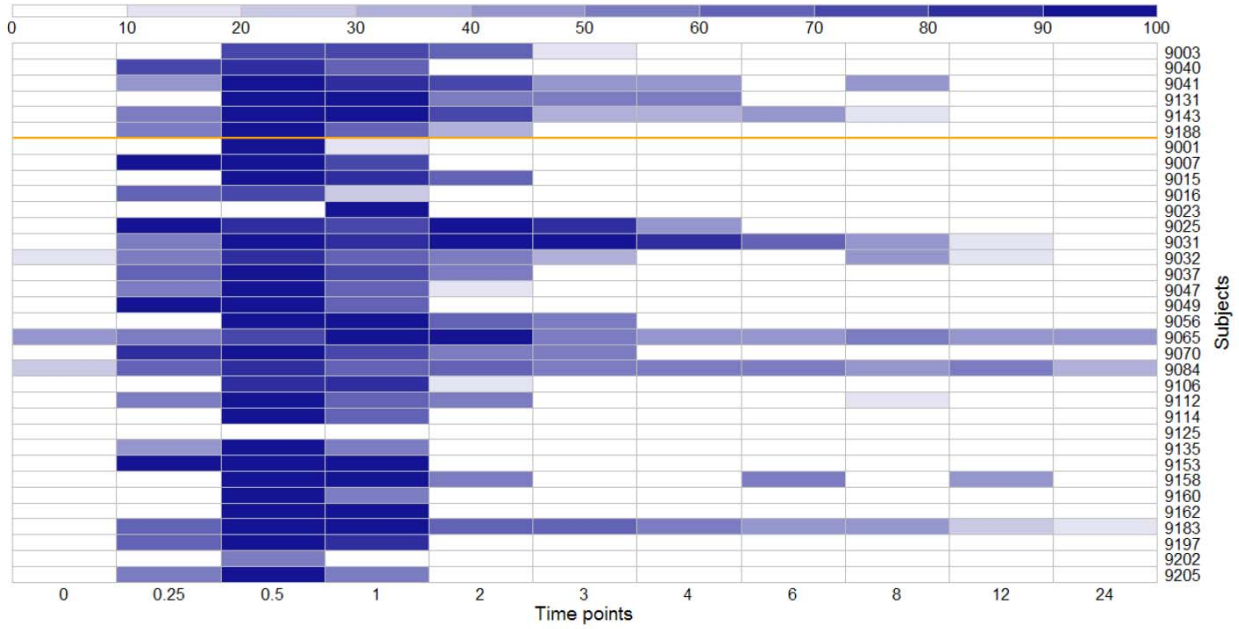

Figure 34: Time course response profiles for individual subjects to ketamine 100 mg for High VAS

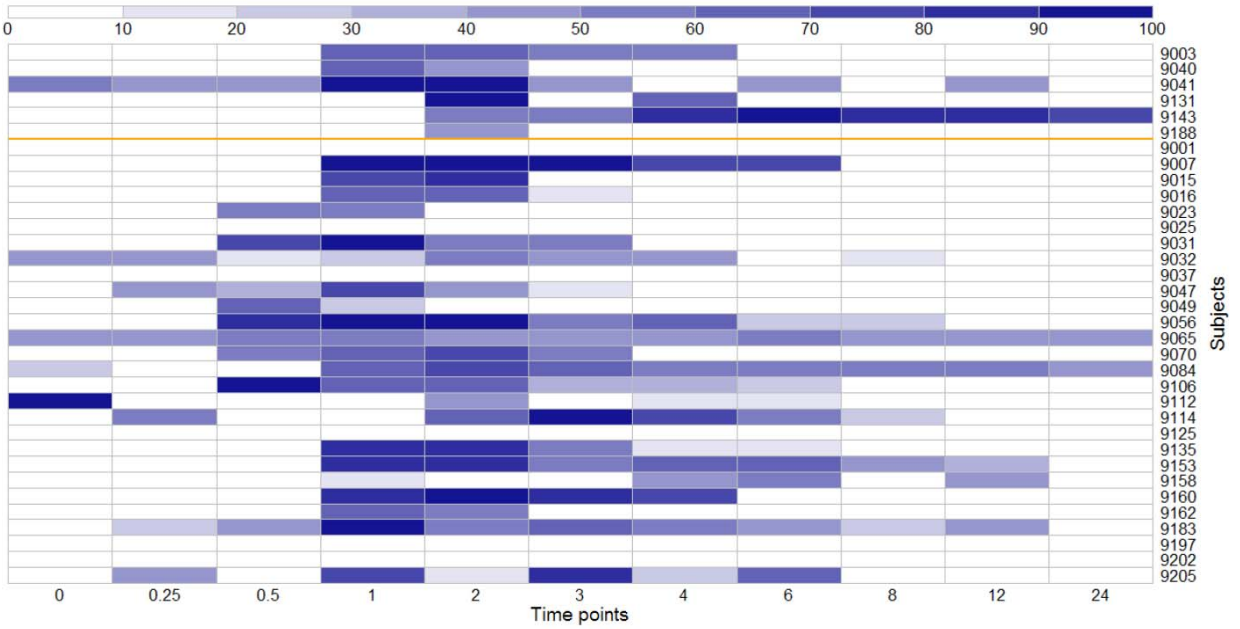

Figure 35: Time course response profiles for individual subjects to perampanel 8 mg for High VAS

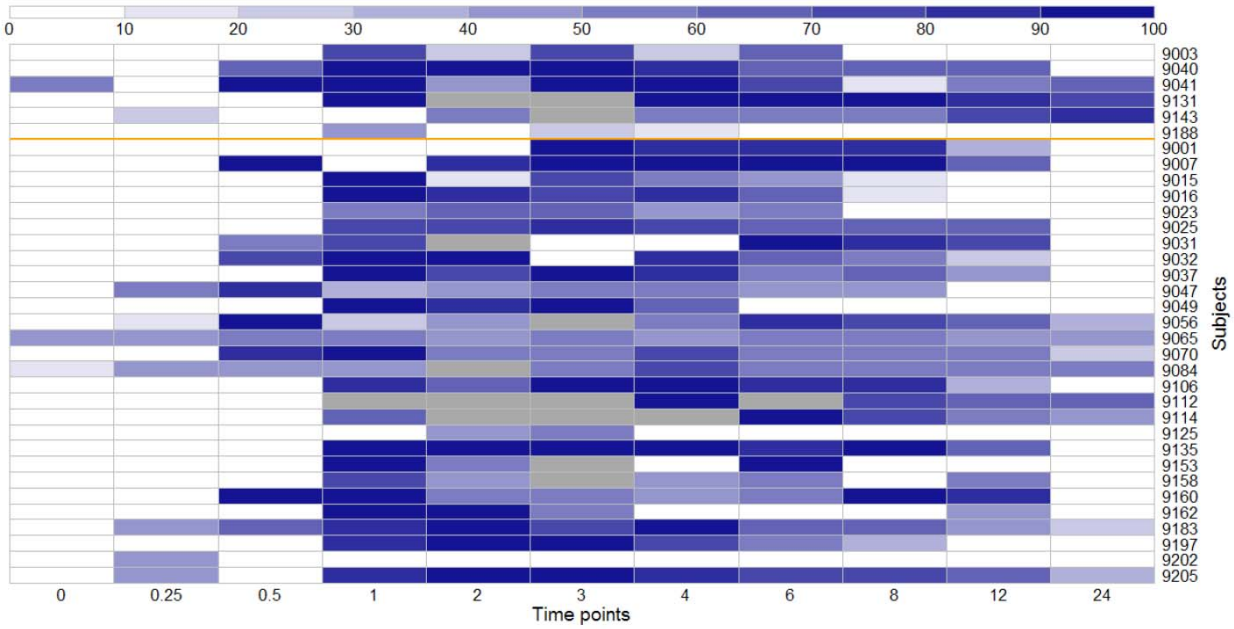

Figure 36: Time course response profiles for individual subjects to perampanel 24 mg for High VAS

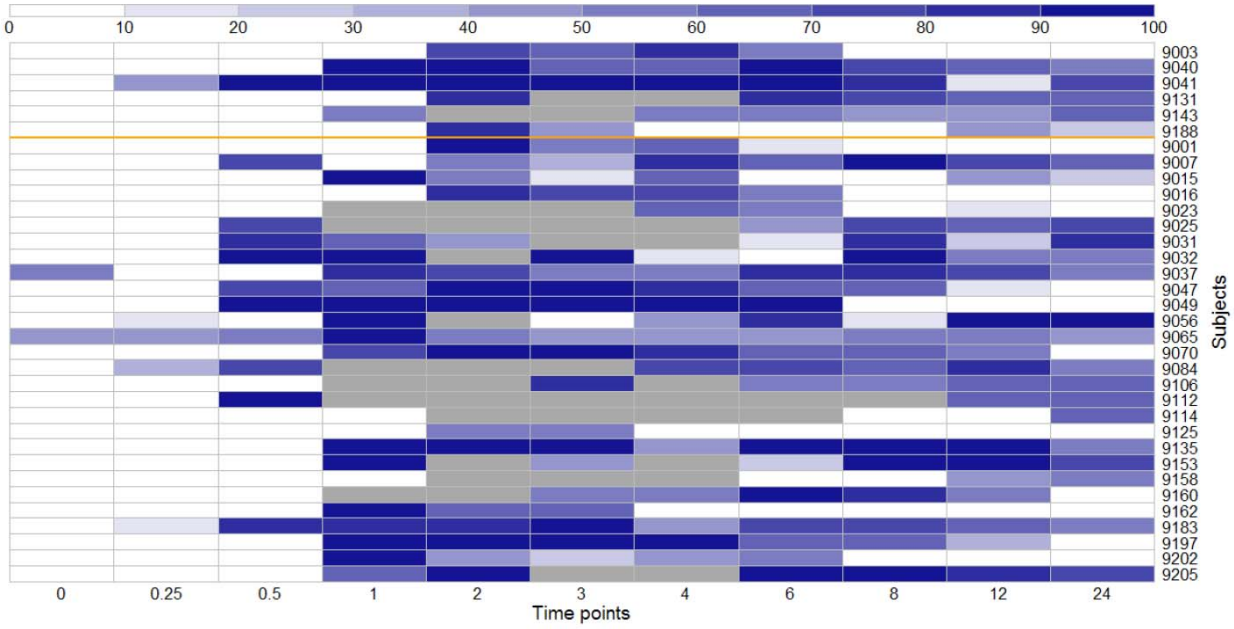

Figure 37: Time course response profiles for individual subjects to perampanel 36 mg for High VAS

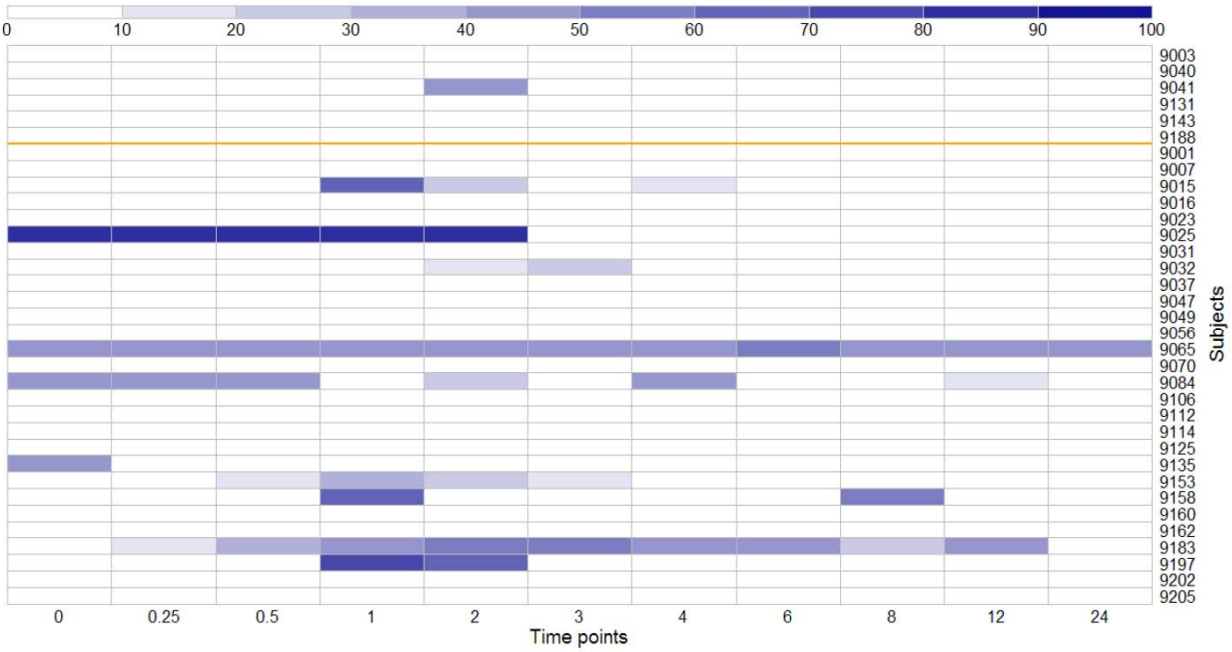

Figure 38: Time course response profiles for individual subjects to placebo for High VAS

4.5 Appendix V: Heat map displays for Emax by treatment by subjects for Overall Drug Liking VAS and Take Drug Again

Note: The horizontal orange line separates females and males, and the vertical orange line separates treatments and dummy placebos.

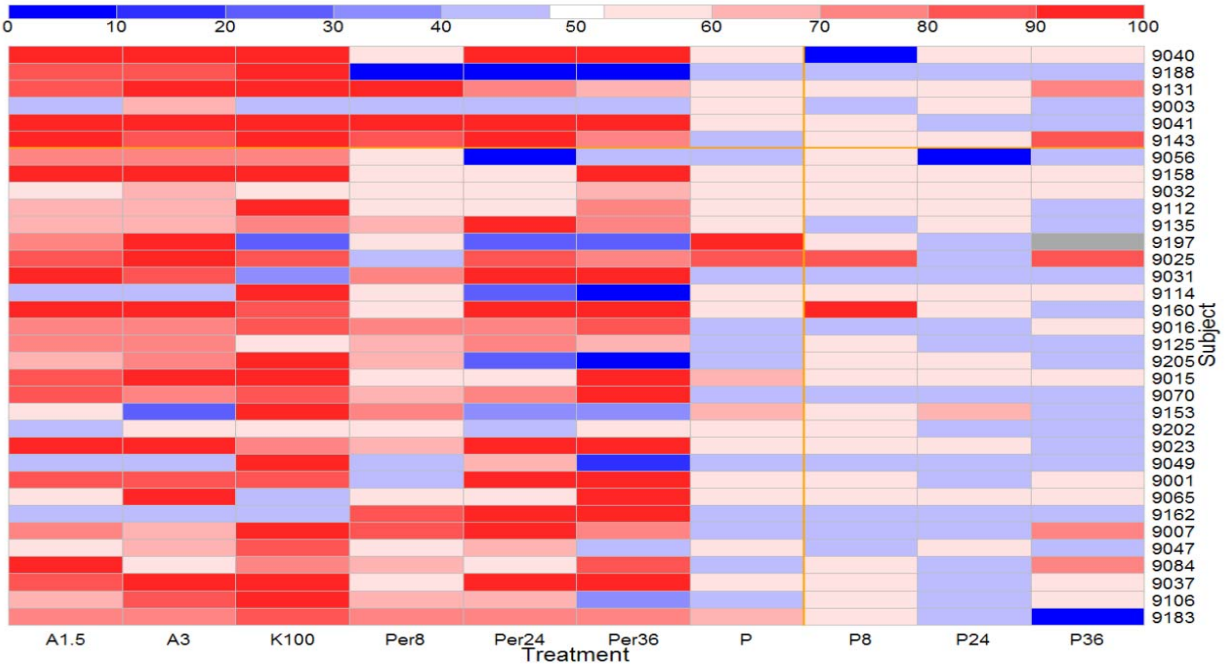

Figure 39: Emax of Overall Drug Liking by treatment by subject

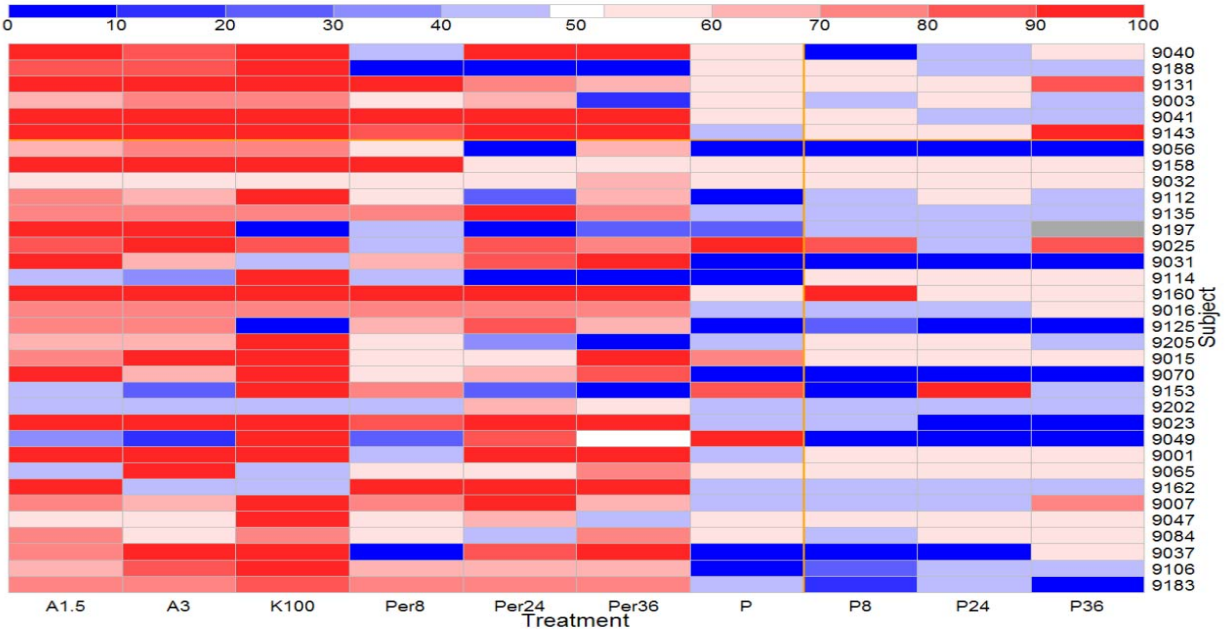

Figure 40: Emax of Take Drug Again by treatment by subject

4.6 Appendix VI: Analysis results for ARCI MBG, Drug Liking VAS, SDV ($) (using the mixed effects model)

---------- Question Name=Subjective Drug Value (SDV) ($) ----------

The Mixed Procedure

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTNAME	6	189	12.26	<.0001
PERIOD	9	189	0.48	0.8869
SEQ	9	24	2.92	0.0173

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|
A1.5 vs. P	16.9405	2.9177	189	5.81	<.0001
A3 vs. P	18.9103	2.8762	189	6.57	<.0001
K100 vs. P	20.7599	2.9224	189	7.10	<.0001
per8 vs. P	9.8791	2.9990	189	3.29	0.0012
Per24 vs. P	16.5575	3.1482	189	5.26	<.0001
Per36 vs. P	17.4840	2.9836	189	5.86	<.0001
K100 vs. Per8	10.8808	2.9215	189	3.72	0.0003
K100 vs. Per24	4.2024	2.9982	189	1.40	0.1627
K100 vs. Per36	3.2759	2.9339	189	1.12	0.2656
A1.5 vs. Per8	7.0615	2.9176	189	2.42	0.0165
A1.5 vs. Per24	0.3831	3.0250	189	0.13	0.8994
A1.5 vs. Per36	-0.5434	2.9241	189	-0.19	0.8528
A3 vs. Per8	9.0312	3.0045	189	3.01	0.0030
A3 vs. Per24	2.3528	3.2027	189	0.73	0.4635
A3 vs. Per36	1.4263	2.9838	189	0.48	0.6332
Per36 vs. Per8	7.6049	2.8830	189	2.64	0.0090
Per36 vs. Per24	0.9265	3.1296	189	0.30	0.7675
Per24 vs. Per8	6.6784	3.0703	189	2.18	0.0309

Least Squares Means

Effect	Name of Treatment	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRTNAME	A1.5	22.6854	2.7908	189	8.13	<.0001	0.05	17.1803	28.1905
TRTNAME	A3	24.6551	2.8536	189	8.64	<.0001	0.05	19.0260	30.2842
TRTNAME	K100	26.5047	2.7907	189	9.50	<.0001	0.05	20.9999	32.0096
TRTNAME	P	5.7449	2.8380	189	2.02	0.0443	0.05	0.1467	11.3430
TRTNAME	Per24	22.3023	2.9300	189	7.61	<.0001	0.05	16.5226	28.0820
TRTNAME	Per36	23.2288	2.8480	189	8.16	<.0001	0.05	17.6108	28.8468
TRTNAME	Per8	15.6239	2.8341	189	5.51	<.0001	0.05	10.0333	21.2145

---------- Question Name=**Drug Liking VAS** ----------

The Mixed Procedure

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTNAME	6	189	21.64	<.0001
PERIOD	9	189	0.93	0.5042
SEQ	9	24	0.55	0.8213

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|
A1.5 vs. P	20.7471	3.2016	189	6.48	<.0001
A3 vs. P	21.9298	3.1560	189	6.95	<.0001
K100 vs. P	34.2983	3.2067	189	10.70	<.0001
per8 vs. P	16.0345	3.2908	189	4.87	<.0001
Per24 vs. P	26.6536	3.4544	189	7.72	<.0001
Per36 vs. P	23.5275	3.2738	189	7.19	<.0001
K100 vs. Per8	18.2638	3.2057	189	5.70	<.0001
K100 vs. Per24	7.6447	3.2899	189	2.32	0.0212
K100 vs. Per36	10.7708	3.2193	189	3.35	0.0010
A1.5 vs. Per8	4.7126	3.2015	189	1.47	0.1427
A1.5 vs. Per24	-5.9065	3.3193	189	-1.78	0.0768
A1.5 vs. Per36	-2.7804	3.2086	189	-0.87	0.3873
A3 vs. Per8	5.8952	3.2968	189	1.79	0.0753
A3 vs. Per24	-4.7239	3.5143	189	-1.34	0.1805
A3 vs. Per36	-1.5978	3.2741	189	-0.49	0.6261
Per36 vs. Per8	7.4930	3.1635	189	2.37	0.0189
Per36 vs. Per24	-3.1261	3.4340	189	-0.91	0.3638
Per24 vs. Per8	10.6191	3.3690	189	3.15	0.0019

Least Squares Means

Effect	Name of Treatment	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRTNAME	A1.5	76.5416	2.8484	189	26.87	<.0001	0.05	70.9228	82.1603
TRTNAME	A3	77.7242	2.9224	189	26.60	<.0001	0.05	71.9595	83.4890
TRTNAME	K100	90.0928	2.8483	189	31.63	<.0001	0.05	84.4743	95.7113
TRTNAME	P	55.7945	2.9040	189	19.21	<.0001	0.05	50.0660	61.5229
TRTNAME	Per24	82.4481	3.0120	189	27.37	<.0001	0.05	76.5066	88.3896
TRTNAME	Per36	79.3220	2.9158	189	27.20	<.0001	0.05	73.5702	85.0737
TRTNAME	Per8	71.8290	2.8995	189	24.77	<.0001	0.05	66.1095	77.5485

---------- Question Name=**ARCI Morphine Benzedrine Group (MBG**) ----------

The Mixed Procedure

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTNAME	6	189	21.39	<.0001
PERIOD	9	189	0.58	0.8091
SEQ	9	24	3.45	0.0074

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|
A1.5 vs. P	4.6111	0.8903	189	5.18	<.0001
A3 vs. P	7.4723	0.8776	189	8.51	<.0001
K100 vs. P	7.4304	0.8917	189	8.33	<.0001
per8 vs. P	2.6586	0.9151	189	2.91	0.0041
Per24 vs. P	6.7277	0.9606	189	7.00	<.0001
Per36 vs. P	7.1439	0.9104	189	7.85	<.0001
K100 vs. Per8	4.7718	0.8915	189	5.35	<.0001
K100 vs. Per24	0.7027	0.9149	189	0.77	0.4434
K100 vs. Per36	0.2865	0.8952	189	0.32	0.7493
A1.5 vs. Per8	1.9525	0.8903	189	2.19	0.0295
A1.5 vs. Per24	-2.1166	0.9231	189	-2.29	0.0229
A1.5 vs. Per36	-2.5328	0.8923	189	-2.84	0.0050
A3 vs. Per8	4.8137	0.9168	189	5.25	<.0001
A3 vs. Per24	0.7446	0.9773	189	0.76	0.4471
A3 vs. Per36	0.3285	0.9105	189	0.36	0.7187
Per36 vs. Per8	4.4852	0.8797	189	5.10	<.0001
Per36 vs. Per24	0.4161	0.9550	189	0.44	0.6635
Per24 vs. Per8	4.0691	0.9369	189	4.34	<.0001

Least Squares Means

Effect	Name of Treatment	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRTNAME	A1.5	5.4943	0.7185	189	7.65	<.0001	0.05	4.0769	6.9117
TRTNAME	A3	8.3555	0.7412	189	11.27	<.0001	0.05	6.8935	9.8176
TRTNAME	K100	8.3136	0.7185	189	11.57	<.0001	0.05	6.8963	9.7309
TRTNAME	P	0.8832	0.7355	189	1.20	0.2314	0.05	-0.5677	2.3341
TRTNAME	Per24	7.6109	0.7684	189	9.90	<.0001	0.05	6.0952	9.1267
TRTNAME	Per36	8.0271	0.7392	189	10.86	<.0001	0.05	6.5690	9.4851
TRTNAME	Per8	3.5418	0.7342	189	4.82	<.0001	0.05	2.0936	4.9900

4.7 Appendix VII: Analysis results for ARCI PCAG, High VAS, Overall Drug Liking VAS, and Take Drug Again VAS (using the Wilcoxon sign-rank test)

A1.5 vs. P

Obs	QSTEST	Q3	Median	Q1	pSignRank
1	ARCI Pentobarbitol Chlorpromazine Alcoho	10	7	5	.000000042
2	High VAS	82	66	44	3.1844E-10
3	Overall Drug Liking VAS	39	20	0	.000001210
4	Take Drug Again VAS	50	44	14	.000001342

A3 vs. P

Obs	QSTEST	Q3	Median	Q1	pSignRank
1	ARCI Pentobarbitol Chlorpromazine Alcoho	10	8.0	6	1.5312E-11
2	High VAS	89	73.5	41	5.0648E-11
3	Overall Drug Liking VAS	39	21.5	12	.000000125
4	Take Drug Again VAS	50	35.0	16	.000012442

K100 vs. P

Obs	QSTEST	Q3	Median	Q1	pSignRank
1	ARCI Pentobarbitol Chlorpromazine Alcoho	7	3.0	1	.000000616
2	High VAS	100	95.5	59	1.2492E-11
3	Overall Drug Liking VAS	49	33.0	6	.000001135
4	Take Drug Again VAS	50	43.5	12	.000000005

Per8 vs. P

Obs	QSTEST	Q3	Median	Q1	pSign Rank
1	ARCI Pentobarbitol Chlorpromazine Alcoho	7	3.5	0	0.000038
2	High VAS	91	60.5	0	0.000008
3	Overall Drug Liking VAS	17	9.0	0	0.022145
4	Take Drug Again VAS	49	24.0	0	0.002696

Per24 vs. P

Obs	QSTEST	Q3	Median	Q1	pSign Rank
1	ARCI Pentobarbitol Chlorpromazine Alcoho	10	7.5	4	0.000000
2	High VAS	100	89.5	54	0.000000
3	Overall Drug Liking VAS	46	15.0	-1	0.015948
4	Take Drug Again VAS	50	24.5	0	0.001008

Per36 vs. P

Obs	QSTEST	Q3	Median	Q1	pSign Rank
1	ARCI Pentobarbitol Chlorpromazine Alcoho	10	9.0	7	0.000000
2	High VAS	100	82.5	61	0.000000
3	Overall Drug Liking VAS	45	22.0	-7	0.028812
4	Take Drug Again VAS	50	21.0	0	0.005561

A1.5 vs. Per8

Obs	QSTEST	Q3	Median	Q1	pSign Rank
1	ARCI Pentobarbitol Chlorpromazine Alcoho	6	2.5	1	0.00008
2	High VAS	17	2.5	-11	0.10573
3	Overall Drug Liking VAS	30	4.5	0	0.00360
4	Take Drug Again VAS	25	6.0	0	0.00001

A1.5 vs. Per24

Obs	QSTEST	Q3	Median	Q1	pSign Rank
1	ARCI Pentobarbitol Chlorpromazine Alcoho	2	0.0	-3	0.57604
2	High VAS	0	-9.5	-26	0.00014
3	Overall Drug Liking VAS	15	0.0	-4	0.21624
4	Take Drug Again VAS	26	2.5	-5	0.04318

A1.5 vs. Per36

Obs	QSTEST	Q3	Median	Q1	pSign Rank
1	ARCI Pentobarbitol Chlorpromazine Alcoho	1	-1	-3	0.02530
2	High VAS	0	-14	-27	0.00295
3	Overall Drug Liking VAS	19	0	-5	0.17137
4	Take Drug Again VAS	16	3	0	0.00328

A3 vs. Per8

Obs	QSTEST	Q3	Median	Q1	pSign Rank
1	ARCI Pentobarbitol Chlorpromazine Alcoho	7	3.0	1	0.000000
2	High VAS	31	10.0	0	0.007439
3	Overall Drug Liking VAS	41	8.0	0	0.000716
4	Take Drug Again VAS	27	5.5	-1	0.010915

A3 vs. Per24

Obs	QSTEST	Q3	Median	Q1	pSign Rank
1	ARCI Pentobarbitol Chlorpromazine Alcoho	2	1.0	-2	0.55364
2	High VAS	0	-5.5	-23	0.01208
3	Overall Drug Liking VAS	18	0.0	-7	0.15826
4	Take Drug Again VAS	32	3.0	-5	0.13819

A3 vs. Per36

Obs	QSTEST	Q3	Median	Q1	pSign Rank
1	ARCI Pentobarbitol Chlorpromazine Alcoho	1	0	-2	0.19521
2	High VAS	5	-7	-22	0.04440
3	Overall Drug Liking VAS	22	0	-6	0.14414
4	Take Drug Again VAS	26	0	-1	0.07643

K100 vs. Per8

Obs	QSTEST	Q3	pSign Median	Q1	Rank
1	ARCI Pentobarbitol Chlorpromazine Alcoho	3	0	-3	0.80320
2	High VAS	51	19	7	0.00000
3	Overall Drug Liking VAS	40	16	0	0.00013
4	Take Drug Again VAS	47	18	0	0.00181

K100 vs. Per24

Obs	QSTEST	Q3	Median	Q1	pSign Rank
1	ARCI Pentobarbitol Chlorpromazine Alcoho	-1	-4.0	-6	0.00000
2	High VAS	9	0.0	0	0.16171
3	Overall Drug Liking VAS	35	1.5	-1	0.03853
4	Take Drug Again VAS	36	5.0	0	0.01019

K100 vs. Per36

Obs	QSTEST	Q3	Median	Q1	pSign Rank
1	ARCI Pentobarbitol Chlorpromazine Alcoho	-2	-4	-7	0.00000
2	High VAS	13	0	-1	0.27402
3	Overall Drug Liking VAS	29	0	-12	0.08562
4	Take Drug Again VAS	33	5	0	0.01908

Per36 vs. Per24

Obs	QSTEST	Q3	Median	Q1	Rank
1	ARCI Pentobarbitol Chlorpromazine Alcoho	3	0.5	-1	0.09926
2	High VAS	4	0.0	-10	0.82435
3	Overall Drug Liking VAS	6	0.0	-15	0.76463
4	Take Drug Again VAS	13	0.0	-12	0.79014

Per36 vs. Per8

Obs	QSTEST	Q3	Median	Q1	pSign Rank
1	ARCI Pentobarbitol Chlorpromazine Alcoho	8	3.5	2	0.00000
2	High VAS	49	20.0	1	0.00004
3	Overall Drug Liking VAS	27	7.5	-16	0.27363
4	Take Drug Again VAS	19	0.0	-10	0.62962

Per24 vs. Per8

Obs	QSTEST	Q3	Median	Q1	pSign Rank
1	ARCI Pentobarbitol Chlorpromazine Alcoho	6	3.0	0	0.00000
2	High VAS	37	13.5	5	0.00000
3	Overall Drug Liking VAS	17	5.0	-1	0.12333
4	Take Drug Again VAS	18	3.5	-19	0.53292

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/s/

LING CHEN
09/17/2012

STELLA G MACHADO
09/17/2012

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA202-834/0011
Drug Name:	Perampanel Tablets
Indication(s):	Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older
Applicant:	Eisai Inc
Date(s):	Date of Document: December 22, 2011 PDUFA Due Date: October 22, 2012
Review Priority:	Standard
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Ququan Liu, M.D., M.S.
Concurring Reviewers:	Kun Jin, Ph.D., James Hung, Ph.D.
Medical Division:	Division of Neurology Drug Products, HFD-120
Clinical Team:	Martin Rusinowitz, M.D., Norman Hershkowitz, M.D., Russell Katz, M.D.
Project Manager:	Stephanie Parncutt
Keywords:	Perampanel, Refractory partial seizures, Epilepsy, ITT analysis

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The three clinical studies 304, 305 and 306 support that perampanel 4, 8 and 12 mg are effective in reducing seizure frequencies in subjects with refractory partial seizures. However, the results of the efficacy in Study 304 are not consistent because the statistical significance in the test of efficacy varies, depending on the patient population included in the analysis, and the change of patient population was made after the study completed. Therefore Study 304 may be used as supportive for efficacy.

1.2 Brief Overview of Clinical Studies

This NDA includes three randomized, double-blind, parallel-group, placebo-controlled phase III studies (304, 305, and 306) to support the safety and efficacy of perampanel in the treatment of partial-onset seizures with or without secondary generalized seizures in patients with epilepsy aged 12 years and older. The studies are described as follows (Table 1):

Table 1 List of Study Included in Analysis

Study	Sample Size	Phase and Design	Treatment Period	Follow-up Period	# of Subjects Per Arm	Study Population
304	390	Randomized, double-blind, placebo-controlled, parallel-group, Phase III	6- week titration, 13-week maintenance	4 weeks	Placebo: 122 8 mg: 133 12 mg: 135	epilepsy
305	389	Randomized, double-blind, placebo-controlled, parallel-group, Phase III	6- week titration, 13-week maintenance	4 weeks	Placebo: 138 8 mg: 130 12 mg: 121	epilepsy
306	712	Randomized, double-blind, placebo-controlled, parallel-group,Phase III	6- week titration, 13-week maintenance	4 weeks	Placebo: 187 2 mg: 180 4 mg: 174 8 mg: 171	epilepsy

1.3 Statistical Issues and Findings

Use of the full analysis set for primary analysis is important in clinical trials. The full analysis set includes all randomized subjects by intention-to-treat principle, and tends to avoid over-optimistic estimates of efficacy resulting from the analysis set that excludes subjects with condition. In the three studies of this NDA, the ITT analysis set was pre-specified for the primary analysis in the protocol and SAP. The ITT analysis set excludes subjects who did not have at least two weeks of seizure frequency data from the pre-randomization phase and from the double-blind Phase. In reviewing the sponsor's protocol and SAP, the agency recommended that the full ITT analysis set should be used for the primary analysis , but the sponsor did not take the agency's recommendation into consideration until later time in the trial prior to data un-blinded for Study 305, and when Study 304 and Study 306 have completed.

Pre-specification of the analysis is also necessary to avoid any potential bias in interpretation of study result. An amendment was made to Study 304 and Study 306 when both studies have completed. The analysis set for the primary analysis was changed to the full ITT analysis set instead of the ITT analysis set as originally planned. The results were consistent from both analysis sets in Study 305 and Study 306, but were inconsistent in Study 304. Study 304 would fail on the primary analysis when the originally planned ITT analysis set was used, but would win only when the full ITT analysis set was used ,

2. INTRODUCTION

2.1 Overview

Epilepsies are among the most common neurologic disorders affecting individuals of all ages. Over the past 15 years, several antiepileptic drugs (AEDs) have been developed with the objective of improving efficacy, tolerability, and ease of use when compared with classic currently-used AEDs. While these newer medications are efficacious and relatively safe, none have completely met the treatment needs of all patients with epilepsy. Perampanel is an orally active, noncompetitive, and highly selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist that has been developed as adjunctive treatment for patients with partial-onset seizures.

2.2 Data Sources

The sponsor's SAS datasets were stored in the directory of \\cdsesub1\EVSPROD\NDA202834\0011 of the Center's electronic document room.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Objectives

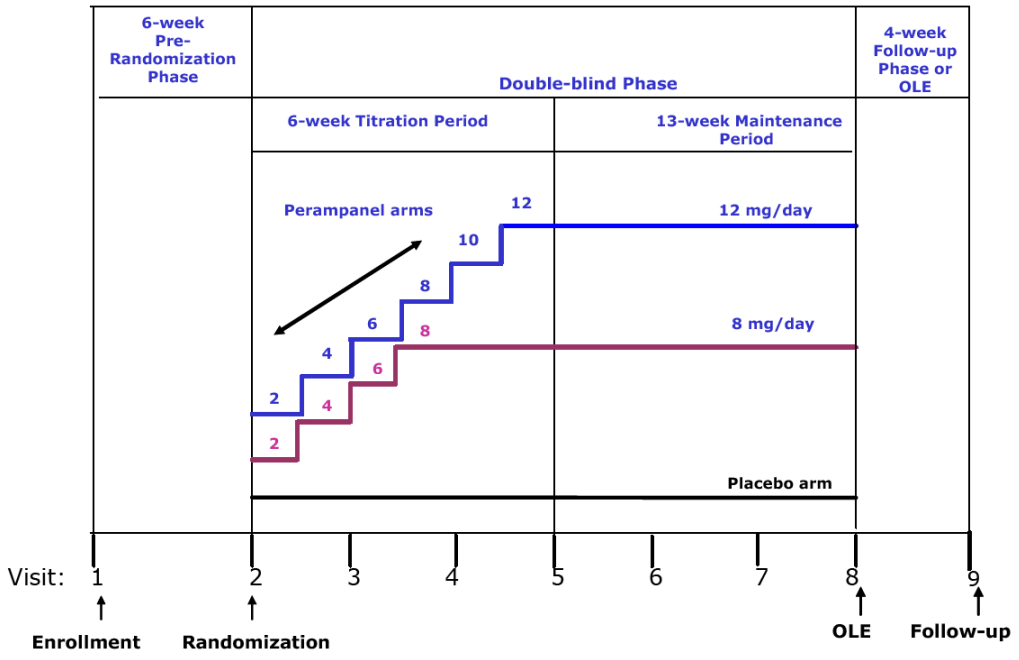
The primary objective of the studies was to evaluate the efficacy of two or three doses of perampanel (8 and 12 mg for Study 304 & 305; 2, 4 and 8 mg for Study 306) given as adjunctive therapy in subjects with refractory partial seizures.

3.1.2 Study Design

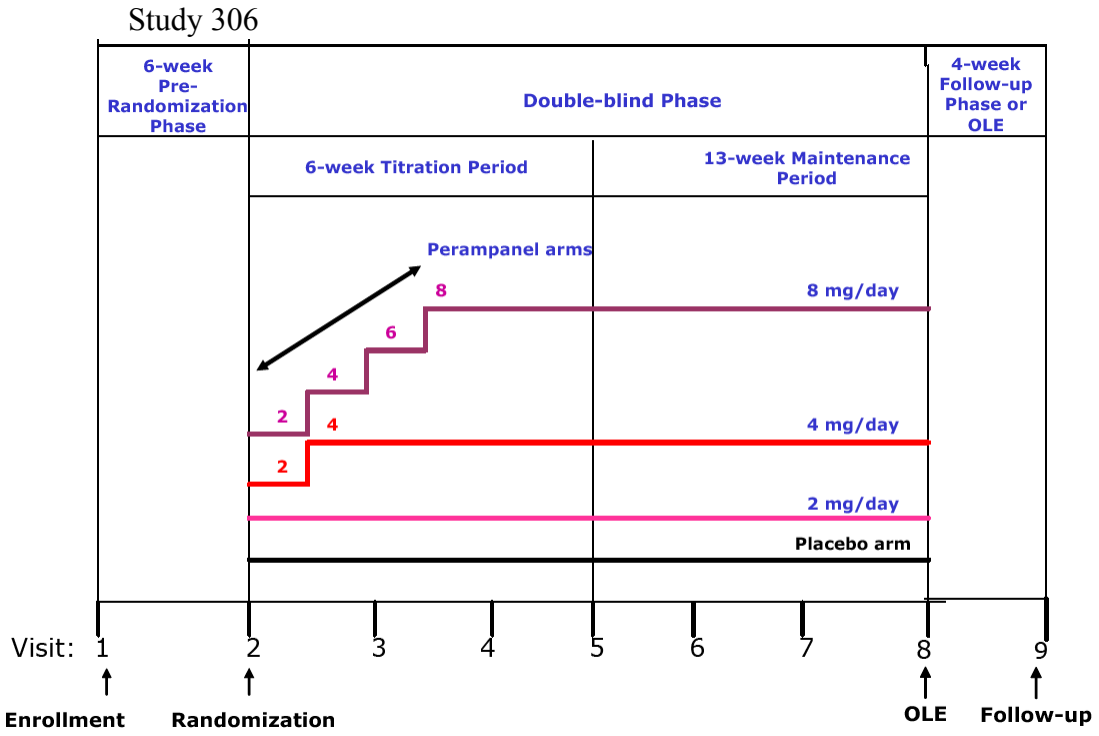
The studies were double-blind, placebo-controlled, dose-escalation, parallel-group, multiple-region studies to evaluate the efficacy and safety of perampanel given as adjunctive therapy in subjects with refractory partial seizures. The studies include three phases: Prerandomization, Double-blind (including titration and maintenance periods) and Follow-up. The detail of the study design is described as follows (Figure 1).

Figure 1 Study Design

Study 304 and 305



OLE = open-label extension



OLE = open-label extension

(Source: Sponsor's Figure 9.1)

3.1.3 Efficacy Measures

1) Primary Efficacy Endpoint

Percent change in seizure frequency: The primary efficacy measure was the percent change in seizure frequency per 28 days in the Maintenance Period relative to the Pre-randomization Phase in the ITT Analysis set using LOCF imputation. Primary analysis period is the Maintenance Period **originally planned for all three studies**, **and The Double Blind Period amended later for Study 305.** Seizure frequency will be based on the number of seizures per 28 days, calculated as (the number of seizures over the time interval multiplied by 28) and divided by the number of days in the interval.

2) Secondary Efficacy Endpoints

- Percent change in the frequency of complex partial plus secondarily generalized seizures
- Responder rate: Responder rate is the key secondary endpoint for the non-EMEA registrants
- Dose-response analysis

3.1.4 Statistical Analysis Methodology

1) 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 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 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. Hodges−Lehmann estimator and 95% confidence interval (CI) for the estimator were calculated.

2) Responder rate: An analysis of subjects who experience a 50% or greater reduction in seizure frequency in the Maintenance period of the double-blind phase relative to the pre-randomization phase will be conducted based on Cochran-Mantel-Haenszel (CMH) test adjusting for pooled countries.

3) Handling of missing data, drop-outs, and outliers: The primary analysis of seizure frequency will be based on the Maintenance Period using LOCF imputation. If the overall duration of the Maintenance Period is less than 8 weeks, the diary data from the last 8 weeks during the treatment phase (Titration Period + Maintenance Period) will be used to calculate the seizure frequency per 28 days for Maintenance-LOCF. When the proportion of randomized subjects with less than 2 weeks of Double-blind Phase seizure data is greater than 10%, the endpoint seizure frequency of such subjects will be calculated based on their last 2 weeks of seizure data (including some days before randomization). When the proportion of randomized subjects with less than 2 weeks of Double-blind Phase seizure data is less than or equal to 10%, the Double-blind Phase seizure frequencies of such subject will be set to missing.

4) Multiple Comparisons/Multiplicity: For primary efficacy endpoint, a closed testing procedure will be employed to control family wise type-I error rate. For Study 304 & 305, the test starts from the lower dose, first the 8 mg treatment group will be compared with the placebo at the two-sided alpha level of 0.05. If this comparison demonstrates superiority then the 8 mg treatment group will be declared efficacious; 12 mg treatment group will then be compared to the placebo at the two-sided alpha level of 0.05.

   For Study 306, the test starts from the higher dose. First, the 8 mg treatment group was compared with placebo at the two-sided alpha level of 0.05. If this comparison demonstrated superiority, then the 8 mg treatment group will be declared efficacious. The 4 mg treatment group was then compared with placebo at the two-sided alpha level of 0.05. If both the 8 and 4 mg treatment groups were statistically superior to placebo at the two-sided alpha level of 0.05, the 2 mg treatment group was then compared with placebo at the two-sided alpha level of 0.05 to test for superiority.

5) Pooling of centers: Data from the centers in the same country will be pooled together for analysis purposes. Each of these countries should have at least 12 subjects. If there

are countries with <12 subjects then the countries will be sorted in descending order by the number of subjects. Starting from the smallest, countries will be pooled until the criteria of 12 subjects is fulfilled or there is no country of size <12 left to be pooled. If there is no country of size <12 left to be pooled but the current country is of size <12 then the current country will be pooled with the next country in the order.

3.15 Patient Disposition, Demographic and Baseline Characteristics

Tables 2-4 summarize patient disposition, demographic and baseline characteristics in the three studies.

Table 2 Patient disposition, demographic and baseline characteristics, Full ITT, Study 304

		Perampanel			
Category	Placebo (N=121)	8 mg (N=133)	12 mg (N=133)	Total (N=266)	Combined Total (N=387)
Age(Year)[a]					
n	121	133	133	266	387
Mean (SD)	35.6 (14.67)	35.8 (14.21)	36.7 (14.69)	36.3 (14.43)	36.1 (14.49)
Median	34.0	36.0	36.0	36.0	35.0
Min, Max	12, 73	12, 68	14, 77	12, 77	12, 77
Age Group, n (%)					
<18	14 (11.6)	15 (11.3)	10 (7.5)	25 (9.4)	39 (10.1)
18-64	102 (84.3)	116 (87.2)	118 (88.7)	234 (88.0)	336 (86.8)
>64	5 (4.1)	2 (1.5)	5 (3.8)	7 (2.6)	12 (3.1)
Sex, n (%)					
Male	54 (44.6)	65 (48.9)	69 (51.9)	134 (50.4)	188 (48.6)
Female	67 (55.4)	68 (51.1)	64 (48.1)	132 (49.6)	199 (51.4)
Race, n (%)					
White	103 (85.1)	115 (86.5)	115 (86.5)	230 (86.5)	333 (86.0)
Black or African American	13 (10.7)	6 (4.5)	8 (6.0)	14 (5.3)	27 (7.0)
Asian	0	1 (<1)	1 (<1)	2 (<1)	2 (<1)
Japanese	0	0	0	0	0
Chinese	0	1 (<1)	1 (<1)	2 (<1)	2 (<1)
American Indian or Alaska Native	0	4 (3.0)	2 (1.5)	6 (2.3)	6 (1.6)
Native Hawaiian or other Pacific Islander	0	0	0	0	0
Other	5 (4.1)	6 (4.5)	6 (4.5)	12 (4.5)	17 (4.4)
Ethnicity, n (%)					
Hispanic or Latino	53 (43.8)	66 (49.6)	57 (42.9)	123 (46.2)	176 (45.5)
Not Hispanic or Latino	68 (56.2)	67 (50.4)	76 (57.1)	143 (53.8)	211 (54.5)
Weight(kg)					
n	121	132	133	265	386
Mean (SD)	72.55 (20.535)	71.07 (17.953)	73.87 (18.717)	72.47 (18.360)	72.50 (19.041)
Median	68.60	71.95	69.70	71.00	70.00
Min, Max	33.1, 141.2	37.8, 116.2	40.0, 136.3	37.8, 136.3	33.1, 141.2
Height(cm)					
n	116	131	133	264	380
Mean (SD)	164.08 (11.209)	165.63 (9.024)	167.25 (9.976)	166.45 (9.532)	165.72 (10.118)
Median	164.10	165.60	167.60	167.00	165.10
Min, Max	139.0, 193.0	143.0, 188.0	146.0, 193.0	143.0, 193.0	139.0, 193.0
BMI(kg/m2)[b]					
n	116	130	133	263	379
Mean (SD)	26.72 (6.169)	25.87 (5.507)	26.38 (6.190)	26.12 (5.857)	26.30 (5.952)
Median	25.33	25.35	25.25	25.25	25.27
Min, Max	16.7, 50.5	15.1, 45.3	17.6, 43.9	15.1, 45.3	15.1, 50.5
Baseline of seizure frequency					
N	121	133	133	266	387
Mean (SD)	26.76 (32.23)	35.45 (94.04)	41.38 (109.55)	38.41 (101.94)	34.77 (86.52)
Median	13.66	14.34	12.00	12.98	13.30
Min, Max	3.3, 227.4	2.4, 1030.8	2.9, 1083.1	2.4, 1083.1	2.4, 1083.1

(Source: Sponsor's Table 14.1.10, confirmed by the reviewer's analysis)

Table 3 Patient disposition, demographic and baseline characteristics, Full ITT, Study 305

Category	Placebo (N=136)	Perampanel 8 mg (N=129)	Perampanel 12 mg (N=121)	Perampanel Total (N=250)	Combined Total (N=386)
Age(Year)[a]					
n	136	129	121	250	386
Mean (SD)	34.4 (13.62)	36.7 (14.35)	35.5 (14.12)	36.1 (14.22)	35.5 (14.02)
Median	35.0	37.0	35.0	35.5	35.0
Min, Max	12, 76	12, 72	12, 74	12, 74	12, 76
Age Group, n (%)					
<18	17 (12.5)	17 (13.2)	10 (8.3)	27 (10.8)	44 (11.4)
18-64	118 (86.8)	109 (84.5)	109 (90.1)	218 (87.2)	336 (87.0)
>64	1 (<1)	3 (2.3)	2 (1.7)	5 (2.0)	6 (1.6)
Sex, n (%)					
Male	71 (52.2)	65 (50.4)	50 (41.3)	115 (46.0)	186 (48.2)
Female	65 (47.8)	64 (49.6)	71 (58.7)	135 (54.0)	200 (51.8)
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)
Japanese	0	0	0	0	0
Chinese	0	0	0	0	0
American Indian or Alaska Native	1 (<1)	0	0	0	1 (<1)
Native Hawaiian or other Pacific Islander	0	0	0	0	0
Other	7 (5.1)	6 (4.7)	4 (3.3)	10 (4.0)	17 (4.4)
Ethnicity, n (%)					
Hispanic or Latino	13 (9.6)	9 (7.0)	6 (5.0)	15 (6.0)	28 (7.3)
Not Hispanic or Latino	123 (90.4)	120 (93.0)	115 (95.0)	235 (94.0)	358 (92.7)
Weight(kg)					
n	136	129	121	250	386
Mean (SD)	71.64 (17.589)	72.00 (19.011)	71.90 (18.693)	71.95 (18.820)	71.84 (18.373)
Median	69.25	72.30	67.00	69.80	69.55
Min, Max	40.0, 128.0	34.0, 136.3	34.7, 130.5	34.0, 136.3	34.0, 136.3
Height(cm)					
n	136	128	118	246	382
Mean (SD)	168.26 (9.777)	167.43 (9.235)	166.26 (9.868)	166.87 (9.543)	167.36 (9.637)
Median	168.00	167.00	167.00	167.00	167.60
Min, Max	139.5, 193.0	142.0, 189.2	140.5, 193.5	140.5, 193.5	139.5, 193.5
BMI(kg/m2)[b]					
n	136	128	118	246	382
Mean (SD)	25.17 (5.223)	25.57 (6.116)	25.70 (5.963)	25.63 (6.031)	25.47 (5.754)
Median	24.27	24.82	24.92	24.86	24.73
Min, Max	15.6, 44.8	15.4, 44.5	15.9, 45.7	15.4, 45.7	15.4, 45.7
Baseline of seizure frequency					
N	136	129	121	250	386
Mean (SD)	32.03 (52.72)	37.59 (80.94)	42.29 (94.79)	39.86 (87.77)	37.11 (77.27)
Median	11.79	13.02	13.69	13.67	12.95
Min, Max	3.4, 358.4	3.3, 652.2	1.4, 598.4	1.4, 652.2	1.4, 652.2

(Source: Sponsor's Table 14.1.5.2, confirmed by the reviewer's analysis)

Table 4 Patient disposition, demographic and baseline characteristics, Full ITT, Study 306

		Perampanel				
Category	Placebo (N=184)	2 mg (N=180)	4 mg (N=172)	8 mg (N=169)	Total (N=521)	Combined Total (N=705)
Age(Year)[a]						
n	184	180	172	169	521	705
Mean (SD)	33.4 (12.58)	33.8 (13.62)	33.6 (12.19)	34.6 (12.77)	34.0 (12.87)	33.8 (12.79)
Median	31.0	32.0	32.0	33.0	32.0	32.0
Min, Max	12, 66	13, 72	12, 68	12, 69	12, 72	12, 72
Age Group, n (%)						
<18	14 (7.6)	21 (11.7)	13 (7.6)	12 (7.1)	46 (8.8)	60 (8.5)
18-64	168 (91.3)	156 (86.7)	158 (91.9)	153 (90.5)	467 (89.6)	635 (90.1)
>64	2 (1.1)	3 (1.7)	1 (<1)	4 (2.4)	8 (1.5)	10 (1.4)
Sex, n (%)						
Male	95 (51.6)	85 (47.2)	88 (51.2)	77 (45.6)	250 (48.0)	345 (48.9)
Female	89 (48.4)	95 (52.8)	84 (48.8)	92 (54.4)	271 (52.0)	360 (51.1)
Race, n (%)						
White	119 (64.7)	119 (66.1)	105 (61.0)	116 (68.6)	340 (65.3)	459 (65.1)
Black or African American	0	0	0	0	0	0
Asian	33 (17.9)	35 (19.4)	37 (21.5)	28 (16.6)	100 (19.2)	133 (18.9)
Japanese	0	0	0	0	0	0
Chinese	31 (16.8)	25 (13.9)	29 (16.9)	25 (14.8)	79 (15.2)	110 (15.6)
American Indian or Alaska Native	0	0	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0	0	0
Other	1 (<1)	1 (<1)	1 (<1)	0	2 (<1)	3 (<1)
Ethnicity, n (%)						
Hispanic or Latino	10 (5.4)	9 (5.0)	9 (5.2)	10 (5.9)	28 (5.4)	38 (5.4)
Not Hispanic or Latino	174 (94.6)	171 (95.0)	163 (94.8)	159 (94.1)	493 (94.6)	667 (94.6)
Weight(kg)						
n	184	180	172	169	521	705
Mean (SD)	67.54 (16.007)	65.37 (16.173)	69.49 (17.210)	68.47 (16.284)	67.73 (16.621)	67.68 (16.452)
Median	67.00	64.10	68.65	67.00	67.00	67.00
Min, Max	30.6, 126.7	35.0, 114.0	23.3, 132.5	36.0, 114.0	23.3, 132.5	23.3, 132.5
Height(cm)						
n	184	179	172	169	520	704
Mean (SD)	167.65 (10.076)	166.11 (9.208)	167.94 (11.185)	167.22 (10.188)	167.08 (10.221)	167.23 (10.179)
Median	168.00	165.00	167.25	167.00	167.00	167.00
Min, Max	136.0, 193.0	144.5, 190.5	126.0, 198.0	142.0, 193.0	126.0, 198.0	126.0, 198.0
BMI(kg/m2)[b]						
n	184	179	172	169	520	704
Mean (SD)	23.89 (4.754)	23.51 (4.584)	24.46 (4.745)	24.36 (4.896)	24.10 (4.751)	24.05 (4.749)
Median	23.06	23.23	23.82	23.93	23.71	23.52
Min, Max	14.0, 43.2	16.4, 41.7	12.1, 39.6	15.7, 39.0	12.1, 41.7	12.1, 43.2
Baseline of seizure frequency						
N	184	180	172	169	521	705
Mean (SD)	23.94 (50.54)	31.20 (55.42)	62.56 (354.87)	32.61 (73.13)	42.01 (210.73)	37.30 (183.11)
Median	9.33	10.12	10.02	10.93	10.24	9.84
Min, Max	3.3, 569.1	3.2, 429.6	2.9, 4503.9	3.4, 723.2	2.9, 4503.9	2.9, 4503.9

(Source: Sponsor's Table 14.1.10, confirmed by the reviewer's analysis)

3.16 Sponsor's Primary Efficacy Results

Percent Change in Seizure Frequency:

1) The median changes in both doses of perampanel are statistically significant larger comparing to placebo in both Study 304 and Study 305 (Study 304: p=0.0261, and p=0.0184 for 8 mg and 12 mg perampanel, respectively; Study 305: p=0.0008 and p=0.0105 for 8 mg and 12 mg perampanel, respectively) (Tables 5, 6).

Table 5 Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (Full 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	0.0158

(Source: Sponsor's Table 11.5, confirmed by the reviewer's analysis)

Table 6 Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (Full 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)		-19.10 (-29.17, -8.45)	-13.69 (-25.20, -2.26)
P-value		0.0008	0.0105

(Source: Sponsor's Table 11.5, confirmed by the reviewer's analysis)

2) In Study 306, the median changes in the two higher doses of perampanel are statistically significant larger comparing to placebo ($p=0.0026$, $p<0.0001$ for 4 mg and 8 mg perampanel, respectively) (Table 7).

Table 7 Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (Full ITT), 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

(Source: Sponsor's Table 11.5, confirmed by the reviewer's analysis)

3.17 Sponsor's Secondary Efficacy Results

1) Responder Rate

In Study 304, the percentage of subjects who experienced a decrease in seizure frequency of at least 50% relative to baseline was greater in both dose groups compared to placebo (26.4%, 37.6%, and 36.1% for placebo, 8 mg, 12 mg, respectively), but the difference in responder rate between perampanel and placebo was not statistically significant (Table 8).

Table 8 Responder Analysis (Full ITT, Maintenance-LOCF), Study 304

		Perampanel	
Analysis Window Responder	Placebo (N=121) n (%)	8 mg (N=133) n (%)	12 mg (N=133) n (%)
Maintenance-LOCF			
Yes	32 (26.4)	50 (37.6)	48 (36.1)
No	89 (73.6)	83 (62.4)	85 (63.9)
Total	121 (100)	133 (100)	133 (100)
p-value[a]			
Compared with Placebo		0.0760	0.0914

(Source: Sponsor's Table 11.7, confirmed by the reviewer's analysis)

In Study 305, the percentage of subjects who experienced a decrease in seizure frequency of at least 50% relative to baseline was greater in both dose groups compared to placebo (14.7%, 33.3%, and 33.9% for placebo, 8 mg, 12 mg perampanel , respectively), the difference in responder rate between perampanel and placebo was statistically significant (Table 9).

Table 9 Responder Analysis (Full ITT, Maintenance-LOCF), Study 305

		Perampanel	
Analysis Window Responder	Placebo (N=136) n (%)	8 mg (N=129) n (%)	12 mg (N=121) n (%)
Maintenance-LOCF			
Yes	20 (14.7)	43 (33.3)	41 (33.9)
No	116 (85.3)	86 (66.7)	80 (66.1)
Total	136 (100)	129 (100)	121 (100)
p-value[a]			
Compared with Placebo		0.0018	0.0006

(Source: Sponsor's Table 11.6, confirmed by the reviewer's analysis)

In Study 306, the percentage of subjects who experienced a decrease in seizure frequency of at least 50% relative to baseline was greater in the two higher dose groups compared to placebo (17.9%, 28.5%, and 34.9% for placebo, 4 mg, 8 mg perampanel, respectively), the difference in responder rate between perampanel and placebo was statistically significant (Table 10).

Table 10 Responder Analysis (Full ITT, Maintenance-LOCF), Study 306

Analysis Window Responder	Placebo (N=184) n (%)	Perampanel 2 mg (N=180) n (%)	Perampanel 4 mg (N=172) n (%)	Perampanel 8 mg (N=169) n (%)
Maintenance-LOCF				
Yes	33 (17.9)	37 (20.6)	49 (28.5)	59 (34.9)
No	151 (82.1)	143 (79.4)	123 (71.5)	110 (65.1)
Total	184 (100)	180 (100)	172 (100)	169 (100)
p-value[a]				
Compared with Placebo		0.4863	0.0132	0.0003

(Source: Sponsor's Table 11.6, confirmed by the reviewer's analysis)

2) Percent Change in Frequency of Complex Partial Plus Secondarily Generalized Seizures

Complex partial plus secondarily generalized seizures include complex partial seizures and complex partial with secondary generalization seizures.

In Study 304 and Study 3.5, the median changes in both doses of perampanel are statistically significant larger comparing to placebo (Study 304: p=0.002, and p=0.0081 for 8 mg and 12 mg perampanel, respectively; Study 305: p=0.0007, and p=0.0045 for 8 mg and 12 mg perampanel, respectively) (Tables 11-12).

In Study 306, the median changes in the two higher doses of perampanel are statistically significant larger comparing to placebo (p=0.0070, p=0.0005 for 4 mg and 8 mg perampanel, respectively) (Table 13).

Table 11 Percent Change in Seizure Frequency per 28 Days -Complex Partial Plus Secondarily Generalized Seizure (Full ITT), Study 304

Statistic	Placebo	Perampanel	
		8 mg	12 mg
n	110	120	120
Median	-17.88	-33.03	-33.06
Median Difference to Placebo (95% CI)		-20.37 (-33.16, -7.74)	-17.90 (-30.31, -4.67)
P-value		0.0020	0.0081

(Source: Sponsor's Table 11.9, confirmed by the reviewer's analysis)

Table 12 Percent Change in Seizure Frequency per 28 Days –Complex Partial Plus Secondarily Generalized Seizure (Full ITT), Study 305

Statistic	Placebo	Perampanel	
		8 mg	12 mg
n	126	119	113
Median	-8.05	-32.72	-21.89
Median Difference to Placebo (95% CI)		-23.07 (-34.80, -10.55)	-17.45 (-29.27, -5.70)
P-value		0.0007	0.0045

(Source: Sponsor's Table 11.7, confirmed by the reviewer's analysis)

Table 13 Percent Change in Seizure Frequency per 28 Days –Complex Partial Plus Secondarily Generalized Seizure (Full ITT), Study 306

Statistic	Placebo	Perampanel		
		2 mg	4 mg	8 mg
n	169	167	157	154
Median	-17.63	-20.50	-31.18	-38.69
Median Difference to Placebo (95% CI)		-3.26 (-13.69, 7.40)	-14.40 (-25.08, -3.50)	-19.32 (-29.79, -8.63
P-value		0.6506	0.0070	0.0005

(Source: Sponsor's Table 11.7, confirmed by the reviewer's analysis)

3.18 Reviewer's Results

1) The reviewer verified the sponsor's primary and secondary efficacy analyses and concurred with their results.

2) An amendment was made to Study 305 in a later time of the trial prior to data un-blinded, the analysis set for the primary analysis was changed to the full ITT analysis set instead of the ITT analysis set as originally planned. This change was also made to Study 304 and Study 306 when both studies have completed. The results were consistent from both analysis sets in Study 305 and Study 306, but were inconsistent in Study 304. Study 304 would fail on the primary analysis based on the originally planned ITT analysis set, but would win only when the full ITT analysis set was used (Tables 14, 15 & 16).

Table 14 Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline(Full ITT/ITT Analysis Set), Study 304

	Full ITT Analysis Set			ITT Analysis Set		
Statistic	Placebo	Perampanel		Placebo	Perampanel	
		8 mg	12 mg		8 mg	12 mg
n	121	133	133	119	132	130
Median	-20.95	-26.34	-34.49	-22.86	-32.13	-39.48
Median Difference to Placebo (95% CI)		-13.53 (-26.17, -1.94)	-14.20 (-25.03, -2.73)		-11.67 (-23.69, 1.25	-12.64 (-24.17, -1.13)
P-Value		0.0261	0.0158		0.0812	0.0304

(Source: Sponsor's Table 11.5 & Table 14.2.1.1.1.1)

Table 15 Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (Full ITT/ITT Analysis Set), Study 305

	Full ITT Analysis Set			ITT Analysis Set		
Statistic	Placebo	Perampanel		Placebo	Perampanel	
		8 mg	12 mg		8 mg	12 mg
n	136	129	121	135	126	118
Median	-9.72	-30.52	-17.57	-10.44	-31.32	-17.66
Median Difference to Placebo (95% CI)		-19.10 (-29.17, -8.45)	-13.69 (-25.20, -2.26)		-19.49 (-29.70, -9.05)	-13.38 (-24.83, -2.06)
P-Value		0.0008	0.0105		0.0007	0.0142

(Source: Sponsor's Table 11.5 & Table Table 14.2.1.1.7.1)

Table 16 Percent Change in Seizure Frequency per 28 Days During the Double-blind Phase Relative to Baseline (Full ITT/ITT Analysis Set), Study 306

Statistic	Placebo	Perampanel		
		2 mg	4 mg	8 mg
Full ITT Analysis Set				
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
ITT Analysis Set				
n	182	177	168	166
Median	-10.11	-14.13	-23.99	-31.34
Median Difference to Placebo (95% CI)		-5.88 (-15.59, 3.78	-14.83 (-24.42, -5.55)	-20.78 (-30.33, -11.00
P-value		0.26	0.0008	<0.0001

(Source: Sponsor's Table 11.5 & Table 14.2.1.1.1.1)

3) The reviewer compared and checked the discrepancy between the two analysis sets. According to the original protocol, six patients who did not have at least 2 weeks of seizure frequency data from the pre-randomization phase and at least 2 weeks of seizure frequency data from the double-blind Phase were excluded from the Full ITT analysis set. The six patients discontinued the study due to adverse event(s) in a short time after receiving treatments (1-13 days). There are no special patterns observed, in terms of treatment received and the LOCF value of the primary endpoint. Two patients were in the placebo group, and 4 patients in the 12 mg parampanel group. The LOCF values of the primary endpoint range from 38.46% to -100% (Table 17).

   The discrepancy in the analysis sets seems to have an impact on the efficacy result. It maybe due to a large variation in the imputed LOCF values of the primary endpoint since these patients withdraw early from the study.

Table 17 Patients Excluded from the Full ITT Analysis Set

Subject	Treatment Group	Days on Treatment	LOCF Value
1	12 mg	4	-100.00%
2	Placebo	7	-100.00%
3	12 mg	11	43.66%
4	12 mg	3	-8.40%
5	Placebo	13	38.46%
6	12 mg	1	-100.00%

(Source: The reviewer's analysis)

3.19 Conclusions

Both analysis sets yield a consistent efficacy results in Study 305 and Study 306, but not in Study304. In Study 304, a statistically significant result of efficacy is shown only if the full analysis set is used, and use of the full analysis set for the primary analysis was not planned in the protocol and SAP.

3.2 Evaluation of Safety

Please refer to Dr. Rusinowitz's review for safety assessment.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Subgroup analysis—age group

It appears that the efficacy of parampanel is in a right direction across all doses in subjects aged 64 years old or younger in all three studies (Table 18).

Table 18 Subgroup Analysis of Primary endpoint by Age Group, (Full ITT)

Age (years)	Placebo		Parampanel							
			2 mg		4 mg		8 mg		12 mg	
	n	% Change	n	% Change	n	% Change	n	% Change	n	% Change
Study 304										
<18	14	-15.90					15	-56.45	10	-35.56
18-64	102	-21.68					116	-25.38	118	-34.71
>64	5	-1.8					2	13.6	5	-12.49
Study 305										
<18	17	-22.86					17	-32.72	10	-43.87
18-64	118	-7.13					119	-26.64	119	-17.28
>64	1	-8.77					3	1.73	2	-40.60
Study 306										
<18	14	4.57	21	12.77	13	-23.91	12	-34.61		
18-64	166	-10.36	153	-16.55	154	-24.11	150	-30.62		
>64	2	-59.45	3	-66.57	1	19.31	4	-28.37		

(Source: Sponsor's Tables 14.2.1.2.2.1, 14.2.1.2.3.1, 14.2.1.2.4.1)

4.2 Subgroup analysis—sex

The efficacy of parampanel is also in a right direction in both genders across all doses in all three studies (Table 19).

Table 19 Subgroup Analysis of Primary endpoint by Sex, (Full ITT)

Sex	Placebo		Parampanel							
			2 mg		4 mg		8 mg		12 mg	
	n	% Change	n	% Change	n	% Change	n	% Change	n	% Change
Study 304										
Male	54	-21.97					65	-21.82	69	-30.11
Female	67	-15.90					68	-39.91	64	-38.11
Study 305										
Male	71	-11.85					65	-30.52	50	-14.64
Female	65	-8.77					64	-30.15	71	-17.57
Study 306										
Male	95	-10.94	83	-16.55	85	-19.02	77	-21.43		
Female	87	-8.54	94	-12.43	83	-26.14	89	-37.93		

(Source: Sponsor's Tables 14.2.1.2.2.1, 14.2.1.2.3.1, 14.2.1.2.4.1)

4.3 Subgroup analysis—race

The efficacy of parampanel is shown in a right direction in both ethnicity groups across all doses in all three studies (Table 20).

Table 20 Subgroup Analysis of Primary endpoint by Race, (Full ITT)

Race	Placebo		Parampanel							
			2 mg		4 mg		8 mg		12 mg	
	n	% Change	n	% Change	n	% Change	n	% Change	n	% Change
Study 304										
White	103	-21.74					115	-25.25	115	-33.51
Non-white	18	-15.63					18	-32.04	18	-42.16
Study 305										
White	115	-8.77					107	-26.64	100	-20.16
Non-white	21	-29.55					22	-52.30	21	-21.64
Study 306										
White	119	-11.11	116	-11.63	103	-23.91	115	-26.20		
Non-white	63	-7.69	61	-19.05	65	-24.14	51	-38.89		

(Source: Sponsor's Tables 14.2.1.2.2.1, 14.2.1.2.3.1, 14.2.1.2.4.1)

4.4 Subgroup analysis—region

The efficacy of parampanel is also shown in a right direction in all regions across all doses in Study 304 and Study 305. In Study 306, the efficacy of parampanel seems to be inconsistent across doses in the Russia region, it may be due to a small sample size in this region (Table 21).

Table 21 Subgroup Analysis of Primary endpoint by Region, (Full ITT)

Region	Placebo		2 mg		4 mg		8 mg		12 mg	
	n	% Change	n	% Change	n	% Change	n	% Change	n	% Change
Study 304										
North America	73	-11.34					74	-27.63	80	-36.91
USA	66	-9.52					64	-25.38	72	-35.22
Central & South America	48	-26.18					59	-24.88	53	-20.73
Study 305										
Europe	84	-2.11					75	-20.04	70	-14.88
USA	33	-23.31					31	-41.64	27	-21.64
India	10	-33.79					14	-45.42	14	-30.66
Russia	9	-5.63					9	-23.68	10	-31.02

Study 306										
Europe	103	-12.66	101	-13.72	96	-25.24	100	-34.89		
Asia	62	-8.12	60	-19.78	60	-23.45	50	-36.76		
Russia	17	-3.28	16	14.61	12	-5.83	16	0.46		

(Source: Sponsor's Tables 14.2.1.2.2.1, 14.2.1.2.3.1, 14.2.1.2.4.1 & Reviewer's Analysis)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Use of the full analysis set for primary analysis is important in clinical trials. The full analysis set includes all randomized subjects by intention-to-treat principle, and tends to avoid over-optimistic estimates of efficacy resulting from the analysis set that excludes subjects with condition. In the three studies of this NDA, the ITT analysis set was pre-specified for the primary analysis in the protocol and SAP. The ITT analysis set excludes subjects who did not have at least two weeks of seizure frequency data from the pre-randomization phase and from the double-blind Phase. In reviewing the sponsor's protocol and SAP, the agency recommended that the full ITT analysis set should be used for the primary analysis , but the sponsor did not take the agency's recommendation into consideration until later time in the trial prior to data un-blinded in Study 305, and when both Study 304 and Study 306 have completed.

Pre-specification of the analysis is also necessary to avoid any potential bias in interpretation of study result. An amendment was made to Study 304 and Study 306 when both studies have completed, the analysis set for the primary analysis was changed to the full ITT analysis set instead of the ITT analysis set as originally planned. The results were consistent from both analysis sets in Study 305 and Study 306, but were inconsistent in Study 304. Study 304 would fail on the primary analysis based on the originally planned ITT analysis set, but would win only when the full ITT analysis set was used.

5.2 Conclusions and Recommendations

The three clinical studies 304, 305 and 306 support that perampanel 4, 8 and 12 mg are effective in reducing seizure frequencies in subjects with refractory partial seizures. However, the results of the efficacy in Study 304 are not consistent because the statistical significance in the test of efficacy varies, depending on the patient population included in the analysis, and the change of patient population was made after the study completed. Therefore Study 304 may be used as supportive for efficacy.

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/s/

QUQUAN LIU
08/30/2012

KUN JIN
08/30/2012
I concur with the review.

HSIEN MING J HUNG
08/30/2012