CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

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

CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 22-345
Drug Name:	Retigabine (Potiga) Tablets
Indication(s):	104 Week Rat and 52 Week Mouse Carcinogenicity Study
Applicant:	**Sponsor:** Valeant Pharmaceuticals North America One Enterprise, Aliso Viejo, CA 92656
	Test Facility: (b) (4)
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Biometrics Division:	Division of Biometrics -6
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Keywords:	Carcinogenicity, Dose response

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1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in neonatal mice. These studies were intended to assess the carcinogenic potential of Retigabine (Potiga) tablets in rats when administered orally by gavage once daily at appropriate drug levels for about 104 weeks and in mice when administered orally by gavage twice, once on PND 8 (Post-Natal Day 8) and once on PND 15 and followed for 52 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Fisher.

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.

2. Rat Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, a vehicle control group and a water (or negative) control group. The dose levels for treated groups were 5, 20, and 50 mg/kg/day. In this review these dose groups were referred to as the low, medium, and high dose group, respectively. The animals in the vehicle control received the vehicle (USP Propylene glycol) by gavage, while the animals in the water control received purified water by gavage. Two hundred and ninety Crl:WI(Glx/BRL/Han)IGSBR rats of each sex were randomly allocated to treated and control groups. For each sex the group sizes were 70 animals for the high and medium dose groups, and 50 animals for low dose, and the two control groups.

During the administration period all animals were observed daily for clinical signs of effect or toxicity, weekly detailed physical examinations on all rats that included palpation for masses. Morbidity/mortality checks were made twice daily beginning 1 week prior to dose initiation and continuing throughout the dosing period. Body weights were recorded prior to initiation, on Day-1, weekly for 26 weeks and monthly thereafter. A complete histopathological examination was performed on all animals from all groups found dead, killed moribund, or sacrificed during or at the end of the experiment.

2.1. Sponsor's analyses

2.1.1. Survival analysis

The sponsor performed two separate sets of analysis, once using the vehicle control along with the treated groups and then using the water control along with the treated group. Survival function of each treatment group was estimated using the Kaplan-Meier product limit method and was presented graphically. A log-rank dose response relationship test of survival rates was performed using doses as the scores. The log-rank test for survival was also used to make pairwise comparisons of each treated group with the control groups. In addition, the log-rank test was used to compare the two control groups. The dose response relationship test and pairwise comparisons were conducted at the 0.05 significance level.

Sponsor's findings: For male rats the sponsor's analysis showed mortality rates of 50%, 16%, 34%, 46%, and 74% in vehicle control, water control, low, medium, and high dose groups, respectively; and for female rats 40%, 30%, 60%, 50%, and 66% in vehicle control , water control, low, medium, and high dose groups, respectively.

The sponsor's analysis showed that the morality rates in high dose group in both male and female rats were statistically significantly higher compared to both of their respective vehicle and water control groups. The decreased survival rates in the low and medium dose males and females were statistically significant compared to their respective water control group. In males the survival rate in the vehicle control group was statistically significantly decreased compared to in the water control group. A dose related increase in mortality was noted upon comparison of survival rates of control and treated groups in both sexes. From these mortality data, the sponsor commented that the maximum tolerated dose (MTD) was apparently exceeded at 50 mg/kg/day.

2.1.2. Tumor data analysis

Similar to the survival data analysis, the sponsor performed two separate sets of analysis, once using the vehicle control along with the treated groups and then using the water control along with the treated group. The incidences of tumors were analyzed using the Peto's mortality-prevalence method (Peto et al. 1980), without continuity correction, incorporating the context (incidental, fatal, or mortality independent) in which tumors were observed. The following fixed intervals were used for incidental tumor analyses: weeks 0-52, 53-78, 79-92, 93-end of study, scheduled interim sacrifice, and scheduled terminal sacrifice. However, the planned intervals might have been adjusted to account for the distribution of necropsies during the study.

The incidence of each tumor type that occurred in a target organ was analyzed with a 1-sided dose response relationship test using the dose as the score. At the discretion of the study director some combined tumor types were also analyzed. In addition, each active treatment group was compared with each control group with 1-sided pairwise comparisons. Lastly, the vehicle control group was compared to the water control group with a 1-sided pairwise comparison. All comparisons were for increasing onset of tumor incidence. The comparison of control groups was in the direction of increased onset of tumor incidence in the vehicle control group. An exact permutation test was conducted for analysis tumors with low incidence.

To adjust for the multiple testing, following the FDA guidance for carcinogenicity data analysis, statistical significance was determined as follows: dose response relationship tests were conducted at the 0.005 and 0.025 significance levels for common and rare tumors, respectively; pairwise comparisons were conducted with the control group at the 0.01 and 0.05 significance levels for common and rare tumors, respectively. The study director classified tumors as rare or common using a 1% benchmark. The concurrent controls, laboratory historical control database, and animal supplier database were considered in the determination of the historical spontaneous tumor rate.

Sponsor's findings: Sponsor's analyses showed a statistically significant dose response relationship in the incidence of interstitial cell tumor in the testis. The sponsor commented that even though the analysis showed a statistically significant dose response relationship, the actual incidence rates were within the range of historical incidences (b) (4), March, 2003) and the difference was considered to be spurious. When tumor types were combined in the skin or preputial gland in male rats, statistical significance was noted in the 5 mg/kg/day group and/or the 20 mg/kg/day group compared to the water control group, but not compared to the vehicle control group, with the exception of preputial gland carcinoma. The incidence of combined preputial gland neoplasms in the two control groups was also statistically different.

2.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were

provided by the sponsor electronically.

2.2.1. Survival analysis

The survival distributions of animals in all five treatment groups were estimated by the Kaplan-Meier product limit method. The dose response relationship was tested using the likelihood ratio test and homogeneity of survival distributions was tested using the log-rank test. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female rats, respectively.

Reviewer's findings: This reviewer's analysis showed male mortality rates of 50%, 16%, 34%, 46%, and 74% in vehicle control, water control, low, medium, and high dose groups, respectively; and female mortality rates of 40%, 30%, 58%, 50%, and 66% in vehicle control, water control, low, medium, and high dose groups, respectively. This reviewer's analysis showed statistically significant dose response relationship in mortality across treatment groups in both sexes. The pairwise comparisons showed statistically significant increased mortality in high dose group compared to the both controls in both sexes. In both sexes the pairwise comparisons also showed statistically significant increased mortality in low and medium dose groups compared to the water control. Statistically significant increased mortality was also found in vehicle control compared to the water control.

Reviewer's comment: The sponsor's count shows 60% mortality in female low dose group, while this reviewer's count shows 58%. This discrepancy is due to the fact that one animal (#CEL2F366) in low dose group died naturally during the sacrifice week. This reviewer counted it in the terminal sacrifice group, while the sponsor counted it in the naturally death group.

2.2.2. Tumor data analysis

This reviewer analyzed the tumor data twice, once using the vehicle control along with the treated groups and once using the water control along with the treated group.

The tumor data were analyzed for dose response relationships and pairwise comparisons of control with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice with at least one tumor gets a score of s_h =1. An animal that dies at week w_h without a tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}}\right)^k$ <1. The adjusted group size is defined as $N_A = \Sigma s_h$. 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 N_A 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, otherwise N_A is less than N. The adjusted group sizes of all treatment groups are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used.

The tumor rates and the p-values of the tumor types tested for dose response relationship and pairwise comparisons of vehicle control and treated groups are given in Table 3A_VC, and 3B_VC in the appendix for male and female rats, respectively. The tumor rates and the p-values of the tumor types tested for dose response relationship and pairwise comparisons of water control and treated groups are given in Table 3A_WC, and 3B_WC in the appendix for male and female rats, respectively.

Multiple testing adjustment: 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 test levels α=0.005 for common tumors and α=0.025 for rare tumors for a submission with two year study in two species (rat and mouse), and a significance level α=0.01 for common tumors and α=0.05 for rare tumors for a submission with two year study in one species, 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 the suggested the use of test levels α=0.01 for common tumors and α=0.05 for rare tumors, in order to keep the false-positive rate at the nominal level of approximately 10% for both submissions with two or one submission.

The present submission contains a rat and a mouse study. The length of the rat study was two years; however, the length of the mouse study was one year. Hence, the multiple testing adjustment rules described in the FDA guidance may not be applicable for this submission. To be conservative, for dose response relationship tests, this reviewer used a significance level α=0.01 for common tumors and α=0.05 for rare tumors in rat study, and used a significance level α=0.05 for all tumors in mouse study.

Reviewer's findings: Following tumor types showed p-values less than or equal to 0.05 either for dose response relationship and/or pairwise comparisons of control and treated groups.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons

Male Rats Using Vehicle Control

Organ Name	Tumor Name	Veh. Cont. N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dose Response	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
TESTIS	Interstitial Cell Tumor	1	0	1	4	0.0120	0.5128	0.3200	0.1458

Male Rats Using Water Control

Organ Name	Tumor Name	Wat. Cont. N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dose Response	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
PREPUTIAL GLAND	Carcinoma	0	5	7	3	0.2040	0.0191*	0.0084*	0.0739
	adenoma+carcinoma	0	6	7	3	0.2605	0.0083*	0.0084*	0.0739
	Squamous Cell Papilloma	0	4	2	0	0.8048	0.0434*	0.2631	.
SKIN LESION	Keratoacanthoma	0	4	1	1	0.5638	0.0434*	0.5155	0.4198
TESTIS	Interstitial Cell Tumor	2	0	1	4	0.0249	0.7110	0.5234	0.1989

Based on the criterion of adjustment for multiple testing discussed above none of the tested tumor types was considered to have a statistically significant positive dose response relationship. The pairwise comparisons in male rats showed statistically significant increased incidences of preputial gland/carcinoma, preputial

gland/combined incidences of adenoma and carcinoma in low and medium dose groups, preputial gland/squamous cell papilloma in low dose group, and skin lesion/ keratoacanthoma in low dose group, all compared to the water control.

3. Mouse Study

This study was designed to determine the carcinogenic potential of Retigabine using a neonatal mouse model. The test/control article was administered by oral intubation (gavage) once on PND 8 (Post-Natal Day 8) and once on PND 15. Animals were then maintained until necropsy at about 1 year of age.

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one vehicle control group, one water (or negative) control group, and one positive control group. The dose levels for treated groups were 32, 64, and 96 mg/kg. In this review these dose groups were referred to as the low, medium, and high dose group, respectively. The water control received distilled tap water, the vehicle control received the vehicle (Propylene Glycol), and the positive control received 2 mg/kg diethylnitrosamine (DEN).

Initially one hundred and sixty eight (168) CD-1® [Crl:CD-1®(ICR)] Albino Mice of each sex were planned to be randomly allocated to treated and control groups in equal size of 28 animals. The initial number of animals on test were planned to be sufficient to allow for early litter loss and ensure that there were 24 pups/sex/ group at the study termination, which is the current recommended standard (McClain et. al., 2001) for the detection of tumors in the neonatal mouse model. The actual numbers of animals assigned per group and examined microscopically were as follows:

Treatment Group	Vehicle Control	Water Control	Retigabine 32 mg/kg	Retigabine 64 mg/kg	Retigabine 96 mg/kg	Positive Control
Initial total male mouse	28	27	29	28	28	28
Initial total female mouse	28	29	27	28	28	28
*Elective sacrifice/missing male mouse	0	3	0	0	0	0
*Elective sacrifice/missing female mouse	0	5	1	0	0	0
**Microscopic pathology male mouse	27	24	29	25	25	28
**Microscopic pathology female mouse	27	24	24	25	27	28

*** During the dosing phase of the study, in the water-control group, 1 litter (3 males and 5 females) was electively euthanized on PND 17 because of the death of the dam.**

****Microscopic pathology evaluations were conducted on all animals at the scheduled sacrifice interval and on all animals found dead or sacrificed during the Maintenance phase of the study.**

However, the sponsor's submitted data had observation from 27, 24, 28, 25, 25, and 28 males, and 26, 24, 24, 25, 26, and 28 females in vehicle control, water control, low, medium, and high dose groups, respectively. This reviewer's analyses are based on these numbers of animals.

Dams and offspring were observed in their cages twice daily for mortality and signs of severe toxic or pharmacologic effects. Animals in extremely poor health or in a possible moribund condition were identified for further monitoring and possible euthanasia. Offspring were removed from their cages and examined approximately twice weekly from receipt through weaning (PND 22) and then weekly through study termination. Examinations included observations of general condition, skin and fur, eyes, nose, oral cavity, abdomen and external genitalia as well as evaluations of respiration. Body weights of animals were taken on PND 6, 8, 12, 15, 18, 21 and 28, and then weekly until termination.

Necropsy was performed on all treated animals approximately 1 year after dosing. All tissues were evaluated for animals in vehicle control and high dose groups (Groups 2 and 5), while liver, lungs and gross lesions were evaluated for water control group, the low and medium dose groups and the positive control group.

3.1. Sponsor's analyses

3.1.1. Survival analysis

Survival data from the mouse study were analyzed using the same statistical methodologies as were used to analyze the survival data from the rat study. The sponsor performed the following comparisons: 1) Vehicle control vs. Water control, 2) Retigabine-treated groups vs. Vehicle control, and 3) DEN positive control vs. Water control.

Sponsor's findings: Sponsor's analysis showed that the percentage of survivors in male vehicle control, water control, low dose, medium dose, high dose, and positive control groups were 85.7, 83.3, 89.7, 71.4, 85.7, and 85.7, respectively and those in female vehicle control, water control, low dose, medium dose, high dose, and positive control groups were 89.3, 95.8, 88.5, 78.6, 89.3, and 89.3, respectively. The sponsor's described that the mortality in the retigabine treated groups during the dosing phase was generally comparable to that of the vehicle control group. Most of the deaths were clustered after the first dose on PND 8 or the second dose on PND 15. The percentage of animals surviving at the end of the maintenance phase was lower in the 64-mg/kg retigabine group, as compared to the vehicle control. The sponsor commented that in the absence of a dose response relationship, this increased mortality was considered not to be test article related. During the dosing phase of the study, there were no mortalities in the animals treated with the positive control article. During the maintenance phase of the study, mortality in the DEN treated animals was similar to that of the water-control group.

3.1.2. Tumor data analysis

Similar to the survival data analysis, the sponsor performed the following pairwise comparisons for the tumor data were analysis: 1) Vehicle control vs. Water control, 2) Retigabine-treated groups vs. Vehicle control, and 3) DEN positive control vs. Water control. The data were analyzed using the Fisher's Exact test.

Sponsor's findings: The sponsor described that the spontaneous neoplasms occurred mainly in the lungs and liver. The sponsor's analysis showed that there were no statistically significant difference in the incidences of the lung and liver neoplasms (adenomas, carcinomas, and combined adenomas and carcinomas) in the test article treated males or females as compared to the controls. In the male mice at 64 mg/kg, there were statistically significant increases in some metastatic neoplasms. However, the sponsor did not consider them as test article related. The sponsor's analyses showed that the incidences of spontaneously occurring neoplasms in the lung and liver in water and vehicle treated control males were generally comparable and also comparable to the published data of McClain *et al.* (2001).

The animals in active control group showed a high incidence of bronchioloalveolar adenomas/carcinomas and hepatocellular adenomas/carcinomas. The sponsor commented that this validated the ability of this model to detect carcinogenic effects.

3.2. Reviewer's analyses

This reviewer independently performed survival and tumor data analyses from the mouse study. For the mouse data analyses this reviewer used similar methodologies as he used to analyze the data from the rat study. Data used in this reviewer's analyses were provided by the sponsor electronically.

3.2.1. Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for male and female mice, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the appendix for male and female mice, respectively. Results for test of dose response relationship and homogeneity of survivals among treatment groups are given in Tables 5A and 5B in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's analysis showed 92.59, 83.33, 92.86, 80.00, 96.00, and 89.29 percent survivors in male vehicle control, water control, low dose, medium dose, high dose, and positive control groups, respectively and 96.15, 95.83, 95.83, 88.00, 92.31, and 92.86 percent survivors in female vehicle control, water control, low dose, medium dose, high dose, and positive control groups, respectively. This reviewer's analysis showed no statistically significant dose response relationship in mortality across treatment groups in either sex. The pairwise comparisons also did not show statistically significant increased mortality in any of the treated group compared to the either of the controls.

Reviewer's comment: *Clearly, there are various numerical differences in the calculated percentages of survivors found by the sponsor and found by this reviewer. These discrepancies are due to the fact that the sponsor calculated the percentages of survivors based on the initial number of animals excluding the electively euthanized animals and one missing female in the low dose group. As mentioned earlier, during the dosing phase of the study, in the water-control group, 1 litter (3 males and 5 females) was electively euthanized on PND 17 because of the death of the dam. This reviewer's calculations are based on the animals those went under microscopic pathology. Note that the data of only these animals (animals went under microscopic pathology) were included in the data set.*

3.2.2. Tumor data analysis

As mentioned earlier, all tissues and organs from mice in the vehicle control and high dose group were examined microscopically. In addition, the lungs and liver from mice in the water control, low and medium dose groups, and the positive control (DEN) group, as well as tissues and organs with macroscopic abnormalities were microscopically examined. Therefore, this reviewer performed dose response relationship analysis on tumors found in lung and liver only. For tumors found in any other organs only pairwise comparisons of treated groups with the controls were performed.

The tumor rates and the p-values of the tumor types tested for dose response relationship and pairwise comparisons of vehicle control and treated groups are given in Table 6A_VC, and 6B_VC in the appendix for male and female mice, respectively. The tumor rates and the p-values of the tumor types tested for dose response relationship and pairwise comparisons of water control and treated groups are given in Table 6A_WC, and 6B_WC in the appendix for male and female mice, respectively. The pairwise comparisons of vehicle control, water control, and positive control are given in Table 6A_VWP and Table 6B_VWP in the appendix for male and female mice, respectively.

Reviewer's findings: Using 5% level of significance, this reviewer's analysis did not show statistically significant dose response relationship in the incidence of any of the observed tumor types using either the vehicle control or water control along with the retigabine treated groups. This reviewer's analysis also did not show statistically significant increased incidence of any of the observed tumor types in the retigabine treated groups compared to the vehicle control or water control. The positive control showed statistically significant increased incidences of hepatocellular adenoma, hepatocellular carcinoma, and bronchiolar alveolar adenoma compared to either of the controls.

4. Evaluation of validity of the designs

As has been noted, the tumor data analyses from both rat and mouse study showed no statistically significant dose-response relationship in any of the tested tumor types. However, before drawing any conclusion regarding the carcinogenic or non-carcinogenic potential of the drug in rats and mice, it is important to look into the following two issues, as have been pointed out in the paper by Haseman (1984).

(i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumors?
(ii) 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 about fifty animals per treatment group. The following are some rules of thumb regarding these two issues as suggested by experts in this field.

Haseman (1985) 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 consider as a sufficient number and adequate exposure. In addition Chu, Cueto and Ward (1981), 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 (1981), the following criteria are mentioned for dose adequacy. A high dose is considered as close to MTD if any of the criteria is met.

(i) "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."

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

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

We will now investigate the validity of the Retigabine rat and mouse carcinogenicity study, in the light of the above guidelines.

4.1. Rat Study

The following is the summary of survival data of rats in the high dose groups:

Percentage of survival in the high dose group at the end of Weeks 52, 78, and 91

	Percentage of survival		
	End of 52 weeks	End of 78 weeks	End of 91 weeks
Male	76%	49%	40%
Female	64%	47%	37%

Based on the survival criterion Haseman proposed, it may be concluded that not enough rats were exposed to the high dose for a sufficient amount of time in either sex, especially in females.

The following table shows the percent difference in mean body weight gain in rats from the concurrent control, defined as

$$\text{Percent difference} = \frac{(\text{Final BW} - \text{Baseline BW})_{\text{Treated}} - (\text{Final BW} - \text{Baseline BW})_{\text{Control}}}{(\text{Final BW} - \text{Baseline BW})_{\text{Control}}} \times 100$$

Percent Difference in Mean body Weight Gain from Vehicle Controls

Male			Female		
5 mg	20 mg	50 mg	5 mg	20 mg	50 mg
4.09	-0.70	-16.97	-2.07	3.19	-8.72

Source: Table 2 of sponsor's submission

Percent Difference in Mean body Weight Gain from Water Controls

Male			Female		
5 mg	20 mg	50 mg	5 mg	20 mg	50 mg
-13.86	-17.83	-31.29	-21.21	-16.98	-26.56

Source: Table 2 of sponsor's submission

Therefore, relative to vehicle control the male and female rats had about 17% and 9% decrement respectively, in body weight gain. Also relative to water control the male and female rats had about 31% and 27% decrement respectively, in body weight gain.

The mortality rates at the end of the experiment were as follows:

Mortality Rates at the End of the Experiment

	Vehic. Cont.	**Water Cont.**	**5 mg**	**20 mg**	**50 mg**
Male	50%	16%	34%	46%	74%
Female	40%	30%	58%	50%	65%

This shows that the morality rate of in the high dose group in males is 24% higher than the vehicle control and

58% higher than the water control. Also the morality rate of in the high dose group in females is 18% higher than the vehicle control and 35% higher than the water control.

Thus, from the body weight gain and mortality data it can be concluded that the used high dose level might have exceeded the MTD in both sexes. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

4.2. Mouse Study

Since the mouse study was only one year long, all the criteria stated above for the determination of sufficient exposure and high enough dose level may not be exactly applicable for this study. Therefore, this reviewer did not perform such analysis on mouse data. The appropriate clinical signs and histopathological toxic effects may be used for this determination.

5. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in neonatal mice. These studies were intended to assess the carcinogenic potential of Retigabine (Potiga) tablets in rats when administered orally by gavage once daily at appropriate drug levels for about 104 weeks and in mice when administered orally by gavage twice, once on PND 8 (Post-Natal Day 8) and once on PND 15 and followed for 52 weeks.

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.

Rat Study: Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, a vehicle control group and a water (or negative) control group. The dose levels for treated groups were 5, 20, and 50 mg/kg/day. In this review these dose groups were referred to as the low, medium, and high dose group, respectively. The animals in the vehicle control received the vehicle (USP Propylene glycol) by gavage, while the animals in the water control received purified water by gavage. Two hundred and ninety Crl:WI(Glx/BRL/Han)IGSBR rats of each sex were randomly allocated to treated and control groups. For each sex the group sizes were 70 animals for the high and medium dose groups, and 50 animals for low dose, and the two control groups.

Tests showed statistically significant dose response relationship in mortality across treatment groups in both sexes. The pairwise comparisons showed statistically significant increased mortality in high dose group compared to the both controls in both sexes. In both sexes the pairwise comparisons also showed statistically significant increased mortality in low and medium dose groups compared to the water control. Statistically significant increased mortality was also found in vehicle control compared to the water control.

Tests did not show statistically significant positive dose response relationship in any of the tested tumor types. The pairwise comparisons in male rats showed statistically significant increased incidences of preputial gland/carcinoma, preputial gland/combined incidences of adenoma and carcinoma in low and medium dose groups, preputial gland/squamous cell papilloma in low dose group, and skin lesion/ keratoacanthoma in low dose group, all compares to the water control.

Mouse Study: This study was designed to determine the carcinogenic potential of Retigabine using a neonatal mouse model. The test/control article was administered by oral intubation (gavage) once on PND 8 and once on PND 15. Animals were then maintained until necropsy at about 1 year of age.
Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one water (or negative) control group, one vehicle control group and one positive control group. The dose levels for treated groups were 32, 64, and 96 mg/kg. In this review these dose groups were referred to as the low, medium, and high dose group, respectively. The water control received distilled tap water, the vehicle control received the vehicle (Propylene Glycol), and the positive control received 2 mg/kg diethylnitrosamine (DEN).

Initially one hundred and sixty eight (168) CD-1® [Crl:CD-1®(ICR)] Albino Mice of each sex were planned to be randomly allocated to treated and control groups in equal size of 28 animals. The initial number of animals on test were planned to be sufficient to allow for early litter loss and ensure that there were 24 pups/sex/ group at the study termination, which is the current recommended standard (McClain et. al., 2001) for the detection of tumors in the neonatal mouse model. The actual numbers of animals assigned per group and examined microscopically were as follows:

Treatment Group	Vehicle Control	Water Control	Retigabine 32 mg/kg	Retigabine 64 mg/kg	Retigabine 96 mg/kg	Positive Control
Initial total male mouse	28	27	29	28	28	28
Initial total female mouse	28	29	27	28	28	28
*Elective sacrifice/missing male mouse	0	3	0	0	0	0
*Elective sacrifice/missing female mouse	0	5	1	0	0	0
**Microscopic pathology male mouse	27	24	29	25	25	28
**Microscopic pathology female mouse	27	24	24	25	27	28

*** During the dosing phase of the study, in the water-control group, 1 litter (3 males and 5 females) was electively euthanized on PND 17 because of the death of the dam.**

****Microscopic pathology evaluations were conducted on all animals at the scheduled sacrifice interval and on all animals found dead or sacrificed during the Maintenance phase of the study.**

Tests showed no statistically significant dose response relationship in mortality across treatment groups in either sex. The pairwise comparisons also did not show statistically significant increased mortality in any of the treated group compared to the either of the controls.

Tests did not show statistically significant dose response relationship in the incidence of any of the observed tumor types using either the water control or vehicle control along with the retigabine treated groups. The pairwise comparisons also did not show statistically significant increased incidence of any of the observed tumor types in the retigabine treated groups compared to the water control or vehicle control. The positive control showed statistically significant increased incidences of hepatocellular adenoma, hepatocellular carcinoma, and bronchiolar alveolar adenoma compared to either of the controls.

Evaluation of the study designs: The data showed that there were some early deaths in rats and it seems that not enough rats were exposed long enough for late developing tumors in either sex, especially in females. Also from the mortality and body weight data it can be concluded that the used high dose in rats might have exceeded the MTD in both sexes. Since the length of the mouse study was short and no established statistical

criterion are known to this reviewer to evaluate such design, this reviewer did not perform any evaluation of exposure or dose level for the mouse study. For a final determination of the adequacy of exposure and the doses used in both rat and mouse studies clinical signs and histopathological toxic effects should be considered.

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6. Appendix

Table 1A: Intercurrent Mortality Rate
Male Rats

	Vehicle Control N=50		Water Control N=50		5 mg|kg|day N=50		20 mg|kg|day N=70		50 mg|kg|day N=70	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	3	6.00	.	.	5	10.00	10	14.29	17	24.29
53 - 78	7	20.00	2	4.00	4	18.00	8	25.71	19	51.43
79 - 91	6	32.00	2	8.00	2	22.00	5	32.86	6	60.00
92 - 104	9	50.00	4	16.00	6	34.00	9	45.71	10	74.29
Ter. Sac.	25	50.00	42	84.00	33	66.00	38	54.29	18	25.71

Table 1B: Intercurrent Mortality Rate
Female Rats

	Vehicle Control N=50		Water Control N=50		5 mg|kg|day N=50		20 mg|kg|day N=70		50 mg|kg|day N=70	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	4	8.00	2	4.00	11	22.00	20	28.57	25	35.71
53 - 78	5	18.00	4	12.00	6	34.00	9	41.43	12	52.86
79 - 91	2	22.00	2	16.00	5	44.00	4	47.14	7	62.86
92 - 104	9	40.00	7	30.00	7	58.00	2	50.00	2	65.71
Ter. Sac.	30	60.00	35	70.00	21	42.00	35	50.00	24	34.29

Table 2A: Intercurrent Mortality Comparison
Male Rats

Test	Statistic	P_Value using Vehicle control	P_Value using water control
Dose-Response	Likelihood Ratio	0.0004	<0.0001
Homogeneity	Log-Rank	<0.0001	<0.0001

Table 2B: Intercurrent Mortality Comparison
Female Rats

Test	Statistic	P_Value using Vehicle control	P_Value using water control
Dose-Response	Likelihood Ratio	0.0601	0.0067
Homogeneity	Log-Rank	0.0106	0.0004

Table 3A_VC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using the Vehicle Control
Male Rats

Organ Name	Tumor Name	0 mg Veh Cont N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dose Resp	P_Value NC vs. L	P_Value NC vs. M	P_Value NC vs. H
ABDOMINAL CAVIT	Hemangiosarcoma	0	0	0	1	0.2099	.	.	0.4722
ADIPOSE TISSUE	Histiocytic Sarcoma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
ADRENAL	Cortical Adenoma	0	1	1	0	0.4707	0.5128	0.5682	.
	Cortical Carcinoma	0	1	0	0	0.5185	0.5128	.	.
	Pheochromocytoma	1	0	2	2	0.1428	0.5128	0.6028	0.4688
BRAIN	Astrocytoma	1	0	0	1	0.3844	0.5128	0.5682	0.7325
EPIDIDYMIS	Mesothelioma	1	0	1	0	0.6240	0.5128	0.3200	0.4722
INTESTINE-LARGE	Leiomyosarcoma	1	0	1	0	0.6240	0.5128	0.3200	0.4722
KIDNEY	Malignant Lymphoma	0	1	0	0	0.5185	0.5128	.	.
LIVER	Hepatocellular Adeno	0	0	2	0	0.4707	.	0.3200	.
	Hepatocellular Carci	0	2	0	1	0.4287	0.2597	.	0.4722
	Histiocytic Sarcoma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
LUNG W/BRONCHI	Histiocytic Sarcoma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
	Malignant Lymphoma	0	1	0	0	0.5185	0.5128	.	.
LYMPH NODE, MAN	Malignant Lymphoma	0	1	0	0	0.5185	0.5128	.	.
LYMPH NODE, MES	Hemangioma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
	Hemangiosarcoma	0	0	0	1	0.2099	.	.	0.4722
	Histiocytic Sarcoma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
	Malignant Lymphoma	0	1	0	0	0.5185	0.5128	.	.
MAMMARY GLAND	Fibroadenoma	0	1	0	0	0.5185	0.5128	.	.
PANCREAS	Islet Cell Adenoma	1	1	2	0	0.7123	0.2597	0.6028	0.4722
	Islet Cell Carcinoma	0	1	0	0	0.5185	0.5128	.	.
PARATHYROID	Adenoma	1	2	0	0	0.9048	0.5195	0.5682	0.4722
PITUITARY	Adenoma, Pars Distal	14	8	7	3	0.9963	0.9063	0.9838	0.9940
	Adenoma, Pars Interm	0	1	0	0	0.5153	0.5190	.	.
	Carcinoma, Pars Dist	0	1	0	0	0.5185	0.5128	.	.
PREPUTIAL GLAND	Adenoma	0	1	0	0	0.5153	0.5190	.	.
	Carcinoma	3	5	7	3	0.5271	0.3999	0.3053	0.6226
	Squamous Cell Carcin	5	5	4	3	0.7458	0.4187	0.6827	0.5969
	Squamous Cell Papill	2	4	2	0	0.9519	0.3747	0.4182	0.7250
SALIVARY GLAND,	Malignant Lymphoma	0	1	0	0	0.5185	0.5128	.	.
SEMINAL VESICLE	Histiocytic Sarcoma	1	0	0	0	0.7654	0.5128	0.5682	0.4722

Table 3A_VC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using the Vehicle Control
Male Rats

Organ Name	Tumor Name	0 mg Veh Cont N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dose Resp	P_Value NC vs. L	P_Value NC vs. M	P_Value NC vs. H
SKIN LESION	Basal Cell Carcinoma	0	0	1	0	0.5185	.	0.5682	.
	Keratoacanthoma	1	4	1	1	0.7385	0.2040	0.3200	0.7250
	Sebaceous Cell Carci	0	0	1	0	0.5185	.	0.5682	.
	Squamous Cell Carcin	1	0	0	0	0.7654	0.5128	0.5682	0.4722
	Squamous Cell Papill	0	3	0	0	0.8906	0.1299	.	.
SPLEEN	Histiocytic Sarcoma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
STOMACH	Adenocarcinoma	1	1	0	0	0.8295	0.2597	0.5682	0.4722
SUBCUTANEOUS TI	Fibroma	0	0	1	1	0.1734	.	0.5682	0.4722
	Fibrosarcoma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
	Hemangiosarcoma	0	0	1	0	0.5185	.	0.5682	.
	Histiocytic Sarcoma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
	Malignant Schwannoma	0	1	0	0	0.5153	0.5190	.	.
	Osteosarcoma	0	0	1	0	0.5185	.	0.5682	.
	Undifferentiated Sar	1	0	0	0	0.7654	0.5128	0.5682	0.4722
TESTIS	Hemangioma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
	Interstitial Cell Tu	1	0	1	4	0.0120	0.5128	0.3200	0.1458
	Mesothelioma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
THYMUS	Histiocytic Sarcoma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
	Malignant Lymphoma	0	1	0	0	0.5185	0.5128	.	.
	Thymoma	2	4	0	1	0.8704	0.3624	0.8164	0.4688
THYROID	C-Cell Adenoma	2	6	4	2	0.7041	0.1576	0.4766	0.6495
	C-Cell Carcinoma	0	1	1	0	0.4707	0.5128	0.5682	.
	Follicular Cell Aden	2	1	2	1	0.5768	0.5195	0.4182	0.4688
	Follicular Cell Carc	0	0	2	0	0.4707	.	0.3200	.

Table 3A_WC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using the Water Control
Male Rats

Organ Name	Tumor Name	0 mg Wat. Cont N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ABDOMINAL CAVIT	Hemangiosarcoma	0	0	0	1	0.1988	.	.	0.4198
ADIPOSE TISSUE	Lipoma	1	0	0	0	0.7251	0.4598	0.5155	0.4198
ADRENAL	Cortical Adenoma	2	1	1	0	0.8488	0.4391	0.5234	0.6664
	Cortical Carcinoma	0	1	0	0	0.4912	0.4598	.	.
	Pheochromocytoma	1	0	2	2	0.1213	0.4598	0.5234	0.3897
BRAIN	Astrocytoma	0	0	0	1	0.2035	.	.	0.4268
EPIDIDYMIS	Mesothelioma	0	0	1	0	0.4912	.	0.5155	.
INTESTINE-LARGE	Leiomyosarcoma	0	0	1	0	0.4912	.	0.5155	.
KIDNEY	Malignant Lymphoma	0	1	0	0	0.4912	0.4598	.	.
LIVER	Hepatocellular Adeno	0	0	2	0	0.4433	.	0.2631	.
	Hepatocellular Carci	0	2	0	1	0.3890	0.2085	.	0.4198
LUNG W/BRONCHI	Malignant Lymphoma	0	1	0	0	0.4912	0.4598	.	.
LYMPH NODE, MAN	Malignant Lymphoma	0	1	0	0	0.4912	0.4598	.	.
LYMPH NODE, MES	Hemangiosarcoma	1	0	0	1	0.3591	0.4598	0.5155	0.6664
	Malignant Lymphoma	0	1	0	0	0.4912	0.4598	.	.
MAMMARY GLAND	Fibroadenoma	0	1	0	0	0.4912	0.4598	.	.
PANCREAS	Islet Cell Adenoma	3	1	2	0	0.8941	0.6285	0.5296	0.8100
	Islet Cell Carcinoma	0	1	0	0	0.4912	0.4598	.	.
PARATHYROID	Adenoma	0	2	0	0	0.7426	0.2085	.	.
PITUITARY	Adenoma, Pars Distal	10	8	7	3	0.9507	0.4547	0.7486	0.8887
	Adenoma, Pars Interm	1	1	0	0	0.7955	0.7176	0.5155	0.4198
	Carcinoma, Pars Dist	0	1	0	0	0.4912	0.4598	.	.
	Meningeal Sarcoma	1	0	0	0	0.7251	0.4598	0.5155	0.4198
PREPUTIAL GLAND	Adenoma	0	1	0	0	0.4884	0.4659	.	.
	Carcinoma	0	5	7	3	0.2040	0.0191*	0.0084*	0.0739
	adenoma+carcinoma	0	6	7	3	0.2605	0.0083*	0.0084*	0.0739
	Squamous Cell Carcin	2	5	4	3	0.4083	0.1644	0.3786	0.3614
	Squamous Cell Papill	0	4	2	0	0.8048	0.0434*	0.2631	.
PROSTATE	Adenoma	1	0	0	0	0.7251	0.4598	0.5155	0.4198
SALIVARY GLAND,	Malignant Lymphoma	0	1	0	0	0.4912	0.4598	.	.
SKIN LESION	Basal Cell Carcinoma	0	0	1	0	0.4912	.	0.5155	.
	Keratoacanthoma	0	4	1	1	0.5638	0.0434*	0.5155	0.4198
	Sebaceous Cell Carci	0	0	1	0	0.4912	.	0.5155	.

Table 3A_WC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using the Water Control
Male Rats

Organ Name	Tumor Name	0 mg Wat. Cont N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
SKIN LESION	Squamous Cell Papill	1	3	0	0	0.9379	0.2497	0.5155	0.4198
STOMACH	Adenocarcinoma	0	1	0	0	0.4912	0.4598	.	.
SUBCUTANEOUS TI	Fibroma	0	0	1	1	0.1556	.	0.5155	0.4198
	Granular Cell Tumor	1	0	0	0	0.7251	0.4598	0.5155	0.4198
	Hemangiosarcoma	1	0	1	0	0.5809	0.4598	0.2631	0.4198
	Malignant Schwannoma	0	1	0	0	0.4884	0.4659	.	.
	Osteosarcoma	0	0	1	0	0.4912	.	0.5155	.
	Undifferentiated Sar	1	0	0	0	0.7251	0.4598	0.5155	0.4198
TESTIS	Interstitial Cell Tu	2	0	1	4	0.0249	0.7110	0.5234	0.1989
THYMUS	Malignant Lymphoma	0	1	0	0	0.4912	0.4598	.	.
	Thymoma	1	4	0	1	0.7405	0.1341	0.5155	0.6745
THYROID	C-Cell Adenoma	6	6	4	2	0.8962	0.5203	0.6689	0.7365
	C-Cell Carcinoma	2	1	1	0	0.8488	0.4391	0.5234	0.6664
	Follicular Cell Aden	5	1	2	1	0.8539	0.8572	0.8070	0.8160
	Follicular Cell Carc	1	0	2	0	0.5718	0.4598	0.5234	0.4198
ZYMBAL'S GLAND	Carcinoma	1	0	0	0	0.7251	0.4598	0.5155	0.4198

Table 3B_VC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using the Vehicle Control
Female Rats

Organ Name	Tumor Name	0 mg Veh Cont N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dose Resp	P_Value NC vs. L	P_Value NC vs. M	P_Value NC vs. H
ADIPOSE TISSUE	Lipoma	0	1	0	0	0.5137	0.4366	.	.
	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
ADRENAL	Cortical Adenoma	0	0	2	0	0.4835	.	0.2593	.
	Malignant Lymphoma	0	1	0	1	0.2768	0.4444	.	0.4521
AORTA (THORACIC	Malignant Schwannoma	0	1	0	0	0.5137	0.4366	.	.
BONE, STERNUM	Malignant Lymphoma	0	1	0	1	0.2768	0.4444	.	0.4521
CERVIX	Adenomatous Polyp	0	1	0	0	0.5137	0.4366	.	.
	Endometrial Stromal	0	0	1	0	0.5137	.	0.5122	.
			1	0	0	0.5137	0.4366	.	.
	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
CLITORAL GLAND	Carcinoma	0	1	0	0	0.5137	0.4366	.	.
	Squamous Cell Carcin	1	2	1	1	0.5326	0.4041	0.2593	0.7032
DIAPHRAGM	Malignant Lymphoma	0	1	0	0	0.5102	0.4444	.	.
	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
HARDERIAN GLAND	Malignant Lymphoma	0	0	0	1	0.2260	.	.	0.4521
HEART	Malignant Schwannoma	0	1	0	0	0.5137	0.4366	.	.
INTESTINE-LARGE	Leiomyoma	0	0	0	1	0.2260	.	.	0.4521
	Malignant Lymphoma	0	0	0	1	0.2260	.	.	0.4521
	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
INTESTINE-SMALL	Malignant Lymphoma	0	0	0	1	0.2260	.	.	0.4521
	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
KIDNEY	Malignant Lymphoma	0	1	0	1	0.2768	0.4444	.	0.4521
	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
	Tubular Cell Adenoma	1	0	0	0	0.7260	0.4366	0.5122	0.4521
KNEE JOINT (FEM	Malignant Lymphoma	0	1	0	1	0.2768	0.4444	.	0.4521
LIVER	Hepatocellular Adeno	0	1	1	1	0.2687	0.4366	0.5122	0.4521
	Malignant Lymphoma	0	1	0	1	0.2768	0.4444	.	0.4521
	Malignant Schwannoma	0	1	0	0	0.5137	0.4366	.	.
LUNG W/BRONCHI	Malignant Lymphoma	0	1	0	1	0.2768	0.4444	.	0.4521
LYMPH NODE, MAN	Malignant Lymphoma	0	1	0	1	0.2768	0.4444	.	0.4521
	Malignant Schwannoma	0	1	0	0	0.5137	0.4366	.	.
LYMPH NODE, MES	Hemangioma	0	0	0	1	0.2260	.	.	0.4521
	Hemangiosarcoma	0	0	1	0	0.5137	.	0.5122	.
	Malignant Lymphoma	0	1	0	1	0.2768	0.4444	.	0.4521

Table 3B_VC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using the Vehicle Control
Female Rats

Organ Name	Tumor Name	0 mg Veh Cont N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dose Resp	P_Value NC vs. L	P_Value NC vs. M	P_Value NC vs. H
LYMPH NODE, MES	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
MAMMARY GLAND	Adenocarcinoma	0	0	0	1	0.2260	.	.	0.4521
	Adenoma	0	0	1	0	0.5137	.	0.5122	.
	Fibroadenoma	2	2	4	1	0.6239	0.6039	0.3615	0.4273
MESENTERY	Lipoma	0	0	1	0	0.5137	.	0.5122	.
	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
NOSE	Squamous Cell Papill	0	1	0	0	0.5137	0.4366	.	.
OVARY	Granulosa Cell Tumor	1	1	0	1	0.5111	0.6861	0.5122	0.7032
	Luteoma	0	1	0	0	0.5137	0.4366	.	.
	Malignant Schwannoma	0	1	0	0	0.5137	0.4366	.	.
	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
	Sertoli Cell Tumor	1	0	1	0	0.6065	0.4366	0.2593	0.4521
	Thecoma	1	0	0	0	0.7260	0.4366	0.5122	0.4521
	Undifferentiated Gon	0	0	0	1	0.2260	.	.	0.4521
PANCREAS	Islet Cell Adenoma	0	0	1	1	0.1808	.	0.5122	0.4521
	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
PITUITARY	Adenoma, Pars Distal	14	15	17	15	0.3784	0.2262	0.4195	0.3284
	Carcinoma, Pars Dist	1	0	0	1	0.4022	0.4366	0.5122	0.7032
SALIVARY GLAND,	Malignant Schwannoma	0	1	0	0	0.5137	0.4366	.	.
SKIN LESION	Squamous Cell Papill	0	0	0	1	0.2260	.	.	0.4521
SPLEEN	Malignant Lymphoma	0	1	0	1	0.2768	0.4444	.	0.4521
STOMACH	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
SUBCUTANEOUS TI	Hemangiosarcoma	0	0	0	1	0.2313	.	.	0.4595
	Malignant Schwannoma	1	1	0	0	0.8092	0.6861	0.5122	0.4521
	Trichoepithelioma	0	0	1	0	0.5137	.	0.5122	.
THORACIC CAVITY	Malignant Schwannoma	0	1	0	0	0.5137	0.4366	.	.
THYMUS	Malignant Lymphoma	0	0	0	1	0.2260	.	.	0.4521
	Malignant Schwannoma	0	1	0	0	0.5137	0.4366	.	.
	Thymoma	3	3	3	0	0.9464	0.5340	0.3615	0.8411
THYROID	C-Cell Adenoma	3	1	3	1	0.6871	0.5907	0.3615	0.6165
	C-Cell Carcinoma	0	0	2	0	0.4835	.	0.2593	.
	Follicular Cell Aden	0	1	1	1	0.2687	0.4366	0.5122	0.4521
	Follicular Cell Carc	0	1	0	0	0.5137	0.4366	.	.
TONGUE	Squamous Cell Papill	0	0	1	0	0.5137	.	0.5122	.

Table 3B_VC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using the Vehicle Control
Female Rats

Organ Name	Tumor Name	0 mg Veh Cont N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dose Resp	P_Value NC vs. L	P_Value NC vs. M	P_Value NC vs. H
TRACHEA	Malignant Lymphoma	0	0	0	1	0.2260	.	.	0.4521
URINARY BLADDER	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
UTERUS	Endometrial Adenocar	1	4	3	0	0.8851	0.1097	0.3265	0.4521
	Endometrial Stromal	0	0	1	0	0.5170	.	0.5181	.
		5	4	6	5	0.3683	0.6162	0.5352	0.5023
	Malignant Schwannoma	0	1	0	0	0.5137	0.4366	.	.
	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
VAGINA	Malignant Schwannoma	0	1	0	0	0.5137	0.4366	.	.
ZYMBAL'S GLAND	Carcinoma	0	0	0	1	0.2313	.	.	0.4595

Table 3B_WC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using the Water Control
Female Rats

Organ Name	Tumor Name	0 mg Wat. Cont. N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ADIPOSE TISSUE	Lipoma	3	1	0	0	0.9743	0.5603	0.8751	0.8245
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
ADRENAL	Cortical Adenoma	3	0	2	0	0.8687	0.8096	0.4887	0.8245
	Malignant Lymphoma	1	1	0	1	0.4904	0.6681	0.4884	0.6767
	Pheochromocytoma	1	0	0	0	0.7114	0.4189	0.4941	0.4342
AORTA (THORACIC	Malignant Schwannoma	0	1	0	0	0.5034	0.4189	.	.
BONE, STERNUM	Malignant Lymphoma	0	1	0	1	0.2658	0.4267	.	0.4342
CERVIX	Adenomatous Polyp	0	1	0	0	0.5034	0.4189	.	.
	Endometrial Stromal	0	1	0	0	0.5034	0.4189	.	.
		1	0	1	0	0.5863	0.4133	0.7412	0.4286
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
CLITORAL GLAND	Carcinoma	1	1	0	0	0.7972	0.6657	0.4941	0.4342
	Squamous Cell Carcin	1	2	1	1	0.5145	0.3778	0.7471	0.6832
DIAPHRAGM	Malignant Lymphoma	0	1	0	0	0.5000	0.4267	.	.
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
EAR	Neural Crest Tumor	1	0	0	0	0.7114	0.4189	0.4941	0.4342
HARDERIAN GLAND	Malignant Lymphoma	0	0	0	1	0.2215	.	.	0.4342
HEART	Malignant Schwannoma	0	1	0	0	0.5034	0.4189	.	.
INTESTINE-LARGE	Leiomyoma	0	0	0	1	0.2215	.	.	0.4342
	Malignant Lymphoma	1	0	0	0	0.7114	0.4189	0.4941	0.4342
					1	0.3951	0.4189	0.4941	0.6832
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
INTESTINE-SMALL	Malignant Lymphoma	0	0	0	1	0.2215	.	.	0.4342
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
KIDNEY	Liposarcoma	1	0	0	0	0.7114	0.4189	0.4941	0.4342
	Malignant Lymphoma	1	1	0	1	0.4904	0.6681	0.4884	0.6767
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
KNEE JOINT (FEM	Malignant Lymphoma	0	1	0	1	0.2658	0.4267	.	0.4342
LIVER	Hepatocellular Adeno	2	1	1	1	0.5714	0.3778	0.4911	0.4006
	Malignant Lymphoma	1	1	0	1	0.4904	0.6681	0.4884	0.6767
	Malignant Schwannoma	0	1	0	0	0.5034	0.4189	.	.
LUNG W/BRONCHI	Malignant Lymphoma	1	1	0	1	0.4904	0.6681	0.4884	0.6767
LYMPH NODE, MAN	Malignant Lymphoma	1	1	0	1	0.4904	0.6681	0.4884	0.6767
	Malignant Schwannoma	0	1	0	0	0.5034	0.4189	.	.

Table 3B_WC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using the Water Control
Female Rats

Organ Name	Tumor Name	0 mg Wat. Cont. N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
LYMPH NODE, MES	Hemangioma	0	0	0	1	0.2215	.	.	0.4342
	Hemangiosarcoma	0	0	1	0	0.5034	.	0.4941	.
	Lymphangioma	1	0	0	0	0.7114	0.4189	0.4941	0.4342
	Malignant Lymphoma	2	1	0	1	0.6096	0.3810	0.7412	0.3922
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
MAMMARY GLAND	Adenocarcinoma	4	0	0	1	0.7894	0.8927	0.9391	0.7275
	Adenoma	1	0	1	0	0.5912	0.4189	0.7471	0.4342
	Fibroadenoma	6	2	4	1	0.9131	0.7511	0.6156	0.8932
MESENTERY	Lipoma	1	0	1	0	0.5912	0.4189	0.7471	0.4342
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
NOSE	Squamous Cell Papill	0	1	0	0	0.5034	0.4189	.	.
OVARY	Granulosa Cell Tumor	2	1	0	1	0.6182	0.3778	0.7471	0.4006
	Luteoma	0	1	0	0	0.5034	0.4189	.	.
	Malignant Schwannoma	0	1	0	0	0.5034	0.4189	.	.
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
	Sertoli Cell Tumor	2	0	1	0	0.8098	0.6657	0.4911	0.6832
	Thecoma	1	0	0	0	0.7114	0.4189	0.4941	0.4342
	Undifferentiated Gon	1	0	0	1	0.3951	0.4189	0.4941	0.6832
PANCREAS	Islet Cell Adenoma	0	0	1	1	0.1736	.	0.4941	0.4342
	Malignant Lymphoma	1	0	0	0	0.7067	0.4133	0.4884	0.4286
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
PITUITARY	Adenoma, Pars Distal	29	15	17	15	0.9533	0.9251	0.9872	0.9659
	Carcinoma, Pars Dist	0	0	0	1	0.2215	.	.	0.4342
SALIVARY GLAND,	Malignant Schwannoma	0	1	0	0	0.5034	0.4189	.	.
SKIN LESION	Squamous Cell Papill	0	0	0	1	0.2215	.	.	0.4342
SPLEEN	Malignant Lymphoma	0	1	0	1	0.2658	0.4267	.	0.4342
STOMACH	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
SUBCUTANEOUS TI	Fibroma	1	0	0	0	0.7114	0.4189	0.4941	0.4342
	Hemangiosarcoma	0	0	0	1	0.2267	.	.	0.4416
	Lipoma	1	0	0	0	0.7114	0.4189	0.4941	0.4342
	Malignant Schwannoma	1	1	0	0	0.7933	0.6591	0.4884	0.4286
	Trichoepithelioma	0	0	1	0	0.5034	.	0.4941	.
THORACIC CAVITY	Malignant Schwannoma	0	1	0	0	0.5034	0.4189	.	.
THYMUS	Malignant Lymphoma	2	0	0	1	0.4923	0.6591	0.7412	0.3922
	Malignant Schwannoma	0	1	0	0	0.5034	0.4189	.	.
	Thymoma	4	3	3	0	0.9659	0.6283	0.4866	0.9038

Table 3B_WC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using the Water Control
Female Rats

Organ Name	Tumor Name	0 mg Wat. Cont. N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
THYROID	C-Cell Adenoma	5	1	3	1	0.8490	0.8060	0.6302	0.8268
	C-Cell Carcinoma	0	0	2	0	0.4732	.	0.2412	.
	Follicular Cell Aden	2	1	1	1	0.5714	0.3778	0.4911	0.4006
	Follicular Cell Carc	0	1	0	0	0.5034	0.4189	.	.
TONGUE	Squamous Cell Papill	0	0	1	0	0.5034	.	0.4941	.
TRACHEA	Malignant Lymphoma	0	0	0	1	0.2215	.	.	0.4342
URINARY BLADDER	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
UTERUS	Carcinoma, Anaplasti	1	0	0	0	0.7114	0.4189	0.4941	0.4342
	Endometrial Adenocar	4	4	3	0	0.9752	0.4352	0.4736	0.8997
	Endometrial Stromal	0	0	1	0	0.5067	.	0.5000	.
		4	4	6	5	0.2548	0.4489	0.3539	0.3331
	Malignant Schwannoma	0	1	0	0	0.5034	0.4189	.	.
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
VAGINA	Malignant Schwannoma	0	1	0	0	0.5034	0.4189	.	.
ZYMBAL'S GLAND	Carcinoma	0	0	0	1	0.2267	.	.	0.4416

Table 4A: Intercurrent Mortality Rate in Male Mice

	Vehicle Control		Water Control		32 mg|kg|day		64 mg|kg|day		96 mg|kg|day		Positive Control	
	N=27		N=24		N=28		N=25		N=25		N=28	
	No. of		No. of		No. of		No. of		No. of		No. of	
Week	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %
0 - 47	2	7.41	4	16.67	2	7.14	5	20.00	1	4.00	3	10.71
Ter. Sac.	25	92.59	20	83.33	26	92.86	20	80.00	24	96.00	25	89.29

Table 4B: Intercurrent Mortality Rate Female Mice

	Vehicle Control		Water Control		32 mg|kg|day		64 mg|kg|day		96 mg|kg|day		Positive Control	
	N=26		N=24		N=24		N=25		N=26		N=28	
	No. of		No. of		No. of		No. of		No. of		No. of	
Week	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %
0 - 47	1	3.85	1	4.17	1	4.17	3	12.00	2	7.69	2	7.14
Ter. Sac.	25	96.15	23	95.83	23	95.83	22	88.00	24	92.31	26	92.86

Table 5A: Intercurrent Mortality Comparison Male Mice

Test	Statistic	P_Value using Vehicle control	P_Value using water control
Dose-Response	Likelihood Ratio	0.9721	0.7613
Homogeneity	Log-Rank	0.2694	0.2477

Table 5B: Intercurrent Mortality Comparison Female Mice

Test	Statistic	P_Value using Vehicle control	P_Value using water control
Dose-Response	Likelihood Ratio	0.8193	0.8293
Homogeneity	Log-Rank	0.6518	0.6723

Table 6A_VC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Mice Using Vehicle Control

Organ Name	Tumor Name	Vehicle Control N=27	32 mg Low N=28	64 mg Med N=25	96 mg High N=25	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Harderian Gl	B-ADENOMA	1	0	0	0	0.7426	0.5094	0.4694	0.4902
Liver	B-HEPATOCELLULAR ADE	1	1	2	1	0.4707	0.2547	0.4532	0.7451
Lung	BRONCHIOLR_ALVEOLAR_	1	1	2	3	0.1324	0.2547	0.4532	0.2899
Lungs	B-BRONCHIOLO/ALVEOLA	1	1	2	1	0.4707	0.2547	0.4532	0.7451
	M-BRONCHIOLO/ALVEOLA	0	0	0	2	0.0594	.	.	0.2353
	BRONCHIOLO/ALVEOLA ADENOMA+CARCINOMA	1	1	2	3	0.1324	0.2547	0.4532	0.2899
Lymph Node othe	M-HEMANGIOSARCOMA	0	1	0	0	0.4752	0.5094	.	.
Lymph/Retic Sys	M-GRANULOCYTIC LEUKE	0	0	1	0	0.4752	.	0.4694	.
	M-MALIGNANT LYMPHOMA	0	0	1	0	0.4752	.	0.4694	.
Skin	B-SQUAMOUS CELL PAPI	0	0	1	0	0.4752	.	0.4694	.

Table 6A_WC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Mice Using Water Control

Organ Name	Tumor Name	Water Control N=24	32 mg Low N=28	64 mg Med N=25	96 mg High N=25	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Liver	B-HEPATOCELLULAR ADE	3	1	2	1	0.7764	0.7692	0.5218	0.7431
Lungs	B-BRONCHIOLO/ALVEOLA	1	1	2	1	0.5204	0.2985	0.5171	0.2775
	M-BRONCHIOLO/ALVEOLA	0	0	0	2	0.0644	.	.	0.2775
	BRONCHIOLO/ALVEOLA ADENOMA+CARCINOMA	1	1	2	3	0.1621	0.2985	0.5171	0.3546
Lymph Node othe	M-HEMANGIOSARCOMA	0	1	0	0	0.4948	0.5510	.	.
Lymph/Retic Sys	M-GRANULOCYTIC LEUKE	0	0	1	0	0.4948	.	0.5111	.
	M-MALIGNANT LYMPHOMA	0	0	1	0	0.4948	.	0.5111	.
Skin	B-SQUAMOUS CELL PAPI	0	0	1	0	0.4948	.	0.5111	.

Table 6A_VWP: Tumor Rates and P-Values for the Pairwise Comparisons
of Vehicle Control, Water Control and Positive Control
Male Mice

Organ Name	Tumor Name	Water Cont	Veh. Cont	Pos. Cont	P_Value WC vs. VC	P_Value WC vs. PC	P_Value VC vs. PC
Harderian Gl	B-ADENOMA	0	1	1	0.5417	0.5510	0.2547
Liver	B-HEPATOCELLULAR ADE	3	1	24	0.7566	<0.001*	<0.001*
	M-HEPATOCELLULAR CAR	0	0	17	.	<0.001*	<0.001*
Lungs	B-BRONCHIOLO/ALVEOLA	1	1	14	0.2881	<0.001*	<0.001*
	M-BRONCHIOLO/ALVEOLA	0	0	1	.	0.5510	0.5094

Table 6B_VC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice Using Vehicle Control

Organ Name	Tumor Name	Vehicle Control N=26	32 mg Low N=24	64 mg Med N=25	96 mg High N=26	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Harderian Gl	B-ADENOMA	1	0	0	0	0.7396	0.4898	0.4792	0.4898
Liver	B-HEPATOCELLULAR ADE	0	0	1	0	0.4896	.	0.4792	.
Lungs	B-BRONCHIOLO/ALVEOLA	0	0	1	1	0.1816	.	0.4792	0.4898
Lymph/Retic Sys	M-MALIGNANT LYMPHOMA	1	0	0	0	0.7320	0.4800	0.4694	0.4800
Mammary protoco	B-BENIGN MAST CELL T	0	0	0	1	0.2500	.	.	0.4898
Uterus w/ Cervi	B-HEMANGIOMA	0	0	1	0	0.4896	.	0.4792	.

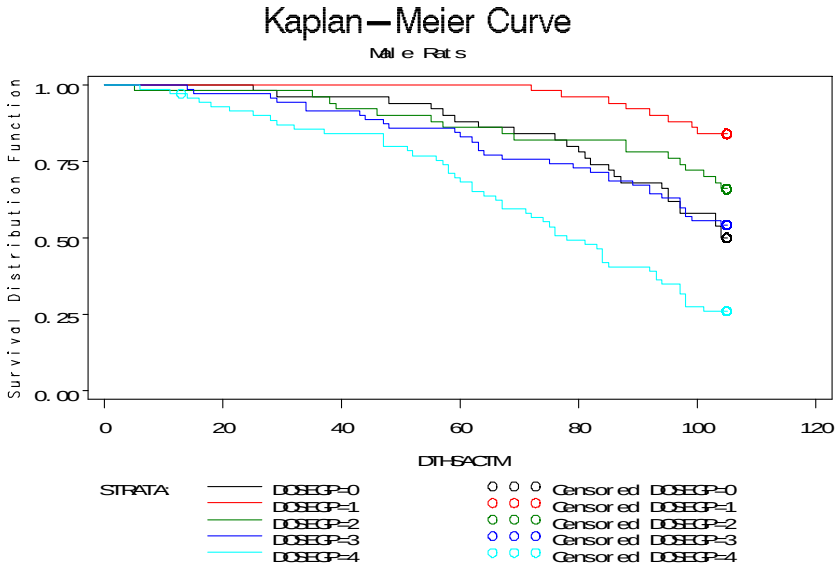
Table 6B_WC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice Using Water Control

Organ Name	Tumor Name	Water Control N=24	32 mg Low N=24	64 mg Med N=25	96 mg High N=26	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Liver	B-HEPATOCELLULAR ADE	0	0	1	0	0.4947	.	0.4894	.
Lungs	B-BRONCHIOLO/ALVEOLA	1	0	1	1	0.4960	0.5000	0.7447	0.7553
Mammary protoco	B-BENIGN MAST CELL T	0	0	0	1	0.2526	.	.	0.5000
Uterus w/ Cervi	B-HEMANGIOMA	0	0	1	0	0.4947	.	0.4894	.

Table 6B_VWP: Tumor Rates and P-Values for the Pairwise Comparisons of Vehicle Control, Water Control and Positive Control
Female Mice

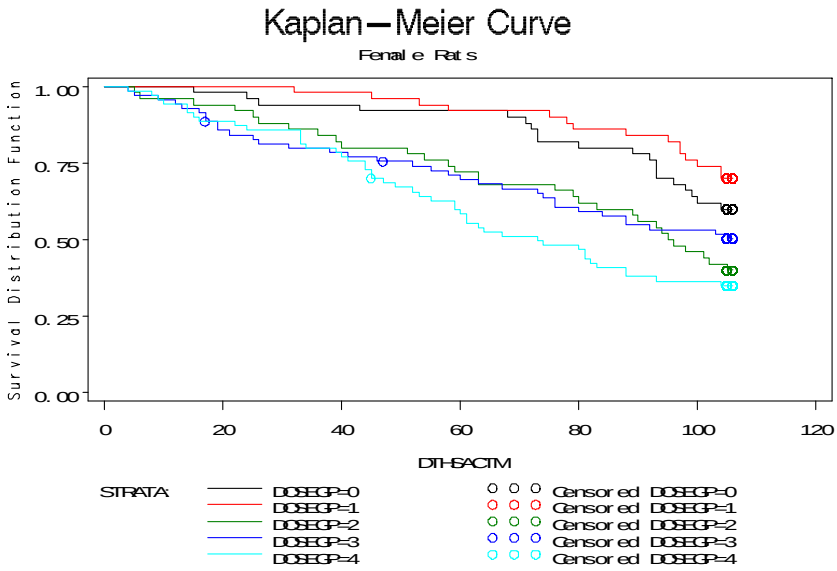
Organ Name	Tumor Name	Water Cont	Veh. Cont	Pos. Cont	P_Value WC vs. VC	P_Value WC vs. PC	P_Value VC vs. PC
Harderian Gl	B-ADENOMA	0	1	0	0.5102	.	0.5192
Liver	B-HEPATOCELLULAR ADE	0	0	12	.	<0.001*	<0.001*
	M-HEPATOCELLULAR CAR	0	0	1	.	0.5294	0.5192
Lungs	B-BRONCHIOLO/ALVEOLA	1	0	11	0.5102	0.0026*	<0.001*
	M-BRONCHIOLO/ALVEOLA	0	0	2	.	0.2753	0.2647
Lymph/Retic Sys	M-MALIGNANT LYMPHOMA	0	1	1	0.5200	0.5294	0.2547

Figure 1A: Kaplan-Meier Survival Functions for Male Rats
Male Rats



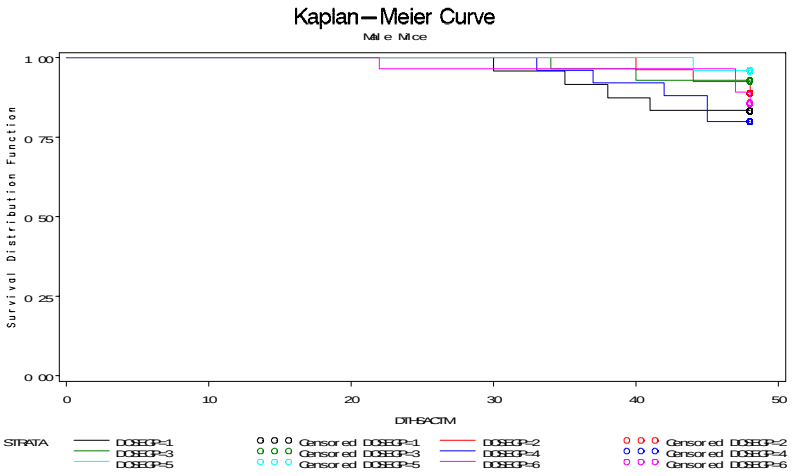
X-Axis: Weeks, Y-Axis: Survival rates

Figure 1B: Kaplan-Meier Survival Functions for Female Rats
Female Rats



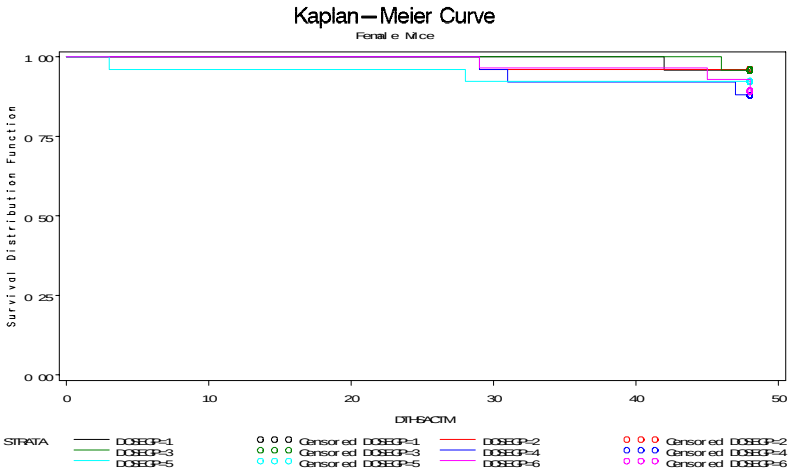
X-Axis: Weeks, Y-Axis: Survival rates

Figure 2A: Kaplan-Meier Survival Functions for Male Mice
Male Mice



X-Axis: Weeks, Y-Axis: Survival rates

Figure 2B: Kaplan-Meier Survival Functions for Female Mice
Female Mice



X-Axis: Weeks, Y-Axis: Survival rates

7. References

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22345	ORIG-1	VALEANT PHARMACEUTICALS NORTH AMERICA	RETIGABINE

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ATIAR MOHAMMAD A RAHMAN
07/23/2010

KARL K LIN
07/27/2010
Concur with review

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA 22-345
Drug Name:	POTIGA
Indication(s):	Partial seizures in adults
Applicant:	Valeant Pharmaceuticals North America
Date of Document:	October 30, 2009
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 1 (HFD-710)
Statistical Reviewer:	Ohidul Siddiqui, Ph.D
Medical Reviewer:	Steven Dinsmore, MD
Concurring Reviewers:	Kun Jin, Ph.D; James Hung, Ph.D
Medical Division:	HFD-120
Clinical Team:	Norman Hershkowitz MD, PhD
Project Manager:	Stephanie Keefe

Keywords: *NDA review, endpoint analysis/LOCF, multi-center*

Table of Contents

1. EXECUTIVE SUMMARY

The sponsor submitted findings of three adequate and well-controlled studies to demonstrate effectiveness of retigabine in treating patients with partial-onset epilepsy. Among the three studies, there are two Phase III studies (Studies 301 and 302) and one Phase IIB study (Study 205). All the three studies were international, multicenter, parallel-group randomized, and double-blind placebo-controlled studies.

1.1. Conclusions and Recommendations

With respect to the primary endpoint- percent change from baseline in 28-day total partial seizure frequency during the double-blind phase in the ITT double-blind population and also in the ITT Maintenance phase, retigabine demonstrated its significant efficacy in each of the three studies. In Study 205, retigabine at 900 mg/day and 1200 mg/day were statistically superior to placebo. The statistical significances of retigabine at 900 mg/day and 1200 mg/day were confirmed in Studies 301 and 302.

Although Retigabine 600 mg/day had a numerically greater median percent change from baseline than the change for placebo, it was not statistically significant from placebo in Study 205. However, retigabine 600 mg/day was statistically superior to placebo in Study 302.

There was also an evidence of increasing efficacy with retigabine doses in the cumulative distribution profile for percent change in total partial seizure frequency across the double-blind phase.

Retigabine at 600 mg/day and 900 mg/day (in Study 302) and 1200 mg/day (in Studies 205 and 301) also demonstrated its significant effects with respect to responder rate (the proportion of patients with a ≥50% reduction in 28-day total partial seizure frequency in the ITT maintenance population) during the maintenance phase.

The dropout rates during the double-blind phase in the three studies were relatively high (in a range from 17% to 42%). The sensitivity analyses indicate that the dropout rates have no impact on the efficacy of the doses. That is, the efficacy of each dose remained significant in the sensitivity analyses.

1.2. Brief Overview of Reviewed Clinical Studies

Pivotal Studies

Study 205 was a phase IIb, randomized, double-blind, placebo-controlled, multicenter, dose-ranging study of retigabine (600, 900 and 1200 mg/day) in patients (age 16 to 70 years) with partial-onset seizures. The study consisted of four phases: an 8-week prospective Baseline Phase during which patients were evaluated for seizure frequency, an 8-week Titration Phase to the final targeted randomized dose and an 8-week Maintenance Phase during which patients received

a fixed dose regimen. After completing the double-blind phase, patients could enroll in a long term, open-label, extension study, after a 5-week interim phase of dose adjustment.

Studies 301 and 302 were Phase III studies for assessing the efficacy and safety of retigabine in patients (aged 18 to 75 years) with refractory partial epilepsy. Both were randomized, double blind, placebo-controlled, multi-center, parallel-group studies with similar inclusion and exclusion criteria. Study 301 included assessment of retigabine (1200 mg/day; 400 mg TID) compared with placebo. Study 302 included assessment of retigabine 900 mg/day (300 mg TID) and retigabine 600 mg/day (200 mg TID) compared with placebo. There was an 8-week prospective Baseline Phase and patients were evaluated for seizure frequency, followed by a Titration Phase during which the retigabine dose was increased by 150 mg/week (50 mg TID) [up to 4 weeks in Study 302 and 6 weeks in Study 301]. At the end of the titration period, patients were maintained on a fixed dose for a 12-week Maintenance Period (Figures 2 and 3). In Study 301, patients had a single opportunity to down titrate to 1050 mg/day at the end of Week 7, if they were unable to tolerate the targeted retigabine dose (1200 mg/day). Patients who down-titrated were then to continue at 1050 mg/day for the remainder of the maintenance period. Efficacy data were reported based on the assigned randomized dose and not the actual dose received.

In each of the three studies, the primary endpoint was the percent change in the 28-day total partial seizure frequency occurring between baseline and the double-blind phase ((including all titration and maintenance phase data). The primary analysis was a non-parametric stratified rank analysis of covariance (ANCOVA) to compare the percent change in total partial seizure frequency of the retigabine and placebo treatment groups. Each of the studies demonstrated significant efficacy of retigabine in treating patients with partial-onset epilepsy.

1.3 Statistical Issues and Findings

There was no statistical issue in each of the three studies.

2. INTRODUCTION

2.1. Overview

In this submission, effectiveness of retigabine is claimed based on three adequate and well-controlled studies (N=1244) in patients with partial-onset epilepsy. Among the three studies, there are two Phase III studies (Studies 301 and 302) and one Phase IIB study (Study 205). All the three studies were international, multicenter, parallel-group randomized, double-blind, placebo-controlled studies.

Table 1 lists an overview of the submitted studies. The phase IIb study 205 was designed to assess the efficacy and safety of retigabine 600 mg/day (200 mg three times daily [TID]), 900 mg/day (300 mg TID), and 1200 mg/day (400 mg TID). The study also provides the primary dose-response data. The efficacy of 600 mg/day to 1200 mg/day was assessed in Phase III studies 301 (1200 mg/day) and 302 (600 mg/day and 900 mg/day). In the three studies, patients with partial onset seizures (simple partial seizures and/or complex partial seizures with or without secondary generalization) were recruited.

Table 1: Overview of the three studies.

	Study 205	**Study 301**	**Study 302**
Phase/Sponsor	IIb/Wyeth	III/Valeant	III/Valeant
Treatment Group	600, 900, 1200 mg/day, PBO	1200 mg/day, PBO	600, 900 mg/day, PBO
Dosage Forms Used	50 mg, 100 mg or 200 mg IR capsules (note: 600 mg dose = 2X100 mg capsule TID; 900 mg dose = 3X100 mg capsule TID; 1200 mg dose = 1X 200 mg and 2X 100 mg capsule TID)	50 mg, 100 mg, 300 mg IR tablets (note: 1200 mg dose = 1X 300 mg tablet and 2X 50 mg tablets TID)	50 mg and 100 mg IR tablets (note: 300 mg dose = 3X 100 mg tablets TID)
Duration of Double-blind	16 weeks	18 weeks	16 weeks
Duration of Titration	8 weeks	6 weeks	4 weeks
Duration of Maintenance	8 weeks	12 weeks	12 weeks
Countries	Australia, Belgium, Croatia, Czech Republic, Finland, France, Germany, Israel, Italy, Netherlands, New Zealand, Norway, Poland Portugal ,Slovakia, Spain, Sweden, UK, and US	Argentina, Brazil Canada, Mexico, and US	Australia, Belgium, France, Germany, Hungary, Israel, Poland, Russia, S Africa, Spain, UK Ukraine, and US

Source: Individual study reports

2.2. Data Sources

SAS data sets of the pivotal studies and study reports are available at \\Cdsesub1\evsprod\NDA022345\0000\.

3. STATISTICAL EVALUATION

3.1. Study reviewed

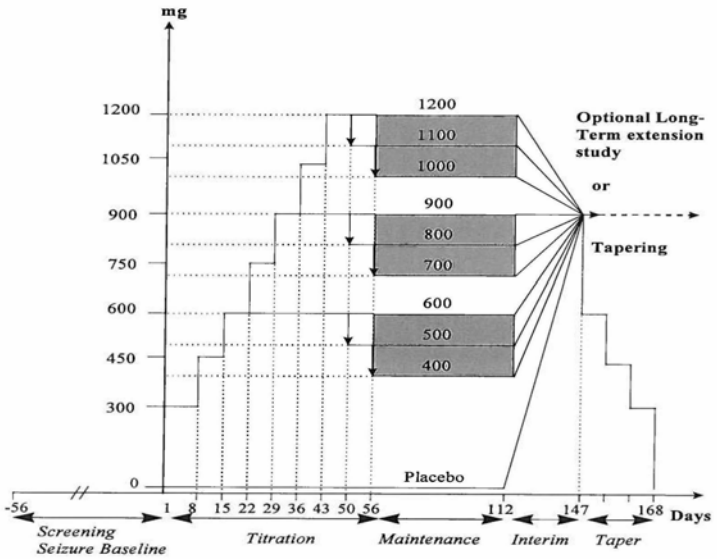
In this statistical review, the efficacy findings of the three studies (Studies 205, 301 and 302) are reviewed as follows.

3.1.1. Study 205

Study 205 was a phase IIb, randomized, double-blind, placebo-controlled, multicenter, dose-ranging study of retigabine (600, 900 and 1200 mg/day) in patients (age 16 to 70 years) with partial-onset seizures. The study consisted of four phases: an 8-week prospective Baseline Phase during which patients were evaluated for seizure frequency, an 8-week Titration Phase to the final targeted randomized dose and an 8-week Maintenance Phase during which patients received a fixed dose regimen. Figure 1 lists the design of the study. After completing the double-blind phase, patients could enroll in a long term, open-label, extension study, after a 5-week interim phase of dose adjustment.

The objectives of the study were to evaluate the efficacy and safety of retigabine 200 mg TID, 300 mg TID and 400 mg TID compared with placebo, when administered as add-on therapy in patients with partial epilepsy receiving one or two pre-specified AEDs.

Figure 1: Schematic design diagram of the study 205

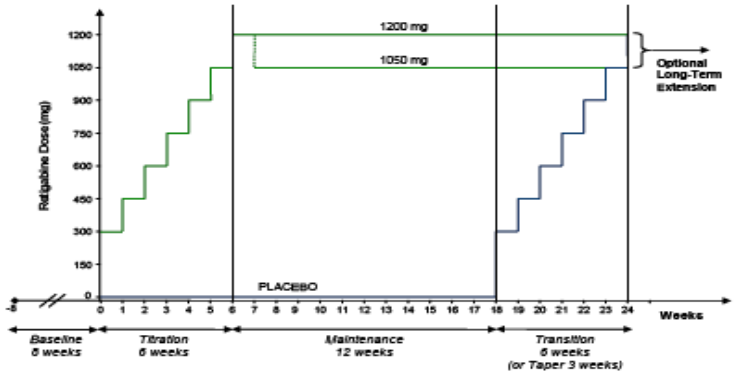


Source: Study report

3.1.2. Studies 301 and 302

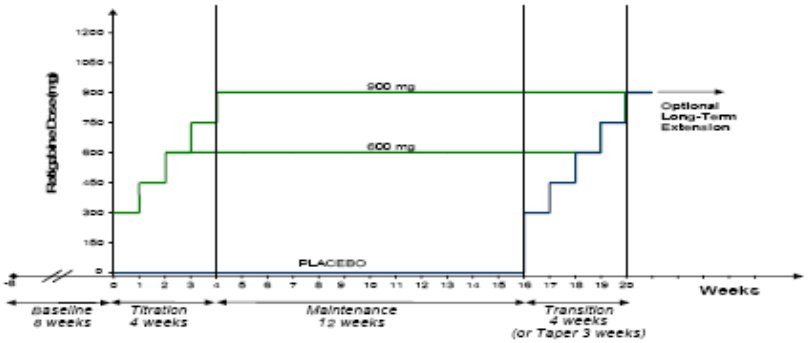
Studies 301 and 302 were Phase III studies for assessing the efficacy and safety of retigabine in patients (aged 18 to 75 years) with refractory partial epilepsy. Both were randomized, double blind, placebo-controlled, multi-center, parallel-group studies with similar inclusion and exclusion criteria. Study 301 included assessment of retigabine (1200 mg/day; 400 mg TID) compared with placebo. Study 302 included assessment of retigabine 900 mg/day (300 mg TID) and retigabine 600 mg/day (200 mg TID) compared with placebo. There was an 8-week prospective Baseline Phase during which patients were evaluated for seizure frequency, followed by a Titration Phase during which the retigabine dose was increased by 150 mg/week (50 mg TID) [up to 4 weeks in Study 302 and 6 weeks in Study 301]. At the end of the titration period, patients were maintained on a fixed dose for a 12-week Maintenance Period (Figures 2 and 3). In Study 301, patients had a single opportunity to down titrate to 1050 mg/day at the end of Week 7, if they were unable to tolerate the targeted retigabine dose (1200 mg/day). Patients who down-titrated were then to continue at 1050 mg/day for the remainder of the maintenance period. Efficacy data were reported based on the assigned randomized dose and not the actual dose received.

Figure 2. Study Design- Study 301



Source: Study report

Figure 3. Study Design- Study 302



Source: Study report

Primary and secondary efficacy variables in Studies (205, 301, 302**)**

In each of the three studies, the primary endpoint was the percent change in the 28-day total partial seizure frequency occurring between baseline and the double-blind phase (including all titration and maintenance phase data).

Secondary efficacy variables were (i) the distribution of change in seizure frequency from baseline by quartiles, (ii) the number of patients who achieve total freedom from seizures, (iii) time without seizures, (iv) potential exacerbation of pre-existing seizures or the development of new seizure types, (v) median percent change in 28-day total seizures in the maintenance phase, and (vi) responder rate in the double-blind phase.

Analysis Population and Primary Statistical Methods

The primary efficacy analysis population consisted of the patients who received at least one dose of study drug, had a baseline seizure evaluation, and at least one seizure evaluation on-therapy.

In the study 205, a rank analysis of covariance (ANCOVA) with the rank of the percentage change in monthly total partial seizure rate as a dependent measure and the rank of baseline monthly seizure rate as a covariate and treatment and center as factors in the model. The dose-response was studied by using appropriate contrasts in the ANCOVA according to a closed test procedure.

In studies 301 and 302, the primary analysis was a non-parametric stratified rank analysis of covariance (ANCOVA) to compare the percent change in total partial seizure frequency of the retigabine and placebo treatment groups. In both studies, the analysis was stratified by geographic region [Canada / United States versus Mexico / South America in study 301, and Central/Eastern Europe versus rest of the world in study 302] and baseline seizure frequency category ($8\leq$, >8] with primary ranks of percent change in seizure frequency for all patients as the response within each stratum and the standardized rank of continuous baseline seizure rate nested within the strata as a covariate. The standardized rank is the rank (regardless of treatment) for a patient within a stratum divided by the number of patients within that stratum, plus 1.

Additional analyses of percent change in total partial seizure frequency was stratified by geographic region only, and then stratified by baseline seizure rate category only. Responder rates for the retigabine group versus the placebo group were compared using logistic regression analysis / Fisher's Exact test.

Dealing with Missing Data in Studies 205, 301 and 302

In the Studies 205, 301 and 302, the rates of 28-day total partial seizure frequency in the double blind phase or maintenance phase were calculated based on the number of total partial seizures reported during that phase. For patients who discontinued treatment prematurely, the number of seizures reported up to the treatment discontinuation before entering the taper phase was used to calculate the 28-day seizure frequency. Patients who did not have any post baseline seizure data

were excluded from the primary analysis of percent change in 28-day total partial seizure frequency.

3.1.3 Sponsor's Findings:

Patient disposition and demographics

Table 2 lists the patient disposition of each study. Withdrawals for any reason were 15% to 22% in the placebo groups, 25% to 28% in the retigabine 600 mg/day groups, 32% to 34% in the 900 mg/day groups, and 37% to 43% in the 1200 mg/day groups. Withdrawals due to adverse events were 8% to 13% in the placebo groups, 14% to 21% in the retigabine 600 mg/day groups, 22% to 26% in the 900 mg/day groups, and 27% to 31% in the 1200 mg/day groups. Withdrawal due to lack of efficacy was not common (≤4% of patients in any treatment group) and there was no clear dose relationship.

Table 2. Patient Disposition during the Double-Blind Phase (Studies 205, 301 and 302)

	Number (%) of Patients								
	Study 205				**Study 301**		**Study 302**		
	Plb	**RTG 600 mg/day**	**RTG 900 mg/day**	**RTG 1200 mg/day**	**Plb**	**RTG 1200 mg/day**	**Plb**	**RTG 600 mg/day**	**RTG 900 mg/day**
Population									
Randomized	97	101	95	106	152	154	179	181	179
ITT	96	99	95	106	152	153	179	181	178
Completed	75 (77.3)	75 (74.3)	67 (70.5)	62 (58.5)	127 (83.6)	97 (63.0)	153 (85.5)	135 (74.6)	121 (67.6)
Discontinued	21 (21.9)	28 (28.0)	32 (33.7)	45 (42.5)	26 (17.1)	56 (36.6)	27 (15.1)	46 (25.4)	56 (31.5)
Reason for Discontinuation									
Adverse Event	12 (12.5)	21 (21.0)	21 (22.1)	33 (31.1)	13 (8.6)	41 (26.8)	14 (7.8)	26 (14.4)	46 (25.8)
Unsatisfactory response-efficacy	4 (4.2)	1 (1.0)	4 (4.2)	1 (0.9)	2 (1.3)	4 (2.6)	5 (2.8)	0	0
Lost to follow-up	0	0	1 (1.1)	0	2 (1.3)	1 (0.7)	2 (1.1)	4 (2.2)	1 (0.6)
Protocol violation	3 (3.1)	3 (3.0)	0	4 (3.9)	4 (2.6)	4 (2.6)	2 (1.1)	6 (3.3)	3 (1.7)
Unrelated to study	1 (1.0)	2 (2.0)	4 (4.2)	4 (3.9)	1 (0.7)	0	1 (0.6)	5 (2.8)	3 (1.7)
Other event	1 (1.0)	1 (1.0)	2 (2.1)	3 (2.8)	4 (2.6)	6 (3.9)	3 (1.7)	5 (2.8)	3 (1.7)

Source: Study Reports

Demographic and Baseline Characteristics

Table 3 lists the demographic characteristics of the randomized patients. There was no difference among treatment groups with respect to age or sex within each study. The majority of patients across all three studies were White/Caucasian. Study 301 included a greater percentage of Hispanic, Black and Other race patients than Studies 205 and 302. Median baseline seizure frequency ranged from 8 to 10 in Study 205, 11 to 12 in Study 301, and 9 to 10 in Study 302. Majority of patients were from non-US geographical regions. The US patients mainly consisted of patients in the retigabine 1200 mg/day group and corresponding placebo group (study 301).

Table 3. Demographic and Baseline Characteristics- Studies 205, 301 and 302

	Study 205				Study 301		Study 302		
	Plb N=96	RTG 600 mg/day N=100	RTG 900 mg/day N=95	RTG 1200 mg/day N=106	Plb N=152	RTG 1200 mg/dayN =153	Plb N=179	RTG 600 mg/day N=181	RTG 900 mg/day N=178
Age, years									
mean	34.5	36.8	37.0	38.3	36.7	37.7	37.7	37.5	37.7
Sex, n (%)									
Female	48 (50)	46 (46)	47 (49)	51 (48)	80 (52.6)	85 (55.6)	90 (50.3)	105 (58.0)	85 (47.8)
Race, n (%)									
Caucasian	89 (93)	98 (98)	92 (97)	103 (97)	78 (51.3)	90 (58.8)	169 (94.4)	173 (95.6)	170 (95.5)
Non-Caucasian	7 (7)	2 (2)	3 (3)	3 (3)	74 (49.7)	63 (41.2)	9 (5.6)	8 (4.4)	8 (4.5)
Baseline Seizure Frequency									
Median	8.5	8.5	7.9	10.4	11.3	12.1	9.3	9.5	10.3
Geographic region (US and Non-US), n (%)									
US	7 (7.3)	8 (8.0)	7 (7.4)	5 (4.7)	71 (46.7)	77 (50.3)	0	3 (1.7)	0
Non-US	89 (92.7)	92 (92.0)	88 (92.6)	101 (95.3)	81 (53.3)	76 (49.7)	179 (100)	178 (98.3)	178 (100)

Source: study reports

Primary efficacy findings

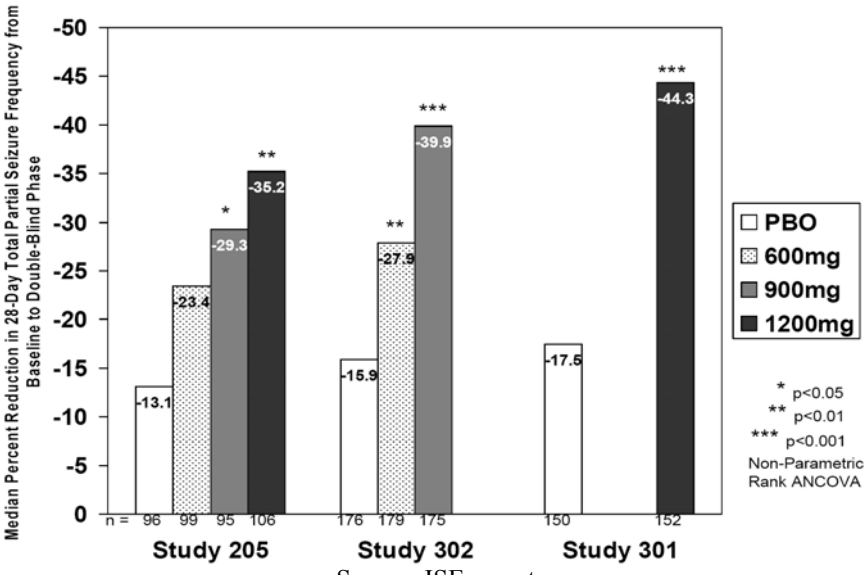
Table 4 and Figures 4-5 list the results of the primary efficacy endpoint- percent change in 28-day total partial seizure frequency from baseline to the double-blind treatment period (titration and maintenance phases combined) are summarized for the ITT double-blind population across Studies 205, 301 and 302. Retigabine 600 mg/day dose was statistically superior to placebo (p-value=0.007) in Study 302. The 900 mg/day dose was statistically superior to placebo (p-value <0.001) in Study 302. The 1200 mg/day dose was statistically superior to placebo (p-value<0.001) in Studies 205 and 301. Across the doses in Study 205, there was a numerical improvement trend (i.e. in Median percent changes) over placebo.

Table 4. Percent Change from Baseline in Total Partial Seizure Frequency ITT Double-Blind Population for Studies 205, 301 and 302

	Placebo	RTG 600 mg/day	RTG 900 mg/day	RTG 1200 mg/day
Study 205				
n	96	99	95	106
Median	-13.1	-23.4	-29.3	-35.2
Range	-100, 533	-100, 1703	-100, 298	-100, 375
P-value	-	0.199	0.043	<0.001
Study 301				
n	150	-	-	151
Median	-17.5	-	-	-44.3
Range	-90, 628	-	-	-100, 302
P-value	-	-	-	<0.001
Study 302				
n	176	179	175	-
Median	-15.9	-27.9	-39.9	-
Range	-100, 1712	-94, 250	-100, 226	-
P-value	-	0.007	<0.001	-

The p-values presented are from non-parametric rank ANCOVA models.
Source: Study reports

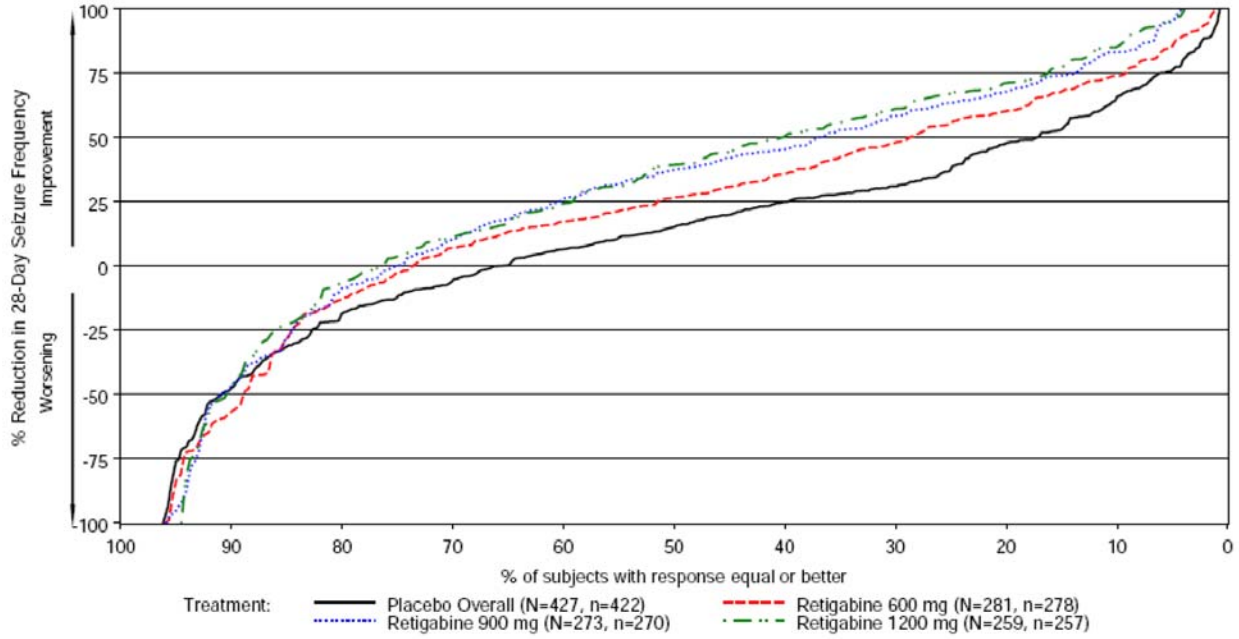
Figure 4. Percent Change from Baseline in Total Partial Seizure Frequency–ITT Double-Blind Population for Studies 205, 301 and 302



Source: ISE report

Figure 5 describes cumulative distribution profiles of the percentage of patients with a response equal to or better than the improvement or worsening of seizure frequency for each dose and placebo. The proportion of patients achieving a particular level of reduction in seizure frequency was consistently higher in the retigabine dose groups compared to placebo.

Figure 5. Distribution Profile of Total Partial Seizure Frequency (Double-Blind Phase) – ITT Double-Blind Population: Studies 205, 301 and 302



Source: ISE report

Sensitivity Analyses Excluding Data from Selected Study Sites in Study 205

The sponsor reported that multiple GCP compliance issues were identified at one site (site #021). In addition, the location/access to the investigator records has yet to be confirmed at another 5 (site #022, #052, #054, #070, #081) out of the 73 sites that participated in Study 205. Excluding these six sites, the sponsor conducted a sensitivity analysis on the primary endpoint (percent change in 28-day total partial seizure frequency from baseline to the double-blind phase) and secondary endpoint of responder rate in the maintenance phase. The magnitude of the treatment effect seen in each sensitivity analysis was similar to the original ITT population analysis.

Secondary Efficacy findings

Percent Change from Baseline in 28-Day Total Partial Seizure Frequency in the ITT Maintenance Population

Table 5 lists the median percent reduction from baseline in the 28-day total partial seizure frequency in the ITT maintenance population for the three studies. RTG 1200 mg/day was significant in Studies 205 and 301 (p-value<0.001), and RTG 600 mg/day and 900 mg/day were significant in Study 302 (p-value≤0.013). In Study 205, there were numerically larger

improvements observed in median percent change in seizure frequency at 600 mg and 900 mg, however, the results were not statistically significant (p-value=0.536 and p-value=0.170, respectively).

Table 5. Percent Change from Baseline in Total Partial Seizure Frequency (ITT-Maintenance Phase)- Studies 205, 301 and 302

	Placebo	RTG 600 mg/day	RTG 900 mg/day	RTG 1200 mg/day
Study 205				
n	78	83	74	68
Median	-22.9	-30.4	-35.8	-43.7
Range	-100, 200	-100, 1653	-100, 292	-100, 503
P-value [a]	-	0.536	0.170	0.008
Study 301				
n	137	-	-	119
Median	-18.9	-	-	-54.5
Range	-100, 1382	-	-	-100, 660
P-value [b]	-	-	-	<0.001
Study 302				
n	164	158	149	-
Median	-17.4	-35.3	-44.3	-
Range	-100, 1589	-100, 253	-100, 714	-
P-value [b]	-	0.002	<0.001	-

The p-values presented are from non-parametric rank ANCOVA models.
Source: ISE report

Responder Rate – ITT Maintenance Population

Table 6 and Figure 6 list the responder rates (defined as those experiencing a ≥50% reduction in 28-day total partial seizure frequency) from baseline to maintenance phase in each treatment group. The findings are consistent with the findings from the percent reduction analysis in the double-blind phase. The responder analysis results demonstrate that retigabine was statistically superior to placebo at all three tested doses in the Phase 3 studies ($p<0.001$ for all comparisons).

Percent Reduction in 28-Day Total Partial Seizure Frequency by Reduction Category - ITT maintenance phase

Table 7 lists the percent reduction in 28-Day Total Partial Seizure Frequency by reduction category in the ITT maintenance phase. The percent of retigabine patients in the ITT maintenance population with ≥75% reduction in seizure rate was greater than placebo, and increased with increasing dose. The proportions of patients with no change or an increase in seizure frequency were larger in the placebo groups than in the retigabine groups, with the exception of the 600 mg/day group in Study 205.

Table 5. Responder Rates – ITT Maintenance Population: Studies 205, 301 and 302

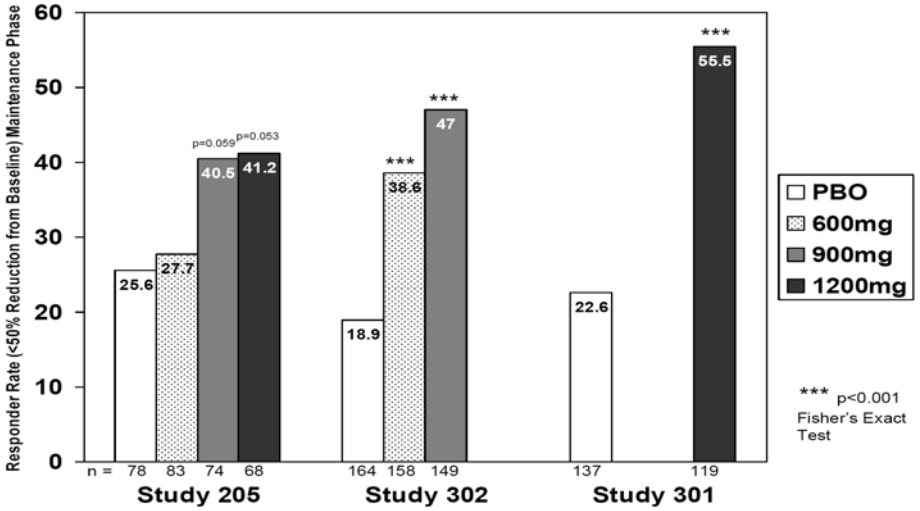
Number (%) of Responders were defined as patients with ≥50% reduction in 28-day total partial seizure frequency				
	Placebo	RTG 600 mg/day	RTG 900 mg/day	RTG 1200 mg/day
Study 205				
n	78	83	74	68
Responders	20 (25.6)	23 (27.7)	30 (40.5)	28 (41.2)
Non-responders	58 (74.4)	60 (72.3)	44 (59.5)	40 (58.8)
P-value [a]	-	0.845	0.057	0.010
Study 301				
n	137	-	-	119
Responders	31 (22.6)	-	-	66 (55.5)
Non-responders	106 (77.4)	-	-	53 (44.5)
P-value [b]	-	-	-	<0.001
Study 302				
n	164	158	149	-
Responders	31 (18.9)	61 (38.6)	70 (47.0)	-
Non-responders	133 (81.1)	97 (61.4)	79 (53.0)	-
P-value [b]	-	<0.001	<0.001	-

[a] The p-values presented are from logistic regression

[b] P-value from Fisher's Exact test.

Source: Study reports/ISE report

Figure 6. Responder Rate– ITT Maintenance Population: Studies 205, 301 and 302



Source: ISE reports

Table 7. Percent Reduction in 28-Day Total Partial Seizure Frequency by Reduction Category (Maintenance Phase) – ITT population: Studies 205, 301 and 302

	Number (%) of Patients			
	Placebo	RTG 600 mg/day	RTG 900 mg/day	RTG 1200 mg/day
Percent Increase/Reduction				
Study 205				
n	78	83	74	68
>75 to 100% decrease	7 (9)	10 (12)	12 (16)	15 (22)
50 to 75% decrease	13 (17)	13 (16)	18 (24)	13 (19)
>0 to <50% decrease	36 (46)	36 (43)	26 (35)	28 (41)
0 to 25% increase	11 (14)	12 (14)	4 (5)	3 (4)
>25% increase	11 (14)	12 (14)	14 (19)	9 (13)
P-value [a]		0.821	0.281	0.043
Study 301				
n	137	-	-	119
>75 to 100% decrease	13 (9)	-	-	37 (31)
50 to 75% decrease	18 (13)	-	-	29 (24)
>0 to <50% decrease	65 (47)	-	-	33 (28)
0 to 25% increase	20 (15)	-	-	4 (3)
>25% increase	21 (15)	-	-	16 (13)
P-value [a]				<0.001
Study 302				
n	164	158	149	-
>75 to 100% decrease	11 (7)	27 (17)	30 (20)	-
50 to 75% decrease	20 (12)	34 (22)	40 (27)	-
>0 to <50% decrease	83 (51)	60 (38)	49 (33)	-
0 to 25% increase	28 (17)	14 (9)	11 (7)	-
>25% increase	22 (13)	23 (15)	19 (13)	-
P-value [a]		0.005	<0.001	-

[a] P-value from CMH test
Source: Study reports

Investigator's judgment on Clinical Global Improvement

Table 8 lists a summary of the investigator's Clinical Global Improvement (CGI) scores at the end of the Maintenance Phase. The investigator's CGI scores indicated that the proportions of patients considered at least minimally improved at the end of the maintenance phase were higher for the retigabine groups than the placebo group within each of the three studies.

Table 8. Clinical Global Improvement at End of Maintenance Phase (ITT Population)- Studies 205, 301 and 302

	Study 205				Study 301		Study 302		
	Plb (N=78)	600mg (N=83)	900mg (N=74)	1200mg (N=68)	PlB (N=152)	1200mg (N=153)	PlB (N=179)	600mg (N=181)	900mg (N=178)
Very much improved	5.3%	9.5%	8.6%	12.5%	7%	14%	7%	8%	7%
Much improved	17.1%	29.7%	42.9%	29.7%	20%	30%	12%	27%	29%
Minimally improved	34.2%	35.1%	22.9%	29.7%	24%	16%	33%	28%	25%
No change	40.8%	23.0%	18.6%	23.4%	41%	28%	44%	31%	27%
Minimally worse	2.6%	2.7%	4.3%	4.7%	5%	5%	2%	3%	5%
Much worse	0	0	2.9%	0	2%	3%	1%	1%	4%
Very much worse	0	0	0	0	2%	3%	1%	0	1%

Source: Study reports

Effects of missing data--Sensitivity Analyses (Maintenance phase) across Studies 205, 301 and 302

The dropout rates during the double-blind phase in the three studies were relatively high (in a range from 17% to 42%). Therefore, two sensitivity analyses of percentage change from baseline in 28-day total partial seizure frequency were conducted across Studies 205, 301 and 302. In the first sensitivity analysis, seizure data from titration phase were used in the analysis for patients who dropped out during titration phase. In the second sensitivity analysis, it was assigned non-responder status for patients who dropped out of the titration phase. Table 9 lists the findings of the sensitivity analyses. The findings are consistent with the efficacy findings of the doses obtained from the protocol specified primary statistical analysis.

FDA Reviewer's Data Analyses and Comments

This reviewer re-analyzed the ITT data sets of the three studies and was able to reproduce the sponsor's reported findings on the primary and secondary efficacy measures. This reviewer did two sensitivity analyses on the primary efficacy measures of the studies. The sensitivity analyses include (i) Rank ANCOVA analysis on the observed total partial seizure frequency at post baseline; and (ii) ANCOVA on the log-transformed total partial seizure frequency at post baseline. Table 10 lists the p-values obtained from the sensitivity analyses. The p-values are similar to the p-values obtained from the protocol specified primary statistical analyses. All of the analyses consistently support the efficacy of retigabine doses. That is, Retigabine 200mg TID (in study 302), 300mg TID (in studies 205 and 302), and 400 mg TID (in study 301) were effective add-on therapy in the treatment of partial seizures in adult patients with refractory epilepsy.

This reviewer also reanalyzed the ITT data excluding the six irregularity sites in study 205, and confirmed the sponsor's findings.

Table 9. Sensitivity Analysis of Responder Rates in the Maintenance Phase – ITT Population for Study 205 and ITT Double-Blind Population for Studies 301 and 302

	Study 205				Study 301		Study 302		
	Plbo N=96	RTG 600 mg /day N=99	RTG 900 mg/day N=95	RTG 1200 mg/day N=106	Placebo N=152	RTG 1200 mg/day N=153	Placebo N=179	RTG 600 mg/day N=181	RTG 900 mg/day N=178
Sensitivity analysis: used titration data to calculate responder status for patients who dropped out of the titration phase									
Responders	24 (25)	27 (27.3)	36 (37.9)	42 (39.6)	32 (21.1)	76 (49.7)	35 (19.6)	63 (34.8)	78 (43.8)
Non-responders	72 (75)	72 (72.7)	59 (62.1)	64 (60.4)	120 (79.0)	77 (50.3)	144 (80.5)	118 (65.2)	100 (56.2)
P-value *	-	0.746	0.062	0.035	-	<0.001	-	0.001	<0.001
Sensitivity analysis: assumed non-responder status for patients who dropped out of the titration phase									
Responders	20 (20.8)	23 (23.2)	30 (31.6)	28 (26.4)	31 (20.4)	66 (43.1)	31 (17.3)	61 (33.7)	70 (39.3)
Non-responders	76 (79.2)	76 (76.8)	65 (68.4)	78 (73.6)	121 (79.6)	87 (56.9)	148 (82.7)	120 (66.3)	108 (60.7)
P-value *	-	0.731	0.101	0.409	-	<0.001	-	<0.001	<0.001

*The p-values are from Fisher's Exact test, Source study reports

Table 10. ANCOVA analyses on the total partial seizure frequency at post baseline-ITT Double-Blind Population for Studies 205, 301 and 302

	Study 205				Study 301		Study 302		
	Plbo N=96	RTG 600 mg /day N=99	RTG 900 mg/day N=95	RTG 1200 mg/day N=106	Plbo N=152	RTG 1200 mg/day N=153	Plbo N=179	RTG 600 mg/day N=181	RTG 900 mg/day N=178
Rank ANCOVA model on 28-day seizure frequency in the original scale									
P-Value	-	0.426	0.105	0.003	-	<0.001	-	0.039	<0.001
ANCOVA model on the log transformed 28-day seizure frequency									
P-Value	-	0.190	0.083	0.004	-	<0.001	-	0.025	<0.001

4. Subgroup Analyses

Subgroup Analyses – studies 205, 301 and 302

Within each study, subgroup analyses on the primary efficacy measure were performed to evaluate the uniformity of treatment effect within patient subgroups (gender, age group, and race). Table 11 lists the median seizure frequency per 28 days by gender and age groups. Within each study, subgroup analyses showed no substantial differences in efficacy of retigabine doses across the subgroups. The FDA reviewer also did the subgroup analyses on the studies. The reviewer's conclusions based on the findings were comparable with the sponsor's conclusions.

Table 11. Subgroup Analysis - Percent Change from Baseline in 28-Day Total Partial Seizure Frequency by Gender, Age Group and Race (Double-Blind Phase) –ITT Double-Blind Population: Studies 205, 301 and 302

	Study 205				**Study 301**		**Study 302**		
	Plb	**RTG 600 mg/day**	**RTG 900 mg/day**	**RTG 1200 mg/day**	**Plb**	**RTG 1200 mg/day**	**Plb**	**RTG 600 mg/day**	**RTG 900 mg/day**
Male									
n	48	54	48	55	71	67	88	75	91
Median	-17.0	-21.1	-31.9	-34.4	-19.8	-25.2	-21.2	-32.4	-34.6
Female									
n	48	45	47	51	79	84	88	104	84
Median	-11.9	-26.9	-26.9	-36.0	-14.8	-51.8	-7.7	-26.3	-44.4
≤44 years									
n	78	78	74	68	110	105	123	128	120
Median	-13.1	-20.7	-24.5	-31.2	-12.5	-39.2	-14.2	-29.1	-38.1
>44 years									
n	18	21	21	38	40	46	53	51	55
Median	-11.5	-35.0	-63.8	-41.9	-27.4	-51.5	-17.4	-26.6	-44.2
White/Caucasian									
n					77	89			
Median					-19.0	-38.5			
Hispanic									
n					47	39			
Median					-21.1	-51.6			
Other									
n					26	23			
Median					-3.4	-28.9			

Source: ISE report. The majority of patients in Studies 205 & 302 were White/Caucasian (>95%).

Table 12 lists subgroup analysis by geographic regions (US/Can=USA and Canada vs. Mex/Sam= Mexico and South America). The difference between treatment groups on the primary efficacy results for the ITT population favored retigabine in both geographic regions although a notably larger decrease in seizure frequency was observed in the Mex/Sam region; the median decrease for the retigabine-treated group was -29% in US/Can and -50% in Mex/Sam regions.

In studies 205 and 302, a few patients were randomized from USA (27 US patients out of 399 randomized patients in study 205; and 3 US patients out of 539 randomized patients in study 302). Therefore, no subgroup analyses were done in these two studies.

Table 12. Analyses of Percent Change in 28-day Total Partial Seizure Frequency From Baseline to Double-blind Phase Stratified by Geographic Region – ITT Population

Study 301	**Placebo (N=152)**		**RTG 400 mg TID (N=153)**	
Geographic region	**US/Can**	**Mex/SAm**	**US/Can**	**Mex/SAm**
Percent change from baseline	n=81	n=69	N=85	n=66
Median	-19.6	-11.7	-28.9	-50.4

Mex/SAm = Mexico and South America, n = number of evaluable patients, RTG = retigabine, US/Can = United State and Canada, Source: Study reports.

5. SUMMARY AND CONCLUSIONS

Collective Evidence of Efficacy in Studies 205, 301 and 302

With respect to the percent change from baseline in 28-day total partial seizure frequency during the double-blind phase in the ITT double-blind population and also in the ITT Maintenance phase, retigabine was able to demonstrate its significant efficacy in each of the three studies. In Study 205, retigabine at 900 mg/day and 1200 mg/day were statistically superior to placebo. The statistical significances of retigabine at 900 mg/day and 1200 mg/day were also confirmed in Studies 301 and 302.

Although Retigabine 600 mg/day had a numerically greater median percent change from baseline than the change for placebo, it was not statistically significant from placebo in Study 205. However, retigabine 600 mg/day was statistically superior to placebo in Study 302.

There was also an evidence of increasing efficacy with retigabine doses in the cumulative distribution profile for percent change in total partial seizure frequency across the double-blind phase.

Retigabine at 600 mg/day 900 mg/day in Study 302, and 1200 mg/day in Studies 205 and 301 also demonstrated its significant effects with respect to responder rate (the proportion of patients with a ≥50% reduction in 28-day total partial seizure frequency in the ITT maintenance population) during the maintenance phase.

The sensitivity analyses indicated that the dropout rates have no impact on the efficacy of the doses. That is, the sensitivity analyses also confirmed the efficacy findings for the doses.

Conclusions and Recommendations

The findings of the three studies confirmed that retigabine (600, 900, and 1200 mg/day) is an effective, add-on therapy in the treatment of partial seizures.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22345	ORIG-1	VALEANT PHARMACEUTICALS NORTH AMERICA	RETIGABINE

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

/s/

OHIDUL I SIDDIQUI
07/06/2010

KUN JIN
07/06/2010
I concur with the review.

HSIEN MING J J HUNG
07/07/2010

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

CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 22-345
Drug Name:	Retigabine (Potiga) Tablets
Indication(s):	104 Week Rat and 52 Week Mouse Carcinogenicity Study
Applicant:	**Sponsor:** Valeant Pharmaceuticals North America One Enterprise, Aliso Viejo, CA 92656
	Test Facility: (b) (4)
Documents Reviewed:	Electronic submission, Dated: Oct. 30, 2009 Electronic data submitted on Nov. 3, 2009
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -6
Statistical Reviewer:	Mohammad Atiar Rahman, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Neurology Products
Reviewing Pharmacologist:	Edward J. Fisher, Ph.D.
Project Manager:	Stephanie Keefe
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in neonatal mice. These studies were intended to assess the carcinogenic potential of Retigabine (Potiga) tablets in rats when administered orally by gavage once daily at appropriate drug levels for about 104 weeks and in mice when administered orally by gavage twice, once on PND 8 (Post-Natal Day 8) and once on PND 15 and followed for 52 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Fisher.

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.

2. Rat Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, a vehicle control group and a water (or negative) control group. The dose levels for treated groups were 5, 20, and 50 mg/kg/day. In this review these dose groups were referred to as the low, medium, and high dose group, respectively. The animals in the vehicle control received the vehicle (USP Propylene glycol) by gavage, while the animals in the water control received purified water by gavage. Two hundred and ninety Crl:WI(Glx/BRL/Han)IGSBR rats of each sex were randomly allocated to treated and control groups. For each sex the group sizes were 70 animals for the high and medium dose groups, and 50 animals for low dose, and the two control groups.

During the administration period all animals were observed daily for clinical signs of effect or toxicity, weekly detailed physical examinations on all rats that included palpation for masses. Morbidity/mortality checks were made twice daily beginning 1 week prior to dose initiation and continuing throughout the dosing period. Body weights were recorded prior to initiation, on Day-1, weekly for 26 weeks and monthly thereafter. A complete histopathological examination was performed on all animals from all groups found dead, killed moribund, or sacrificed during or at the end of the experiment.

2.1. Sponsor's analyses

2.1.1. Survival analysis

The sponsor performed two separate sets of analysis, once using the vehicle control along with the treated groups and then using the water control along with the treated group. Survival function of each treatment group was estimated using the Kaplan-Meier product limit method and was presented graphically. A log-rank dose response relationship test of survival rates was performed using doses as the scores. The log-rank test for survival was also used to make pairwise comparisons of each treated group with the control groups. In addition, the log-rank test was used to compare the two control groups. The dose response relationship test and pairwise comparisons were conducted at the 0.05 significance level.

Sponsor's findings: For male rats the sponsor's analysis showed mortality rates of 50%, 16%, 34%, 46%, and 74% in vehicle control, water control, low, medium, and high dose groups, respectively; and for female rats 40%, 30%, 60%, 50%, and 66% in vehicle control , water control, low, medium, and high dose groups, respectively.

The sponsor's analysis showed that the morality rates in high dose group in both male and female rats were statistically significantly higher compared to both of their respective vehicle and water control groups. The decreased survival rates in the low and medium dose males and females were statistically significant compared to their respective water control group. In males the survival rate in the vehicle control group was statistically significantly decreased compared to in the water control group. A dose related increase in mortality was noted upon comparison of survival rates of control and treated groups in both sexes. From these mortality data, the sponsor commented that the maximum tolerated dose (MTD) was apparently exceeded at 50 mg/kg/day.

2.1.2. Tumor data analysis

Similar to the survival data analysis, the sponsor performed two separate sets of analysis, once using the vehicle control along with the treated groups and then using the water control along with the treated group. The incidences of tumors were analyzed using the Peto's mortality-prevalence method (Peto et al. 1980), without continuity correction, incorporating the context (incidental, fatal, or mortality independent) in which tumors were observed. The following fixed intervals were used for incidental tumor analyses: weeks 0-52, 53-78, 79-92, 93-end of study, scheduled interim sacrifice, and scheduled terminal sacrifice. However, the planned intervals might have been adjusted to account for the distribution of necropsies during the study.

The incidence of each tumor type that occurred in a target organ was analyzed with a 1-sided dose response relationship test using the dose as the score. At the discretion of the study director some combined tumor types were also analyzed. In addition, each active treatment group was compared with each control group with 1-sided pairwise comparisons. Lastly, the vehicle control group was compared to the water control group with a 1-sided pairwise comparison. All comparisons were for increasing onset of tumor incidence. The comparison of control groups was in the direction of increased onset of tumor incidence in the vehicle control group. An exact permutation test was conducted for analysis tumors with low incidence.

To adjust for the multiple testing, following the FDA guidance for carcinogenicity data analysis, statistical significance was determined as follows: dose response relationship tests were conducted at the 0.005 and 0.025 significance levels for common and rare tumors, respectively; pairwise comparisons were conducted with the control group at the 0.01 and 0.05 significance levels for common and rare tumors, respectively. The study director classified tumors as rare or common using a 1% benchmark. The concurrent controls, laboratory historical control database, and animal supplier database were considered in the determination of the historical spontaneous tumor rate.

Sponsor's findings: Sponsor's analyses showed a statistically significant dose response relationship in the incidence of interstitial cell tumor in the testis. The sponsor commented that even though the analysis showed a statistically significant dose response relationship, the actual incidence rates were within the range of historical incidences (b) (4), March, 2003) and the difference was considered to be spurious. When tumor types were combined in the skin or preputial gland in male rats, statistical significance was noted in the 5 mg/kg/day group and/or the 20 mg/kg/day group compared to the water control group, but not compared to the vehicle control group, with the exception of preputial gland carcinoma. The incidence of combined preputial gland neoplasms in the two control groups was also statistically different.

2.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were

provided by the sponsor electronically.

2.2.1. Survival analysis

The survival distributions of animals in all five treatment groups were estimated by the Kaplan-Meier product limit method. The dose response relationship was tested using the likelihood ratio test and homogeneity of survival distributions was tested using the log-rank test. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female rats, respectively.

Reviewer's findings: This reviewer's analysis showed male mortality rates of 50%, 16%, 34%, 46%, and 74% in vehicle control, water control, low, medium, and high dose groups, respectively; and female mortality rates of 40%, 30%, 58%, 50%, and 66% in vehicle control, water control, low, medium, and high dose groups, respectively. This reviewer's analysis showed statistically significant dose response relationship in mortality across treatment groups in both sexes. The pairwise comparisons showed statistically significant increased mortality in high dose group compared to the both controls in both sexes. In both sexes the pairwise comparisons also showed statistically significant increased mortality in low and medium dose groups compared to the water control. Statistically significant increased mortality was also found in vehicle control compared to the water control.

Reviewer's comment: The sponsor's count shows 60% mortality in female low dose group, while this reviewer's count shows 58%. This discrepancy is due to the fact that one animal (#CEL2F366) in low dose group died naturally during the sacrifice week. This reviewer counted it in the terminal sacrifice group, while the sponsor counted it in the naturally death group.

2.2.2. Tumor data analysis

This reviewer analyzed the tumor data twice, once using the vehicle control along with the treated groups and once using the water control along with the treated group.

The tumor data were analyzed for dose response relationships and pairwise comparisons of control with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice with at least one tumor gets a score of s_h =1. An animal that dies at week w_h without a tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}}\right)^k$ <1. The adjusted group size is defined as $N_A = \Sigma s_h$. 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 N_A 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, otherwise N_A is less than N. The adjusted group sizes of all treatment groups are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used.

The tumor rates and the p-values of the tumor types tested for dose response relationship and pairwise comparisons of vehicle control and treated groups are given in Table 3A_VC, and 3B_VC in the appendix for male and female rats, respectively. The tumor rates and the p-values of the tumor types tested for dose response relationship and pairwise comparisons of water control and treated groups are given in Table 3A_WC, and 3B_WC in the appendix for male and female rats, respectively.

Multiple testing adjustment: 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 test levels α=0.005 for common tumors and α=0.025 for rare tumors for a submission with two year study in two species (rat and mouse), and a significance level α=0.01 for common tumors and α=0.05 for rare tumors for a submission with two year study in one species, 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 the suggested the use of test levels α=0.01 for common tumors and α=0.05 for rare tumors, in order to keep the false-positive rate at the nominal level of approximately 10% for both submissions with two or one submission.

The present submission contains a rat and a mouse study. The length of the rat study was two years; however, the length of the mouse study was one year. Hence, the multiple testing adjustment rules described in the FDA guidance may not be applicable for this submission. To be conservative, for dose response relationship tests, this reviewer used a significance level α=0.01 for common tumors and α=0.05 for rare tumors in rat study, and used a significance level α=0.05 for all tumors in mouse study.

Reviewer's findings: Following tumor types showed p-values less than or equal to 0.05 either for dose response relationship and/or pairwise comparisons of control and treated groups.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons

Male Rats Using Vehicle Control

Organ Name	Tumor Name	Veh. Cont. N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dose Response	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
PREPUTIAL GLAND	Carcinoma	0	5	7	3	0.2040	0.0191*	0.0084*	0.0739
	adenoma+carcinoma	0	6	7	3	0.2605	0.0083*	0.0084*	0.0739
	Squamous Cell Papilloma	0	4	2	0	0.8048	0.0434*	0.2631	.
SKIN LESION	Keratoacanthoma	0	4	1	1	0.5638	0.0434*	0.5155	0.4198
TESTIS	Interstitial Cell Tumor	2	0	1	4	0.0249	0.7110	0.5234	0.1989

Male Rats Using Water Control

Organ Name	Tumor Name	Wat. Cont. N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dose Response	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
TESTIS	Interstitial Cell Tumor	1	0	1	4	0.0120	0.5128	0.3200	0.1458

Based on the criterion of adjustment for multiple testing discussed above none of the tested tumor types was considered to have a statistically significant positive dose response relationship. The pairwise comparisons in male rats showed statistically significant increased incidences of preputial gland/carcinoma, preputial gland/combined incidences of adenoma and carcinoma in low and medium dose groups, preputial

gland/squamous cell papilloma in low dose group, and skin lesion/ keratoacanthoma in low dose group, all compared to the water control.

3. Mouse Study

This study was designed to determine the carcinogenic potential of Retigabine using a neonatal mouse model. The test/control article was administered by oral intubation (gavage) once on PND 8 (Post-Natal Day 8) and once on PND 15. Animals were then maintained until necropsy at about 1 year of age.

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one vehicle control group, one water (or negative) control group, and one positive control group. The dose levels for treated groups were 32, 64, and 96 mg/kg. In this review these dose groups were referred to as the low, medium, and high dose group, respectively. The water control received distilled tap water, the vehicle control received the vehicle (Propylene Glycol), and the positive control received 2 mg/kg diethylnitrosamine (DEN).

Initially one hundred and sixty eight (168) CD-1® [Crl:CD-1®(ICR)] Albino Mice of each sex were planned to be randomly allocated to treated and control groups in equal size of 28 animals. The initial number of animals on test were planned to be sufficient to allow for early litter loss and ensure that there were 24 pups/sex/ group at the study termination, which is the current recommended standard (McClain et. al., 2001) for the detection of tumors in the neonatal mouse model. The actual numbers of animals assigned per group and examined microscopically were as follows:

Treatment Group	Vehicle Control	Water Control	Retigabine 32 mg/kg	Retigabine 64 mg/kg	Retigabine 96 mg/kg	Positive Control
Initial total male mouse	28	27	29	28	28	28
Initial total female mouse	28	29	27	28	28	28
*Elective sacrifice/missing male mouse	0	3	0	0	0	0
*Elective sacrifice/missing female mouse	0	5	1	0	0	0
**Microscopic pathology male mouse	27	24	29	25	25	28
**Microscopic pathology female mouse	27	24	24	25	27	28

*** During the dosing phase of the study, in the water-control group, 1 litter (3 males and 5 females) was electively euthanized on PND 17 because of the death of the dam.**

****Microscopic pathology evaluations were conducted on all animals at the scheduled sacrifice interval and on all animals found dead or sacrificed during the Maintenance phase of the study.**

However, the sponsor's submitted data had observation from 27, 24, 28, 25, 25, and 28 males, and 26, 24, 24, 25, 26, and 28 females in vehicle control, water control, low, medium, and high dose groups, respectively. This reviewer's analyses are based on these numbers of animals.

Dams and offspring were observed in their cages twice daily for mortality and signs of severe toxic or pharmacologic effects. Animals in extremely poor health or in a possible moribund condition were identified for further monitoring and possible euthanasia. Offspring were removed from their cages and examined approximately twice weekly from receipt through weaning (PND 22) and then weekly through study termination. Examinations included observations of general condition, skin and fur, eyes, nose, oral cavity, abdomen and external genitalia as well as evaluations of respiration. Body weights of animals were taken on PND 6, 8, 12, 15, 18, 21 and 28, and then weekly until termination.

Necropsy was performed on all treated animals approximately 1 year after dosing. All tissues were evaluated for animals in vehicle control and high dose groups (Groups 2 and 5), while liver, lungs and gross lesions were evaluated for water control group, the low and medium dose groups and the positive control group.

3.1. Sponsor's analyses

3.1.1. Survival analysis

Survival data from the mouse study were analyzed using the same statistical methodologies as were used to analyze the survival data from the rat study. The sponsor performed the following comparisons: 1) Vehicle control vs. Water control, 2) Retigabine-treated groups vs. Vehicle control, and 3) DEN positive control vs. Water control.

Sponsor's findings: Sponsor's analysis showed that the percentage of survivors in male vehicle control, water control, low dose, medium dose, high dose, and positive control groups were 85.7, 83.3, 89.7, 71.4, 85.7, and 85.7, respectively and those in female vehicle control, water control, low dose, medium dose, high dose, and positive control groups were 89.3, 95.8, 88.5, 78.6, 89.3, and 89.3, respectively. The sponsor's described that the mortality in the retigabine treated groups during the dosing phase was generally comparable to that of the vehicle control group. Most of the deaths were clustered after the first dose on PND 8 or the second dose on PND 15. The percentage of animals surviving at the end of the maintenance phase was lower in the 64-mg/kg retigabine group, as compared to the vehicle control. The sponsor commented that in the absence of a dose response relationship, this increased mortality was considered not to be test article related. During the dosing phase of the study, there were no mortalities in the animals treated with the positive control article. During the maintenance phase of the study, mortality in the DEN treated animals was similar to that of the water-control group.

3.1.2. Tumor data analysis

Similar to the survival data analysis, the sponsor performed the following pairwise comparisons for the tumor data were analysis: 1) Vehicle control vs. Water control, 2) Retigabine-treated groups vs. Vehicle control, and 3) DEN positive control vs. Water control. The data were analyzed using the Fisher's Exact test.

Sponsor's findings: The sponsor described that the spontaneous neoplasms occurred mainly in the lungs and liver. The sponsor's analysis showed that there were no statistically significant difference in the incidences of the lung and liver neoplasms (adenomas, carcinomas, and combined adenomas and carcinomas) in the test article treated males or females as compared to the controls. In the male mice at 64 mg/kg, there were statistically significant increases in some metastatic neoplasms. However, the sponsor did not consider them as test article related. The sponsor's analyses showed that the incidences of spontaneously occurring neoplasms in the lung and liver in water and vehicle treated control males were generally comparable and also comparable to the published data of McClain *et al.* (2001).

The animals in active control group showed a high incidence of bronchioloalveolar adenomas/carcinomas and hepatocellular adenomas/carcinomas. The sponsor commented that this validated the ability of this model to detect carcinogenic effects.

3.2. Reviewer's analyses

This reviewer independently performed survival and tumor data analyses from the mouse study. For the mouse data analyses this reviewer used similar methodologies as he used to analyze the data from the rat study. Data used in this reviewer's analyses were provided by the sponsor electronically.

3.2.1. Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for male and female mice, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the appendix for male and female mice, respectively. Results for test of dose response relationship and homogeneity of survivals among treatment groups are given in Tables 5A and 5B in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's analysis showed 92.59, 83.33, 92.86, 80.00, 96.00, and 89.29 percent survivors in male vehicle control, water control, low dose, medium dose, high dose, and positive control groups, respectively and 96.15, 95.83, 95.83, 88.00, 92.31, and 92.86 percent survivors in female vehicle control, water control, low dose, medium dose, high dose, and positive control groups, respectively. This reviewer's analysis showed no statistically significant dose response relationship in mortality across treatment groups in either sex. The pairwise comparisons also did not show statistically significant increased mortality in any of the treated group compared to the either of the controls.

Reviewer's comment: *Clearly, there are various numerical differences in the calculated percentages of survivors found by the sponsor and found by this reviewer. These discrepancies are due to the fact that the sponsor calculated the percentages of survivors based on the initial number of animals excluding the electively euthanized animals and one missing female in the low dose group. As mentioned earlier, during the dosing phase of the study, in the water-control group, 1 litter (3 males and 5 females) was electively euthanized on PND 17 because of the death of the dam. This reviewer's calculations are based on the animals those went under microscopic pathology. Note that the data of only these animals (animals went under microscopic pathology) were included in the data set.*

3.2.2. Tumor data analysis

As mentioned earlier, all tissues and organs from mice in the vehicle control and high dose group were examined microscopically. In addition, the lungs and liver from mice in the water control, low and medium dose groups, and the positive control (DEN) group, as well as tissues and organs with macroscopic abnormalities were microscopically examined. Therefore, this reviewer performed dose response relationship analysis on tumors found in lung and liver only. For tumors found in any other organs only pairwise comparisons of treated groups with the controls were performed.

The tumor rates and the p-values of the tumor types tested for dose response relationship and pairwise comparisons of vehicle control and treated groups are given in Table 6A_VC, and 6B_VC in the appendix for male and female mice, respectively. The tumor rates and the p-values of the tumor types tested for dose response relationship and pairwise comparisons of water control and treated groups are given in Table 6A_WC, and 6B_WC in the appendix for male and female mice, respectively. The pairwise comparisons of vehicle control, water control, and positive control are given in Table 6A_VWP and Table 6B_VWP in the appendix for male and female mice, respectively.

Reviewer's findings: Using 5% level of significance, this reviewer's analysis did not show statistically significant dose response relationship in the incidence of any of the observed tumor types using either the vehicle control or water control along with the retigabine treated groups. This reviewer's analysis also did not show statistically significant increased incidence of any of the observed tumor types in the retigabine treated groups compared to the vehicle control or water control. The positive control showed statistically significant increased incidences of hepatocellular adenoma, hepatocellular carcinoma, and bronchiolar alveolar adenoma compared to either of the controls.

4. Evaluation of validity of the design of the mouse study

As has been noted, the tumor data analyses from both rat and mouse study showed no statistically significant dose-response relationship in any of the tested tumor types. However, before drawing any conclusion regarding the carcinogenic or non-carcinogenic potential of the drug in rats and mice, it is important to look into the following two issues, as have been pointed out in the paper by Haseman (1984).

(i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumors?
(ii) 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 about fifty animals per treatment group. The following are some rules of thumb regarding these two issues as suggested by experts in this field.

Haseman (1985) 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 consider as a sufficient number and adequate exposure. In addition Chu, Cueto and Ward (1981), 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 (1981), the following criteria are mentioned for dose adequacy. A high dose is considered as close to MTD if any of the criteria is met.

(i) "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."

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

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

We will now investigate the validity of the Retigabine rat and mouse carcinogenicity study, in the light of the above guidelines.

4.1. Rat Study

The following is the summary of survival data of rats in the high dose groups:

Percentage of survival in the high dose group at the end of Weeks 52, 78, and 91

	Percentage of survival		
	End of 52 weeks	End of 78 weeks	End of 91 weeks
Male	76%	49%	40%
Female	64%	47%	37%

Based on the survival criterion Haseman proposed, it may be concluded that not enough rats were exposed to the high dose for a sufficient amount of time in either sex, especially in females.

The following table shows the percent difference in mean body weight gain in rats from the concurrent control, defined as

$$\text{Percent difference} = \frac{(\text{Final BW} - \text{Baseline BW})_{\text{Treated}} - (\text{Final BW} - \text{Baseline BW})_{\text{Control}}}{(\text{Final BW} - \text{Baseline BW})_{\text{Control}}} \times 100$$

Percent Difference in Mean body Weight Gain from Vehicle Controls

Male			Female		
5 mg	20 mg	50 mg	5 mg	20 mg	50 mg
4.09	-0.70	-16.97	-2.07	3.19	-8.72

Source: Table 2 of sponsor's submission

Percent Difference in Mean body Weight Gain from Water Controls

Male			Female		
5 mg	20 mg	50 mg	5 mg	20 mg	50 mg
-13.86	-17.83	-31.29	-21.21	-16.98	-26.56

Source: Table 2 of sponsor's submission

Therefore, relative to vehicle control the male and female rats had about 17% and 9% decrement respectively, in body weight gain. Also relative to water control the male and female rats had about 31% and 27% decrement respectively, in body weight gain.

The mortality rates at the end of the experiment were as follows:

Mortality Rates at the End of the Experiment

	Vehic. Cont.	**Water Cont.**	**5 mg**	**20 mg**	**50 mg**
Male	50%	16%	34%	46%	74%
Female	40%	30%	58%	50%	65%

This shows that the morality rate of in the high dose group in males is 24% higher than the vehicle control and

58% higher than the water control. Also the morality rate of in the high dose group in females is 18% higher than the vehicle control and 35% higher than the water control.

Thus, from the body weight gain and mortality data it can be concluded that the used high dose level might have exceeded the MTD in both sexes. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

4.2. Mouse Study

Since the mouse study was only one year long, all the criteria stated above for the determination of sufficient exposure and high enough dose level may not be exactly applicable for this study. Therefore, this reviewer did not perform such analysis on mouse data. The appropriate clinical signs and histopathological toxic effects may be used for this determination.

5. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in neonatal mice. These studies were intended to assess the carcinogenic potential of Retigabine (Potiga) tablets in rats when administered orally by gavage once daily at appropriate drug levels for about 104 weeks and in mice when administered orally by gavage twice, once on PND 8 (Post-Natal Day 8) and once on PND 15 and followed for 52 weeks.

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.

Rat Study: Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, a vehicle control group and a water (or negative) control group. The dose levels for treated groups were 5, 20, and 50 mg/kg/day. In this review these dose groups were referred to as the low, medium, and high dose group, respectively. The animals in the vehicle control received the vehicle (USP Propylene glycol) by gavage, while the animals in the water control received purified water by gavage. Two hundred and ninety Crl:WI(Glx/BRL/Han)IGSBR rats of each sex were randomly allocated to treated and control groups. For each sex the group sizes were 70 animals for the high and medium dose groups, and 50 animals for low dose, and the two control groups.

Tests showed statistically significant dose response relationship in mortality across treatment groups in both sexes. The pairwise comparisons showed statistically significant increased mortality in high dose group compared to the both controls in both sexes. In both sexes the pairwise comparisons also showed statistically significant increased mortality in low and medium dose groups compared to the water control. Statistically significant increased mortality was also found in vehicle control compared to the water control.

Tests did not show statistically significant positive dose response relationship in any of the tested tumor types. The pairwise comparisons in male rats showed statistically significant increased incidences of preputial gland/carcinoma, preputial gland/combined incidences of adenoma and carcinoma in low and medium dose groups, preputial gland/squamous cell papilloma in low dose group, and skin lesion/ keratoacanthoma in low dose group, all compares to the water control.

Mouse Study: This study was designed to determine the carcinogenic potential of Retigabine using a neonatal mouse model. The test/control article was administered by oral intubation (gavage) once on PND 8 and once on PND 15. Animals were then maintained until necropsy at about 1 year of age.
Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one water (or negative) control group, one vehicle control group and one positive control group. The dose levels for treated groups were 32, 64, and 96 mg/kg. In this review these dose groups were referred to as the low, medium, and high dose group, respectively. The water control received distilled tap water, the vehicle control received the vehicle (Propylene Glycol), and the positive control received 2 mg/kg diethylnitrosamine (DEN).

Initially one hundred and sixty eight (168) CD-1® [Crl:CD-1®(ICR)] Albino Mice of each sex were planned to be randomly allocated to treated and control groups in equal size of 28 animals. The initial number of animals on test were planned to be sufficient to allow for early litter loss and ensure that there were 24 pups/sex/ group at the study termination, which is the current recommended standard (McClain et. al., 2001) for the detection of tumors in the neonatal mouse model. The actual numbers of animals assigned per group and examined microscopically were as follows:

Treatment Group	Vehicle Control	Water Control	Retigabine 32 mg/kg	Retigabine 64 mg/kg	Retigabine 96 mg/kg	Positive Control
Initial total male mouse	28	27	29	28	28	28
Initial total female mouse	28	29	27	28	28	28
*Elective sacrifice/missing male mouse	0	3	0	0	0	0
*Elective sacrifice/missing female mouse	0	5	1	0	0	0
**Microscopic pathology male mouse	27	24	29	25	25	28
**Microscopic pathology female mouse	27	24	24	25	27	28

*** During the dosing phase of the study, in the water-control group, 1 litter (3 males and 5 females) was electively euthanized on PND 17 because of the death of the dam.**

****Microscopic pathology evaluations were conducted on all animals at the scheduled sacrifice interval and on all animals found dead or sacrificed during the Maintenance phase of the study.**

Tests showed no statistically significant dose response relationship in mortality across treatment groups in either sex. The pairwise comparisons also did not show statistically significant increased mortality in any of the treated group compared to the either of the controls.

Tests did not show statistically significant dose response relationship in the incidence of any of the observed tumor types using either the water control or vehicle control along with the retigabine treated groups. The pairwise comparisons also did not show statistically significant increased incidence of any of the observed tumor types in the retigabine treated groups compared to the water control or vehicle control. The positive control showed statistically significant increased incidences of hepatocellular adenoma, hepatocellular carcinoma, and bronchiolar alveolar adenoma compared to either of the controls.

Evaluation of the study design: The data showed that there were some early deaths in rats and it seems that not enough rats were exposed long enough for late developing tumors in either sex, especially in females. Also from the mortality and body weight data it can be concluded that the used high dose in rats might have exceeded the MTD in both sexes. Since the length of the mouse study was short and no established statistical

criterion are known to this reviewer to evaluate such design, this reviewer did not perform any evaluation of exposure or dose level for the mouse study. For a final determination of the adequacy of exposure and the doses used in both rat and mouse studies clinical signs and histopathological toxic effects should be considered.

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6. Appendix

Table 1A: Intercurrent Mortality Rate
Male Rats

	Vehicle Control N=50		Water Control N=50		5 mg|kg|day N=50		20 mg|kg|day N=70		50 mg|kg|day N=70	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	3	6.00	.	.	5	10.00	10	14.29	17	24.29
53 - 78	7	20.00	2	4.00	4	18.00	8	25.71	19	51.43
79 - 91	6	32.00	2	8.00	2	22.00	5	32.86	6	60.00
92 - 104	9	50.00	4	16.00	6	34.00	9	45.71	10	74.29
Ter. Sac.	25	50.00	42	84.00	33	66.00	38	54.29	18	25.71

Table 1B: Intercurrent Mortality Rate
Female Rats

	Vehicle Control N=50		Water Control N=50		5 mg|kg|day N=50		20 mg|kg|day N=70		50 mg|kg|day N=70	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	4	8.00	2	4.00	11	22.00	20	28.57	25	35.71
53 - 78	5	18.00	4	12.00	6	34.00	9	41.43	12	52.86
79 - 91	2	22.00	2	16.00	5	44.00	4	47.14	7	62.86
92 - 104	9	40.00	7	30.00	7	58.00	2	50.00	2	65.71
Ter. Sac.	30	60.00	35	70.00	21	42.00	35	50.00	24	34.29

Table 2A: Intercurrent Mortality Comparison
Male Rats

Test	Statistic	P_Value using Vehicle control	P_Value using water control
Dose-Response	Likelihood Ratio	0.0004	<0.0001
Homogeneity	Log-Rank	<0.0001	<0.0001

Table 2B: Intercurrent Mortality Comparison
Female Rats

Test	Statistic	P_Value using Vehicle control	P_Value using water control
Dose-Response	Likelihood Ratio	0.0601	0.0067
Homogeneity	Log-Rank	0.0106	0.0004

Table 3A_VC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using the Vehicle Control
Male Rats

Organ Name	Tumor Name	0 mg Veh. Cont N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ABDOMINAL CAVIT	Hemangiosarcoma	0	0	0	1	0.1988	.	.	0.4198
ADIPOSE TISSUE	Lipoma	1	0	0	0	0.7251	0.4598	0.5155	0.4198
ADRENAL	Cortical Adenoma	2	1	1	0	0.8488	0.4391	0.5234	0.6664
	Cortical Carcinoma	0	1	0	0	0.4912	0.4598	.	.
	Pheochromocytoma	1	0	2	2	0.1213	0.4598	0.5234	0.3897
BRAIN	Astrocytoma	0	0	0	1	0.2035	.	.	0.4268
EPIDIDYMIS	Mesothelioma	0	0	1	0	0.4912	.	0.5155	.
INTESTINE-LARGE	Leiomyosarcoma	0	0	1	0	0.4912	.	0.5155	.
KIDNEY	Malignant Lymphoma	0	1	0	0	0.4912	0.4598	.	.
LIVER	Hepatocellular Adeno	0	0	2	0	0.4433	.	0.2631	.
	Hepatocellular Carci	0	2	0	1	0.3890	0.2085	.	0.4198
LUNG W/BRONCHI	Malignant Lymphoma	0	1	0	0	0.4912	0.4598	.	.
LYMPH NODE, MAN	Malignant Lymphoma	0	1	0	0	0.4912	0.4598	.	.
LYMPH NODE, MES	Hemangiosarcoma	1	0	0	1	0.3591	0.4598	0.5155	0.6664
	Malignant Lymphoma	0	1	0	0	0.4912	0.4598	.	.
MAMMARY GLAND	Fibroadenoma	0	1	0	0	0.4912	0.4598	.	.
PANCREAS	Islet Cell Adenoma	3	1	2	0	0.8941	0.6285	0.5296	0.8100
	Islet Cell Carcinoma	0	1	0	0	0.4912	0.4598	.	.
PARATHYROID	Adenoma	0	2	0	0	0.7426	0.2085	.	.
PITUITARY	Adenoma, Pars Distal	10	8	7	3	0.9507	0.4547	0.7486	0.8887
	Adenoma, Pars Interm	1	1	0	0	0.7955	0.7176	0.5155	0.4198
	Carcinoma, Pars Dist	0	1	0	0	0.4912	0.4598	.	.
	Meningeal Sarcoma	1	0	0	0	0.7251	0.4598	0.5155	0.4198
PREPUTIAL GLAND	Adenoma	0	1	0	0	0.4884	0.4659	.	.
	Carcinoma	0	5	7	3	0.2040	0.0191*	0.0084*	0.0739
	adenoma+carcinoma	0	6	7	3	0.2605	0.0083*	0.0084*	0.0739
	Squamous Cell Carcin	2	5	4	3	0.4083	0.1644	0.3786	0.3614
	Squamous Cell Papill	0	4	2	0	0.8048	0.0434*	0.2631	.
PROSTATE	Adenoma	1	0	0	0	0.7251	0.4598	0.5155	0.4198
SALIVARY GLAND,	Malignant Lymphoma	0	1	0	0	0.4912	0.4598	.	.
SKIN LESION	Basal Cell Carcinoma	0	0	1	0	0.4912	.	0.5155	.
	Keratoacanthoma	0	4	1	1	0.5638	0.0434*	0.5155	0.4198
	Sebaceous Cell Carci	0	0	1	0	0.4912	.	0.5155	.

Table 3A_VC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using the Vehicle Control
Male Rats

Organ Name	Tumor Name	0 mg Veh. Cont N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
SKIN LESION	Squamous Cell Papill	1	3	0	0	0.9379	0.2497	0.5155	0.4198
STOMACH	Adenocarcinoma	0	1	0	0	0.4912	0.4598	.	.
SUBCUTANEOUS TI	Fibroma	0	0	1	1	0.1556	.	0.5155	0.4198
	Granular Cell Tumor	1	0	0	0	0.7251	0.4598	0.5155	0.4198
	Hemangiosarcoma	1	0	1	0	0.5809	0.4598	0.2631	0.4198
	Malignant Schwannoma	0	1	0	0	0.4884	0.4659	.	.
	Osteosarcoma	0	0	1	0	0.4912	.	0.5155	.
	Undifferentiated Sar	1	0	0	0	0.7251	0.4598	0.5155	0.4198
TESTIS	Interstitial Cell Tu	2	0	1	4	0.0249	0.7110	0.5234	0.1989
THYMUS	Malignant Lymphoma	0	1	0	0	0.4912	0.4598	.	.
	Thymoma	1	4	0	1	0.7405	0.1341	0.5155	0.6745
THYROID	C-Cell Adenoma	6	6	4	2	0.8962	0.5203	0.6689	0.7365
	C-Cell Carcinoma	2	1	1	0	0.8488	0.4391	0.5234	0.6664
	Follicular Cell Aden	5	1	2	1	0.8539	0.8572	0.8070	0.8160
	Follicular Cell Carc	1	0	2	0	0.5718	0.4598	0.5234	0.4198
ZYMBAL'S GLAND	Carcinoma	1	0	0	0	0.7251	0.4598	0.5155	0.4198

Table 3A_WC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using the Water Control
Male Rats

Organ Name	Tumor Name	0 mg Wat Cont N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dose Resp	P_Value NC vs. L	P_Value NC vs. M	P_Value NC vs. H
ABDOMINAL CAVIT	Hemangiosarcoma	0	0	0	1	0.2099	.	.	0.4722
ADIPOSE TISSUE	Histiocytic Sarcoma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
ADRENAL	Cortical Adenoma	0	1	1	0	0.4707	0.5128	0.5682	.
	Cortical Carcinoma	0	1	0	0	0.5185	0.5128	.	.
	Pheochromocytoma	1	0	2	2	0.1428	0.5128	0.6028	0.4688
BRAIN	Astrocytoma	1	0	0	1	0.3844	0.5128	0.5682	0.7325
EPIDIDYMIS	Mesothelioma	1	0	1	0	0.6240	0.5128	0.3200	0.4722
INTESTINE-LARGE	Leiomyosarcoma	1	0	1	0	0.6240	0.5128	0.3200	0.4722
KIDNEY	Malignant Lymphoma	0	1	0	0	0.5185	0.5128	.	.
LIVER	Hepatocellular Adeno	0	0	2	0	0.4707	.	0.3200	.
	Hepatocellular Carci	0	2	0	1	0.4287	0.2597	.	0.4722
	Histiocytic Sarcoma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
LUNG W/BRONCHI	Histiocytic Sarcoma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
	Malignant Lymphoma	0	1	0	0	0.5185	0.5128	.	.
LYMPH NODE, MAN	Malignant Lymphoma	0	1	0	0	0.5185	0.5128	.	.
LYMPH NODE, MES	Hemangioma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
	Hemangiosarcoma	0	0	0	1	0.2099	.	.	0.4722
	Histiocytic Sarcoma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
	Malignant Lymphoma	0	1	0	0	0.5185	0.5128	.	.
MAMMARY GLAND	Fibroadenoma	0	1	0	0	0.5185	0.5128	.	.
PANCREAS	Islet Cell Adenoma	1	1	2	0	0.7123	0.2597	0.6028	0.4722
	Islet Cell Carcinoma	0	1	0	0	0.5185	0.5128	.	.
PARATHYROID	Adenoma	1	2	0	0	0.9048	0.5195	0.5682	0.4722
PITUITARY	Adenoma, Pars Distal	14	8	7	3	0.9963	0.9063	0.9838	0.9940
	Adenoma, Pars Interm	0	1	0	0	0.5153	0.5190	.	.
	Carcinoma, Pars Dist	0	1	0	0	0.5185	0.5128	.	.
PREPUTIAL GLAND	Adenoma	0	1	0	0	0.5153	0.5190	.	.
	Carcinoma	3	5	7	3	0.5271	0.3999	0.3053	0.6226
	Squamous Cell Carcin	5	5	4	3	0.7458	0.4187	0.6827	0.5969
	Squamous Cell Papill	2	4	2	0	0.9519	0.3747	0.4182	0.7250
SALIVARY GLAND,	Malignant Lymphoma	0	1	0	0	0.5185	0.5128	.	.
SEMINAL VESICLE	Histiocytic Sarcoma	1	0	0	0	0.7654	0.5128	0.5682	0.4722

Table 3A_WC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using the Water Control
Male Rats

Organ Name	Tumor Name	0 mg Wat Cont N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dose Resp	P_Value NC vs. L	P_Value NC vs. M	P_Value NC vs. H
SKIN LESION	Basal Cell Carcinoma	0	0	1	0	0.5185	.	0.5682	.
	Keratoacanthoma	1	4	1	1	0.7385	0.2040	0.3200	0.7250
	Sebaceous Cell Carci	0	0	1	0	0.5185	.	0.5682	.
	Squamous Cell Carcin	1	0	0	0	0.7654	0.5128	0.5682	0.4722
	Squamous Cell Papill	0	3	0	0	0.8906	0.1299	.	.
SPLEEN	Histiocytic Sarcoma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
STOMACH	Adenocarcinoma	1	1	0	0	0.8295	0.2597	0.5682	0.4722
SUBCUTANEOUS TI	Fibroma	0	0	1	1	0.1734	.	0.5682	0.4722
	Fibrosarcoma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
	Hemangiosarcoma	0	0	1	0	0.5185	.	0.5682	.
	Histiocytic Sarcoma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
	Malignant Schwannoma	0	1	0	0	0.5153	0.5190	.	.
	Osteosarcoma	0	0	1	0	0.5185	.	0.5682	.
	Undifferentiated Sar	1	0	0	0	0.7654	0.5128	0.5682	0.4722
TESTIS	Hemangioma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
	Interstitial Cell Tu	1	0	1	4	0.0120	0.5128	0.3200	0.1458
	Mesothelioma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
THYMUS	Histiocytic Sarcoma	1	0	0	0	0.7654	0.5128	0.5682	0.4722
	Malignant Lymphoma	0	1	0	0	0.5185	0.5128	.	.
	Thymoma	2	4	0	1	0.8704	0.3624	0.8164	0.4688
THYROID	C-Cell Adenoma	2	6	4	2	0.7041	0.1576	0.4766	0.6495
	C-Cell Carcinoma	0	1	1	0	0.4707	0.5128	0.5682	.
	Follicular Cell Aden	2	1	2	1	0.5768	0.5195	0.4182	0.4688
	Follicular Cell Carc	0	0	2	0	0.4707	.	0.3200	.

Table 3B_VC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using the Vehicle Control
Female Rats

Organ Name	Tumor Name	0 mg Veh. Cont. N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ADIPOSE TISSUE	Lipoma	3	1	0	0	0.9743	0.5603	0.8751	0.8245
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
ADRENAL	Cortical Adenoma	3	0	2	0	0.8687	0.8096	0.4887	0.8245
	Malignant Lymphoma	1	1	0	1	0.4904	0.6681	0.4884	0.6767
	Pheochromocytoma	1	0	0	0	0.7114	0.4189	0.4941	0.4342
AORTA (THORACIC	Malignant Schwannoma	0	1	0	0	0.5034	0.4189	.	.
BONE, STERNUM	Malignant Lymphoma	0	1	0	1	0.2658	0.4267	.	0.4342
CERVIX	Adenomatous Polyp	0	1	0	0	0.5034	0.4189	.	.
	Endometrial Stromal	0	1	0	0	0.5034	0.4189	.	.
		1	0	1	0	0.5863	0.4133	0.7412	0.4286
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
CLITORAL GLAND	Carcinoma	1	1	0	0	0.7972	0.6657	0.4941	0.4342
	Squamous Cell Carcin	1	2	1	1	0.5145	0.3778	0.7471	0.6832
DIAPHRAGM	Malignant Lymphoma	0	1	0	0	0.5000	0.4267	.	.
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
EAR	Neural Crest Tumor	1	0	0	0	0.7114	0.4189	0.4941	0.4342
HARDERIAN GLAND	Malignant Lymphoma	0	0	0	1	0.2215	.	.	0.4342
HEART	Malignant Schwannoma	0	1	0	0	0.5034	0.4189	.	.
INTESTINE-LARGE	Leiomyoma	0	0	0	1	0.2215	.	.	0.4342
	Malignant Lymphoma	1	0	0	0	0.7114	0.4189	0.4941	0.4342
					1	0.3951	0.4189	0.4941	0.6832
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
INTESTINE-SMALL	Malignant Lymphoma	0	0	0	1	0.2215	.	.	0.4342
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
KIDNEY	Liposarcoma	1	0	0	0	0.7114	0.4189	0.4941	0.4342
	Malignant Lymphoma	1	1	0	1	0.4904	0.6681	0.4884	0.6767
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
KNEE JOINT (FEM	Malignant Lymphoma	0	1	0	1	0.2658	0.4267	.	0.4342
LIVER	Hepatocellular Adeno	2	1	1	1	0.5714	0.3778	0.4911	0.4006
	Malignant Lymphoma	1	1	0	1	0.4904	0.6681	0.4884	0.6767
	Malignant Schwannoma	0	1	0	0	0.5034	0.4189	.	.
LUNG W/BRONCHI	Malignant Lymphoma	1	1	0	1	0.4904	0.6681	0.4884	0.6767
LYMPH NODE, MAN	Malignant Lymphoma	1	1	0	1	0.4904	0.6681	0.4884	0.6767
	Malignant Schwannoma	0	1	0	0	0.5034	0.4189	.	.

Table 3B_VC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using the Vehicle Control
Female Rats

Organ Name	Tumor Name	0 mg Veh. Cont. N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
LYMPH NODE, MES	Hemangioma	0	0	0	1	0.2215	.	.	0.4342
	Hemangiosarcoma	0	0	1	0	0.5034	.	0.4941	.
	Lymphangioma	1	0	0	0	0.7114	0.4189	0.4941	0.4342
	Malignant Lymphoma	2	1	0	1	0.6096	0.3810	0.7412	0.3922
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
MAMMARY GLAND	Adenocarcinoma	4	0	0	1	0.7894	0.8927	0.9391	0.7275
	Adenoma	1	0	1	0	0.5912	0.4189	0.7471	0.4342
	Fibroadenoma	6	2	4	1	0.9131	0.7511	0.6156	0.8932
MESENTERY	Lipoma	1	0	1	0	0.5912	0.4189	0.7471	0.4342
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
NOSE	Squamous Cell Papill	0	1	0	0	0.5034	0.4189	.	.
OVARY	Granulosa Cell Tumor	2	1	0	1	0.6182	0.3778	0.7471	0.4006
	Luteoma	0	1	0	0	0.5034	0.4189	.	.
	Malignant Schwannoma	0	1	0	0	0.5034	0.4189	.	.
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
	Sertoli Cell Tumor	2	0	1	0	0.8098	0.6657	0.4911	0.6832
	Thecoma	1	0	0	0	0.7114	0.4189	0.4941	0.4342
	Undifferentiated Gon	1	0	0	1	0.3951	0.4189	0.4941	0.6832
PANCREAS	Islet Cell Adenoma	0	0	1	1	0.1736	.	0.4941	0.4342
	Malignant Lymphoma	1	0	0	0	0.7067	0.4133	0.4884	0.4286
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
PITUITARY	Adenoma, Pars Distal	29	15	17	15	0.9533	0.9251	0.9872	0.9659
	Carcinoma, Pars Dist	0	0	0	1	0.2215	.	.	0.4342
SALIVARY GLAND,	Malignant Schwannoma	0	1	0	0	0.5034	0.4189	.	.
SKIN LESION	Squamous Cell Papill	0	0	0	1	0.2215	.	.	0.4342
SPLEEN	Malignant Lymphoma	0	1	0	1	0.2658	0.4267	.	0.4342
STOMACH	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
SUBCUTANEOUS TI	Fibroma	1	0	0	0	0.7114	0.4189	0.4941	0.4342
	Hemangiosarcoma	0	0	0	1	0.2267	.	.	0.4416
	Lipoma	1	0	0	0	0.7114	0.4189	0.4941	0.4342
	Malignant Schwannoma	1	1	0	0	0.7933	0.6591	0.4884	0.4286
	Trichoepithelioma	0	0	1	0	0.5034	.	0.4941	.
THORACIC CAVITY	Malignant Schwannoma	0	1	0	0	0.5034	0.4189	.	.
THYMUS	Malignant Lymphoma	2	0	0	1	0.4923	0.6591	0.7412	0.3922
	Malignant Schwannoma	0	1	0	0	0.5034	0.4189	.	.
	Thymoma	4	3	3	0	0.9659	0.6283	0.4866	0.9038

Table 3B_VC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using the Vehicle Control
Female Rats

Organ Name	Tumor Name	0 mg Veh. Cont. N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
THYROID	C-Cell Adenoma	5	1	3	1	0.8490	0.8060	0.6302	0.8268
	C-Cell Carcinoma	0	0	2	0	0.4732	.	0.2412	.
	Follicular Cell Aden	2	1	1	1	0.5714	0.3778	0.4911	0.4006
	Follicular Cell Carc	0	1	0	0	0.5034	0.4189	.	.
TONGUE	Squamous Cell Papill	0	0	1	0	0.5034	.	0.4941	.
TRACHEA	Malignant Lymphoma	0	0	0	1	0.2215	.	.	0.4342
URINARY BLADDER	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
UTERUS	Carcinoma, Anaplasti	1	0	0	0	0.7114	0.4189	0.4941	0.4342
	Endometrial Adenocar	4	4	3	0	0.9752	0.4352	0.4736	0.8997
	Endometrial Stromal	0	0	1	0	0.5067	.	0.5000	.
		4	4	6	5	0.2548	0.4489	0.3539	0.3331
	Malignant Schwannoma	0	1	0	0	0.5034	0.4189	.	.
	Mesothelioma	0	1	0	0	0.5034	0.4189	.	.
VAGINA	Malignant Schwannoma	0	1	0	0	0.5034	0.4189	.	.
ZYMBAL'S GLAND	Carcinoma	0	0	0	1	0.2267	.	.	0.4416

Table 3B_WC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using the Water Control
Female Rats

Organ Name	Tumor Name	0 mg Wat Cont N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dose Resp	P_Value NC vs. L	P_Value NC vs. M	P_Value NC vs. H
ADIPOSE TISSUE	Lipoma	0	1	0	0	0.5137	0.4366	.	.
	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
ADRENAL	Cortical Adenoma	0	0	2	0	0.4835	.	0.2593	.
	Malignant Lymphoma	0	1	0	1	0.2768	0.4444	.	0.4521
AORTA (THORACIC	Malignant Schwannoma	0	1	0	0	0.5137	0.4366	.	.
BONE, STERNUM	Malignant Lymphoma	0	1	0	1	0.2768	0.4444	.	0.4521
CERVIX	Adenomatous Polyp	0	1	0	0	0.5137	0.4366	.	.
	Endometrial Stromal	0	0	1	0	0.5137	.	0.5122	.
			1	0	0	0.5137	0.4366	.	.
	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
CLITORAL GLAND	Carcinoma	0	1	0	0	0.5137	0.4366	.	.
	Squamous Cell Carcin	1	2	1	1	0.5326	0.4041	0.2593	0.7032
DIAPHRAGM	Malignant Lymphoma	0	1	0	0	0.5102	0.4444	.	.
	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
HARDERIAN GLAND	Malignant Lymphoma	0	0	0	1	0.2260	.	.	0.4521
HEART	Malignant Schwannoma	0	1	0	0	0.5137	0.4366	.	.
INTESTINE-LARGE	Leiomyoma	0	0	0	1	0.2260	.	.	0.4521
	Malignant Lymphoma	0	0	0	1	0.2260	.	.	0.4521
	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
INTESTINE-SMALL	Malignant Lymphoma	0	0	0	1	0.2260	.	.	0.4521
	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
KIDNEY	Malignant Lymphoma	0	1	0	1	0.2768	0.4444	.	0.4521
	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
	Tubular Cell Adenoma	1	0	0	0	0.7260	0.4366	0.5122	0.4521
KNEE JOINT (FEM	Malignant Lymphoma	0	1	0	1	0.2768	0.4444	.	0.4521
LIVER	Hepatocellular Adeno	0	1	1	1	0.2687	0.4366	0.5122	0.4521
	Malignant Lymphoma	0	1	0	1	0.2768	0.4444	.	0.4521
	Malignant Schwannoma	0	1	0	0	0.5137	0.4366	.	.
LUNG W/BRONCHI	Malignant Lymphoma	0	1	0	1	0.2768	0.4444	.	0.4521
LYMPH NODE, MAN	Malignant Lymphoma	0	1	0	1	0.2768	0.4444	.	0.4521
	Malignant Schwannoma	0	1	0	0	0.5137	0.4366	.	.
LYMPH NODE, MES	Hemangioma	0	0	0	1	0.2260	.	.	0.4521
	Hemangiosarcoma	0	0	1	0	0.5137	.	0.5122	.
	Malignant Lymphoma	0	1	0	1	0.2768	0.4444	.	0.4521

Table 3B_WC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using the Water Control
Female Rats

Organ Name	Tumor Name	0 mg Wat Cont N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dose Resp	P_Value NC vs. L	P_Value NC vs. M	P_Value NC vs. H
LYMPH NODE, MES	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
MAMMARY GLAND	Adenocarcinoma	0	0	0	1	0.2260	.	.	0.4521
	Adenoma	0	0	1	0	0.5137	.	0.5122	.
	Fibroadenoma	2	2	4	1	0.6239	0.6039	0.3615	0.4273
MESENTERY	Lipoma	0	0	1	0	0.5137	.	0.5122	.
	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
NOSE	Squamous Cell Papill	0	1	0	0	0.5137	0.4366	.	.
OVARY	Granulosa Cell Tumor	1	1	0	1	0.5111	0.6861	0.5122	0.7032
	Luteoma	0	1	0	0	0.5137	0.4366	.	.
	Malignant Schwannoma	0	1	0	0	0.5137	0.4366	.	.
	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
	Sertoli Cell Tumor	1	0	1	0	0.6065	0.4366	0.2593	0.4521
	Thecoma	1	0	0	0	0.7260	0.4366	0.5122	0.4521
	Undifferentiated Gon	0	0	0	1	0.2260	.	.	0.4521
PANCREAS	Islet Cell Adenoma	0	0	1	1	0.1808	.	0.5122	0.4521
	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
PITUITARY	Adenoma, Pars Distal	14	15	17	15	0.3784	0.2262	0.4195	0.3284
	Carcinoma, Pars Dist	1	0	0	1	0.4022	0.4366	0.5122	0.7032
SALIVARY GLAND,	Malignant Schwannoma	0	1	0	0	0.5137	0.4366	.	.
SKIN LESION	Squamous Cell Papill	0	0	0	1	0.2260	.	.	0.4521
SPLEEN	Malignant Lymphoma	0	1	0	1	0.2768	0.4444	.	0.4521
STOMACH	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
SUBCUTANEOUS TI	Hemangiosarcoma	0	0	0	1	0.2313	.	.	0.4595
	Malignant Schwannoma	1	1	0	0	0.8092	0.6861	0.5122	0.4521
	Trichoepithelioma	0	0	1	0	0.5137	.	0.5122	.
THORACIC CAVITY	Malignant Schwannoma	0	1	0	0	0.5137	0.4366	.	.
THYMUS	Malignant Lymphoma	0	0	0	1	0.2260	.	.	0.4521
	Malignant Schwannoma	0	1	0	0	0.5137	0.4366	.	.
	Thymoma	3	3	3	0	0.9464	0.5340	0.3615	0.8411
THYROID	C-Cell Adenoma	3	1	3	1	0.6871	0.5907	0.3615	0.6165
	C-Cell Carcinoma	0	0	2	0	0.4835	.	0.2593	.
	Follicular Cell Aden	0	1	1	1	0.2687	0.4366	0.5122	0.4521
	Follicular Cell Carc	0	1	0	0	0.5137	0.4366	.	.
TONGUE	Squamous Cell Papill	0	0	1	0	0.5137	.	0.5122	.

Table 3B_WC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Using the Water Control
Female Rats

Organ Name	Tumor Name	0 mg Wat Cont N=50	5 mg Low N=50	20 mg Med N=70	50 mg High N=70	P_Value Dose Resp	P_Value NC vs. L	P_Value NC vs. M	P_Value NC vs. H
TRACHEA	Malignant Lymphoma	0	0	0	1	0.2260	.	.	0.4521
URINARY BLADDER	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
UTERUS	Endometrial Adenocar	1	4	3	0	0.8851	0.1097	0.3265	0.4521
	Endometrial Stromal	0	0	1	0	0.5170	.	0.5181	.
		5	4	6	5	0.3683	0.6162	0.5352	0.5023
	Malignant Schwannoma	0	1	0	0	0.5137	0.4366	.	.
	Mesothelioma	0	1	0	0	0.5137	0.4366	.	.
VAGINA	Malignant Schwannoma	0	1	0	0	0.5137	0.4366	.	.
ZYMBAL'S GLAND	Carcinoma	0	0	0	1	0.2313	.	.	0.4595

Table 4A: Intercurrent Mortality Rate in Male Mice

	Vehicle Control		Water Control		32 mg|kg|day		64 mg|kg|day		96 mg|kg|day		Positive Control	
	N=27		N=24		N=28		N=25		N=25		N=28	
	No. of		No. of		No. of		No. of		No. of		No. of	
Week	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %
0 - 47	2	7.41	4	16.67	2	7.14	5	20.00	1	4.00	3	10.71
Ter. Sac.	25	92.59	20	83.33	26	92.86	20	80.00	24	96.00	25	89.29

Table 4B: Intercurrent Mortality Rate Female Mice

	Vehicle Control		Water Control		32 mg|kg|day		64 mg|kg|day		96 mg|kg|day		Positive Control	
	N=26		N=24		N=24		N=25		N=26		N=28	
	No. of		No. of		No. of		No. of		No. of		No. of	
Week	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %
0 - 47	1	3.85	1	4.17	1	4.17	3	12.00	2	7.69	2	7.14
Ter. Sac.	25	96.15	23	95.83	23	95.83	22	88.00	24	92.31	26	92.86

Table 5A: Intercurrent Mortality Comparison Male Mice

Test	Statistic	P_Value using Vehicle control	P_Value using water control
Dose-Response	Likelihood Ratio	0.9721	0.7613
Homogeneity	Log-Rank	0.2694	0.2477

Table 5B: Intercurrent Mortality Comparison Female Mice

Test	Statistic	P_Value using Vehicle control	P_Value using water control
Dose-Response	Likelihood Ratio	0.8193	0.8293
Homogeneity	Log-Rank	0.6518	0.6723

Table 6A_VC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Mice Using Vehicle Control

Organ Name	Tumor Name	Vehicle Control N=27	32 mg Low N=28	64 mg Med N=25	96 mg High N=25	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Harderian Gl	B-ADENOMA	1	0	0	0	0.7426	0.5094	0.4694	0.4902
Liver	B-HEPATOCELLULAR ADE	1	1	2	1	0.4707	0.2547	0.4532	0.7451
Lung	BRONCHIOLR_ALVEOLAR_	1	1	2	3	0.1324	0.2547	0.4532	0.2899
Lungs	B-BRONCHIOLO/ALVEOLA	1	1	2	1	0.4707	0.2547	0.4532	0.7451
	M-BRONCHIOLO/ALVEOLA	0	0	0	2	0.0594	.	.	0.2353
	BRONCHIOLO/ALVEOLA ADENOMA+CARCINOMA	1	1	2	3	0.1324	0.2547	0.4532	0.2899
Lymph Node othe	M-HEMANGIOSARCOMA	0	1	0	0	0.4752	0.5094	.	.
Lymph/Retic Sys	M-GRANULOCYTIC LEUKE	0	0	1	0	0.4752	.	0.4694	.
	M-MALIGNANT LYMPHOMA	0	0	1	0	0.4752	.	0.4694	.
Skin	B-SQUAMOUS CELL PAPI	0	0	1	0	0.4752	.	0.4694	.

Table 6A_WC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Mice Using Water Control

Organ Name	Tumor Name	Water Control N=24	32 mg Low N=28	64 mg Med N=25	96 mg High N=25	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Liver	B-HEPATOCELLULAR ADE	3	1	2	1	0.7764	0.7692	0.5218	0.7431
Lungs	B-BRONCHIOLO/ALVEOLA	1	1	2	1	0.5204	0.2985	0.5171	0.2775
	M-BRONCHIOLO/ALVEOLA	0	0	0	2	0.0644	.	.	0.2775
	BRONCHIOLO/ALVEOLA ADENOMA+CARCINOMA	1	1	2	3	0.1621	0.2985	0.5171	0.3546
Lymph Node othe	M-HEMANGIOSARCOMA	0	1	0	0	0.4948	0.5510	.	.
Lymph/Retic Sys	M-GRANULOCYTIC LEUKE	0	0	1	0	0.4948	.	0.5111	.
	M-MALIGNANT LYMPHOMA	0	0	1	0	0.4948	.	0.5111	.
Skin	B-SQUAMOUS CELL PAPI	0	0	1	0	0.4948	.	0.5111	.

Table 6A_VWP: Tumor Rates and P-Values for the Pairwise Comparisons
of Vehicle Control, Water Control and Positive Control
Male Mice

Organ Name	Tumor Name	Water Cont	Veh. Cont	Pos. Cont	P_Value WC vs. VC	P_Value WC vs. PC	P_Value VC vs. PC
Harderian Gl	B-ADENOMA	0	1	1	0.5417	0.5510	0.2547
Liver	B-HEPATOCELLULAR ADE	3	1	24	0.7566	<0.001*	<0.001*
	M-HEPATOCELLULAR CAR	0	0	17	.	<0.001*	<0.001*
Lungs	B-BRONCHIOLO/ALVEOLA	1	1	14	0.2881	<0.001*	<0.001*
	M-BRONCHIOLO/ALVEOLA	0	0	1	.	0.5510	0.5094

Table 6B_VC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice Using Vehicle Control

Organ Name	Tumor Name	Vehicle Control N=26	32 mg Low N=24	64 mg Med N=25	96 mg High N=26	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Harderian Gl	B-ADENOMA	1	0	0	0	0.7396	0.4898	0.4792	0.4898
Liver	B-HEPATOCELLULAR ADE	0	0	1	0	0.4896	.	0.4792	.
Lungs	B-BRONCHIOLO/ALVEOLA	0	0	1	1	0.1816	.	0.4792	0.4898
Lymph/Retic Sys	M-MALIGNANT LYMPHOMA	1	0	0	0	0.7320	0.4800	0.4694	0.4800
Mammary protoco	B-BENIGN MAST CELL T	0	0	0	1	0.2500	.	.	0.4898
Uterus w/ Cervi	B-HEMANGIOMA	0	0	1	0	0.4896	.	0.4792	.

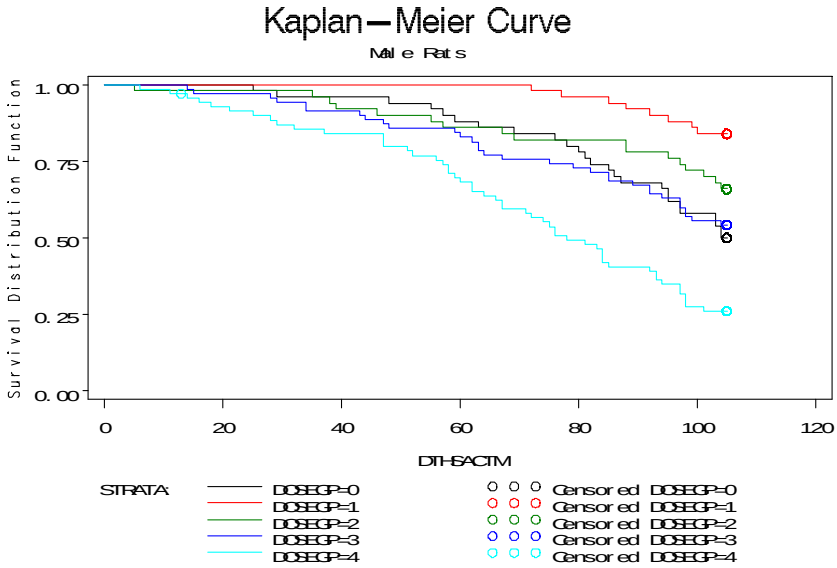
Table 6B_WC: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice Using Water Control

Organ Name	Tumor Name	Water Control N=24	32 mg Low N=24	64 mg Med N=25	96 mg High N=26	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Liver	B-HEPATOCELLULAR ADE	0	0	1	0	0.4947	.	0.4894	.
Lungs	B-BRONCHIOLO/ALVEOLA	1	0	1	1	0.4960	0.5000	0.7447	0.7553
Mammary protoco	B-BENIGN MAST CELL T	0	0	0	1	0.2526	.	.	0.5000
Uterus w/ Cervi	B-HEMANGIOMA	0	0	1	0	0.4947	.	0.4894	.

Table 6B_VWP: Tumor Rates and P-Values for the Pairwise Comparisons of Vehicle Control, Water Control and Positive Control
Female Mice

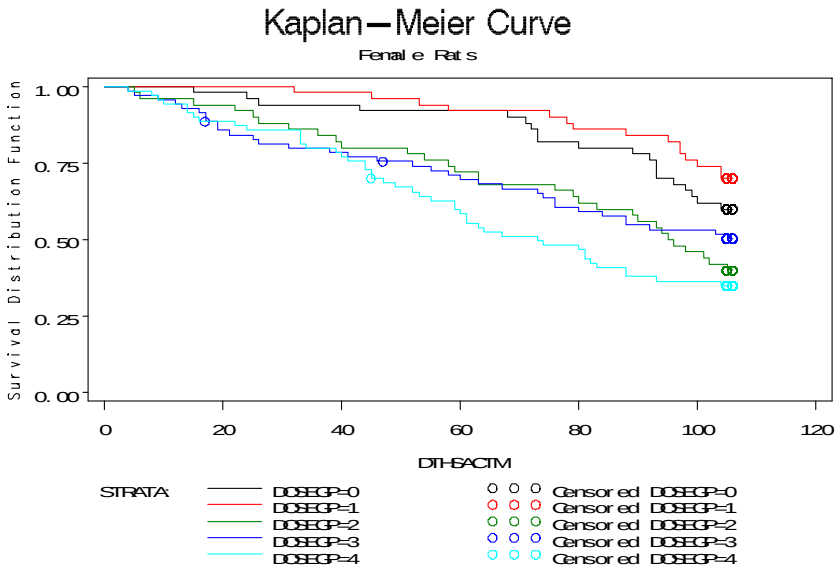
Organ Name	Tumor Name	Water Cont	Veh. Cont	Pos. Cont	P_Value WC vs. VC	P_Value WC vs. PC	P_Value VC vs. PC
Harderian Gl	B-ADENOMA	0	1	0	0.5102	.	0.5192
Liver	B-HEPATOCELLULAR ADE	0	0	12	.	<0.001*	<0.001*
	M-HEPATOCELLULAR CAR	0	0	1	.	0.5294	0.5192
Lungs	B-BRONCHIOLO/ALVEOLA	1	0	11	0.5102	0.0026*	<0.001*
	M-BRONCHIOLO/ALVEOLA	0	0	2	.	0.2753	0.2647
Lymph/Retic Sys	M-MALIGNANT LYMPHOMA	0	1	1	0.5200	0.5294	0.2547

Figure 1A: Kaplan-Meier Survival Functions for Male Rats
Male Rats



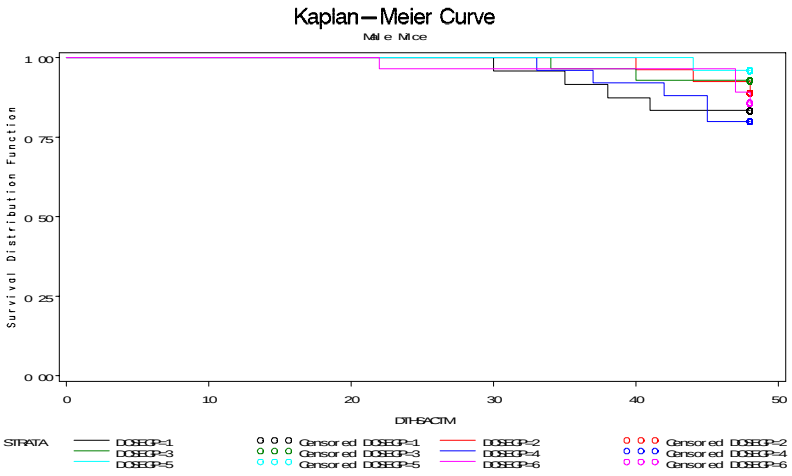
X-Axis: Weeks, Y-Axis: Survival rates

Figure 1B: Kaplan-Meier Survival Functions for Female Rats
Female Rats



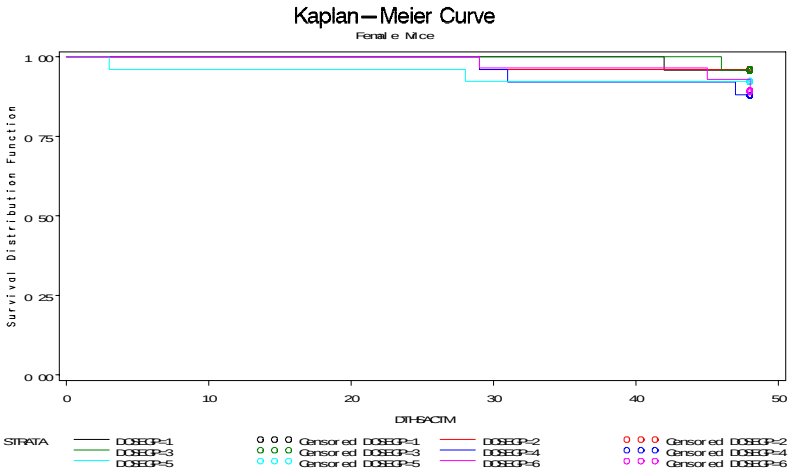
X-Axis: Weeks, Y-Axis: Survival rates

Figure 2A: Kaplan-Meier Survival Functions for Male Mice
Male Mice



X-Axis: Weeks, Y-Axis: Survival rates

Figure 2B: Kaplan-Meier Survival Functions for Female Mice
Female Mice



X-Axis: Weeks, Y-Axis: Survival rates

7. References

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22345	ORIG-1	VALEANT PHARMACEUTICALS NORTH AMERICA	RETIGABINE

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

/s/

ATIAR MOHAMMAD A RAHMAN
05/17/2010

KARL K LIN
05/18/2010
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:	22345
Drug Name:	Potiga™ (retigabine) Tablets
Indication(s):	Adjunctive treatment for patients 18 years of age and older with partial onset seizures with or without secondary generalization
Applicant:	Valeant Pharmaceuticals North America
Date(s):	Filing Mtg: 01/28/2010 PDUFA date: 08/30/2010 Completion date: 04/23/2010
Review Priority:	S
Biometrics Division:	DB VI
Statistical Reviewer:	Ling Chen, Ph.D., Mathematical Statistician, Special Project Team.
Concurring Reviewers:	Stella Machado, Ph.D., Acting Team Leader, Division Director
Medical Division:	Controlled Substance Staff
The CSS Team:	Katherine Bonson, Ph.D., Pharmacologist, OD/CSS
Project Manager:	Corrinne P. Moody, OD/CSS

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

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1. Executive Summary

Study VRX-RET-E22-108 was a randomized, double-blind, placebo- and active-controlled crossover study to evaluate the abuse potential of retigabine in recreational polydrug users. The study consisted of a Screening visit, a Qualification Phase, a Treatment Phase, and a safety Follow-up visit.

There were 8 treatments in the study. These treatments were placebo, alprazolam 1.5 mg (positive control), alprazolam 3 mg (positive control), levetiracetam 4000 mg (negative control), retigabine 300 mg, retigabine 600 mg, and retigabine 900 mg/placebo. Based on an unexpected serious adverse event (SAE) experienced by 1 subject administered retigabine 900 mg (Subject 9077), all subsequent subjects were administered placebo instead of retigabine 900 mg, independent of the individual subject's tolerability of retigabine 600 mg. Therefore, the last treatment retigabine 900 mg/placebo was dropped in this reviewer's analysis. Levetiracetam 4000 mg (negative control) is an unscheduled drug. The reviewer consulted with the CSS about levetiracetam, and was told not to include levetiracetam in the analysis, because levetiracetam has not been fully evaluated for abuse potential, even though it is unscheduled.

For primary measures Drug Liking VAS, Overall Drug Liking VAS, Take Drug Again VAS, and ARCI MBG, this reviewer found that 1) both doses of positive control drug alprazolam 1.5 mg and 3 mg had significantly higher mean (or median) response than placebo on these four measures. That is, both positive control drugs validated the reviewer's primary analysis; 2) there was no significant difference in mean (or median) between alprazolam and retigabine; and 3) both doses of retgabine had significantly higher mean (or median) response than placebo.

Seven commonly used abuse potential measures were included in this reviewer's secondary analysis. These measures were Bad Drug Effects VAS, Good Drug Effects VAS, Any Drug Effects VAS, High VAS, ARCI Amphetamine (A), ARCI PCAG, ARCI LSD. This reviewer found that 1) both doses of positive control drug alprazolam 1.5 mg and 3 mg had significantly higher mean (or median) response than placebo on these seven measures. That is, both doses of the positive control drug validated the reviewer's secondary analysis; 2) the mean (or median) response of retigabine 600 mg was significantly higher than that of placebo for all seven measures, and the mean (or median) response of retigabine 300 mg was significantly higher than that of placebo for six out of 7 measures; 3) No significant difference in mean (or median) was found between alprazolam 3 mg and retigabine 600 mg, and between alprazolam 1.5 mg and any dose of retigabine on all measures except ARCI PCAG; 4) significantly higher mean (or median) response for alprazolam 3 mg than retigabine 300 mg was found for 5 out of 7 measures, even though no significantly higher mean (or median) response of alprazolam than that of retigabine 300 mg was found for Good Drug Effects VAS and ARCI Amphetamine (A); 5) both doses of alprazolam had significantly higher mean response than any dose of retigabine on ARCI PCAG, but the mean response of placebo was significantly lower than that of both doses of retigabine on the same scale.

Based on the study results, this reviewer concluded that the human abuse potential of retigabine appears similar to the positive control drug alprazolam.

2. Review Report on Study VRX-RET-E22-108

2.1 Overview

2.1.1 Objectives of the study

Primary objectives:

- Evaluate the abuse potential of retigabine compared to placebo;
- Evaluate the abuse potential of retigabine compared to alprazolam;
- Evaluate the abuse potential of alprazolam compared to placebo (study validity).

Secondary objectives:

- Evaluate the abuse potential of retigabine compared to levetiracetam
- Evaluate the abuse potential of levetiracetam compared to placebo
- Evaluate the safety and tolerability of retigabine

Reviewer's Comment: alprazolam *is a schedule IV drug, and* levetiracetam *is an unscheduled drug. This review will focus on the primary objective.*

2.1.2 Study design

This study was a randomized, double-blind, placebo- and active-controlled crossover study to evaluate the abuse potential of retigabine in recreational polydrug users. The study consisted of a Screening visit, a Qualification Phase, a Treatment Phase, and a safety Follow-up visit.

There were seven treatments in the study. These treatments were

P - placebo
A1.5 – alprazolam 1.5 mg (positive control)
A3 – alprazolam 3 mg (positive control)
L4000 – levetiracetam 4000 mg (negative control)
R300 – retigabine 300 mg
R600 – retigabine 600 mg
R900/P – retigabine 900 mg/placebo

There were 7 treatment sequences in the study. These sequences were:

C D B E A F G
D C E B F A G
D E C F B G A
E D F C G B A
E F D G C A B
F E G D A C B
F G E A D B C

Treatment sequences were randomly assigned to study subjects. The washout period between two periods is 7 days.

Reviewer's Comments:

Based on the half-life (t1/2) of alprazolam (approximately 11 hours), and that of retigabine *(each approximately 8-9 hours), as well as that of levetiracetam (approximately 6-8 hours), a 7-day washout for each period was considered appropriate.*

The reviewer consulted with the CSS about the negative control, levetiracetam, and was told not to include levetiracetam in the analysis, because levetiracetam has not been fully evaluated for abuse potential, even though it is unscheduled.

The randomization schedule was established such that no subject would receive retigabine 900 mg/placebo prior to receiving 600 mg retigabine. When scheduled for retigabine 900 mg, subjects would only receive retigabine 900 mg if they had tolerated the 600 mg dose; if retigabine 600 mg was not previously tolerated, the subject received placebo instead. Based on an unexpected serious adverse event (SAE) experienced by 1 subject administered retigabine 900 mg (Subject 9077), all subsequent subjects were administered placebo instead of retigabine 900 mg, independent of the individual subject's tolerability of retigabine 600 mg. Therefore, only a total of 6 subjects received retigabine 900 mg in this study.

Reviewer's Comments: Because only 6 subjects received retigabine 900, and serious AE had experienced by one subject, the responses from retigabine 900 mg or replaced placebo are not used in this reviewer's analysis.

Data were collected at -0.5, 0.5, 1.0, 2.0, 3.0, 4.0, 8.0, 12 and 24.0 hours postdose for visual analog scales (VAS) except those measures refer specifically to the study drug, for example, Overall Drug Liking VAS. Data were collected at -0.5, 0.5, 1.0, 2.0, 3.0, 4.0, 8.0, 12 and 24.0 hours postdose for addiction research center inventory (ARCI) scales, collected at 6, 12, and 24 hours postdose for Overall Drug Liking, Take Drug Again VAS and Subjective Drug Value (SDV), and collected at 12 and 24 hours postdose for Drug Similarity VASs.

Reviewer's Comments: In general, sponsors collect data at -0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12, 24) hours during each treatment period. Notice that this Sponsor did not collect the data at hour 1.5 for VAS and ARCI scales. Thus, it is possible that peak responses from subjects at hour 1.5 were not captured.

Because SDV is a measure which has not been validated, therefore, it is not considered in this reviewer's analysis.

2.1.3 Study variables

The primary pharmacodynamic measures consisted of the visual analog scale (VAS) for Drug Liking ("at this moment"), end-of-day and next-day Overall Drug Liking VAS and Take Drug Again VAS, and the Addiction Research Centre Inventory (ARCI) Morphine Benzedrine Group (MBG) scale.

Three Secondary measures were included to evaluate other subjective effects including balance/positive effects (High VAS, Subjective Drug Value [SDV], Good Drug Effects VAS, Pleasant Mental/Pleasant Physical State VASs), negative effects (Bad Drug Effects VAS, ARCI Lysergic Acid Diethylamide [LSD]), sedative effects (ARCI Pentobarbital and Chlorpromazine Group [PCAG]), perceptual/dissociative effects (Floating VAS, Colours Brighter VAS, Sounds Louder VAS), and other drug effects (Any Drug Effects VAS, Alertness/Drowsiness VAS, Drug Similarity VASs, Dizziness VAS, and ARCI Amphetamine and Benzedrine Group [BG] scales). Objective measures were included to assess neurocognitive effects (Choice Reaction Time [CRT] Motor Reaction Time [MRT], Recognition Reaction Time [RRT], Total Reaction Time [TRT], percentage correct and Divided Attention test [DAT], mean hit latency, mean greatest distance, mean percentage over road, Root Mean Square [RMS] distance, percentage of target hits, and number of false alarms).

The primary endpoints were the peak scores (Emax or Emin for some variables) for all measures (primary and secondary variables). Partial time-weighted means from 0 to 4 hours post-dose (TWM(0-4h)) and 0 to 24 hours post-dose (TWM(0-24h)) were also calculated for each variable and considered as supportive endpoints.

Reviewer's Comments: The endpoint of interest to the CSS is Emax during 8 hours after dosing. For some measures, predose responses are collectable, the endpoint of interest to the CSS is Emax of change from predose response during 8 hours after dosing. It is not clear to this reviewer what time period Emax or Emin were calculated by the sponsor.

2.1.4 Number of Subjects

Healthy male and female subjects aged 18 to 55 (inclusive), who are recreational polydrug users with a history of central nervous system (CNS) depressant use, and who met qualification criteria.

Eighty-one subjects were randomized and received at least one dose in the Qualification Phase. A total of 36 subjects were randomized to the Treatment Phase and received at least one dose of study drug. Twenty-six subjects completed the study, had no major protocol violations, and were included in the sponsor's analysis.

2.1.4 Statistical Methodologies Used in the Sponsor's Analyses

Primary endpoints (mean maximum score [Emax] and/or mean minimum score [Emin]) for the primary and secondary measures were analyzed using a mixed-effect model for a crossover study. Time-weighted mean (TWmean) values were calculated as secondary endpoints and analyzed using a mixed-effect model. The contrasts consisted of comparisons of each dose of retigabine to placebo, each dose of alprazolam and levetiracetam, as well as each dose of alprazolam to placebo (study validity), and levetiracetam to placebo.

Reviewer's Comments: It is not clear to this reviewer exactly what was the statistical model used in the study. The sponsor only mentioned that a mixed-effect model was used but the sponsor did not specify what fixed or random effects in the model in neither the report nor the SAP.

2.1.5 Sponsor's results and conclusion

Results

- The trial was valid since the 95% CIs of differences in Emax between both doses of alprazolam and placebo did not include zero, and a non-descending dose-response was observed on each of the primary endpoints. Alprazolam was associated with significant and persistent effects on all measures of balance, positive, sedative, and most other effects compared to placebo. Alprazolam 3 mg also showed significant differences from placebo on measures of negative effects.

- Levetiracetam 4000 mg was also associated with significant differences from placebo on the primary endpoints and most measures of balance, positive, sedative, and other effects. Levetiracetam negative effects were greater than placebo on some but not all measures.

- Retigabine 300 mg and 600 mg were associated with significant balance and positive effects on many of the primary endpoints compared with placebo, other than Overall Drug Liking VAS Emax for retigabine 300 mg. Retigabine was also associated with significant negative, sedative, and other subjective effects compared to placebo. Most Emax values were significantly greater for retigabine compared to placebo, while a few measures showed no significant differences in TWmean values, in particular at the 300 mg dose.

- Retigabine was not significantly different from alprazolam on most measures of positive and balance effects, including the primary endpoints. Significant differences were observed primarily in TWmean values for positive (High VAS and Good Drug Effects VAS), and other effects (Any Drug Effects VAS, Dizziness VAS, Floating VAS, and Colours Brighter VAS);however, at the 300 mg doses some differences were also observed in Emax values. Retigabine was associated with fewer sedative effects compared to alprazolam, and fewer negative effects compared to alprazolam 3 mg.

- Retigabine effects were similar to levetiracetam and were not significantly different on most measures. Retigabine had significantly fewer sedative and other effects (e.g., Any Drug Effects VAS, Floating VAS, and Dizziness VAS) compared to levetiracetam, particularly in TWmean values at the 300 mg dose.

- On most measures, administration of retigabine was associated with a different mean time course profile compared to alprazolam. Similar to levetiracetam, retigabine demonstrated an early increase in scores that peaked within 1 to 2 hours postdose, followed by a relatively rapid decline. In contrast, peak responses to alprazolam occurred slightly later and persisted for a longer duration. The differences in TWmean values observed between retigabine and alprazolam are consistent with retigabine's shorter duration of action.

- Most subjects responded appropriately to placebo and alprazolam on the Drug Similarity VASs. Retigabine was not associated strongly with any of the drugs/classes of abuse except a small effect on the Ecstasy VAS (retigabine 600 mg).

- In contrast to alprazolam and levetiracetam 4000 mg, retigabine did not impair psychomotor and neurocognitive performance as demonstrated by measures of reaction time, manual tracking, information processing, accuracy, and attention.

Conclusion

The Sponsor stated that when retigabine was compared with alprazolam, there were some similarities in balance and positive effects, but retigabine was associated with fewer sedative, negative, and other subjective effects, as well as less cognitive and psychomotor impairment. Retigabine was similar to the negative control, levetiracetam, on most measures; however, retigabine also showed fewer sedative and cognitive impairment effects. In addition, the time course of response differed between the alprazolam and retigabine, with retigabine showing a pattern of response more similar to levetiracetam. The data generated from this study will be used as one of the key components of the eight factor analysis that will be submitted to the regulatory authorities to determine the scheduling status for retigabine.

2.2 Data Location

The dataset used in the reviewer's analysis is located at \\Cdsesub1\evsprod\NDA022345\0012\m5\datasets\vrx-ret-e22-108\analysis.

2.3 Reviewer's Primary Analysis

The reviewer's primary analysis included Drug Liking VAS ("at this moment"), Overall Drug Liking VAS , Take Drug Again VAS, and the Addiction Research Centre Inventory (ARCI) Morphine Benzedrine Group (MBG) scale. Data for Drug Liking VAS and ARCI MBG were collected at hours 0.5, 1, 2, 3, 4, 6, 8, 12, 24, while data for Overall Drug Liking VAS and Take Drug Again VAS were collected only for hours 6, 12, and 24. Predose response was collected for ARCI MBG. Therefore, the primary endpoints of interest are Emax of Drug liking VAS (8 hours postdose), Emax of Overall Drug Liking VAS and Take Drug Again VAS (maximum response among hours 6, 12, and 24), and Emax of ARCI MBG (maximum change predose response 8 hours postdose).

2.3.1 Descriptive statistics on primary measures

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

Table 1: Summary Statistics on Emax for Four Primary Measures

Abuse Potential Measure	TRT	N	Mean	Std	Min	Q1	Med	Q3	Max
Drug Liking VAS	A1.5	26	74.73	17.53	50	61.75	72	94	100
	A3	26	79.04	17.69	49	63.75	81.5	97	100
	P	26	54.85	10.39	50	51	51	53	99
	R300	26	71.08	19.18	50	51	68.5	89.25	100
	R600	26	77.54	18.20	50	63	72.5	100	100
Overall Drug Liking VAS	A1.5	26	67.19	20.80	20	52.5	65	83.25	100
	A3	26	72.08	24.77	15	49.5	76.5	97.25	100
	P	26	51.85	9.76	26	50	50	51	81
	R300	26	64.62	21.12	4	50	62	79.5	100
	R600	26	70.50	23.34	2	63	70	88	100
Take Drug Again VAS	A1.5	26	65.35	27.46	8	50.75	66.5	86	100
	A3	26	68.85	33.11	2	48.25	77.5	99	100
	P	26	34.58	34.93	0	0	34	54.5	100
	R300	26	59.88	34.35	1	30.75	73	88.75	100
	R600	26	71.08	31.32	0	61	78	100	100
ARCI MBG	A1.5	26	5.85	4.34	0	2	5	9.5	16
	A3	26	6.81	4.35	1	3	6	9.25	15
	P	26	1.00	1.88	-1	0	1	1	9
	R300	26	4.96	5.90	-2	0	1.5	11	16
	R600	26	5.76	4.99	-2	1	5	10	16

From Table 1, one may find that R600 had score 100 for Q_3 for both Drug Liking VAS and Take Drug Again. The Q_3 of R600 was larger than that of both doses of the positive control drug on the primary measures except Overall Drug Liking VAS.

Figures 1-4 shows the mean time course profiles for Drug Liking VAS, Overall Drug Liking VAS, Take Drug Again, and ARCI MBG. Because responses to Overall Drug Liking VAS, and Take Drug Again VAS were collected at hours 6, 12, and 24 only, bar charts were used for the mean responses on these two measures. For the graphs of Drug Liking VAS and ARCI MBG, each point on a graph was calculated by averaging responses to the particular primary measure by treatment at a particular time point. This is the graph that most sponsors like to present to the FDA. The disadvantage of the graph is that each subject may reach the highest response at different time point. By averaging responses at each time point by treatment, the peak value of the mean responses for each treatment may be substantially lower than the mean of Emax of the treatment, which is the main interest of the CSS. Nevertheless, such a graph, for a primary measure, shows the mean time course profiles from all treatments in the study.

Figure 1 shows that both the peak mean responses of R300 and R600 were higher than that of both doses of the positive control drug. The peak mean responses of R300 and R600 reached at hour 1 and hour 2, respectively. At hours 12 and 24, the mean response of R600 was still larger than that of both doses of the positive control drug.

Figure 1: Mean Time Course Profiles for Drug Liking VAS

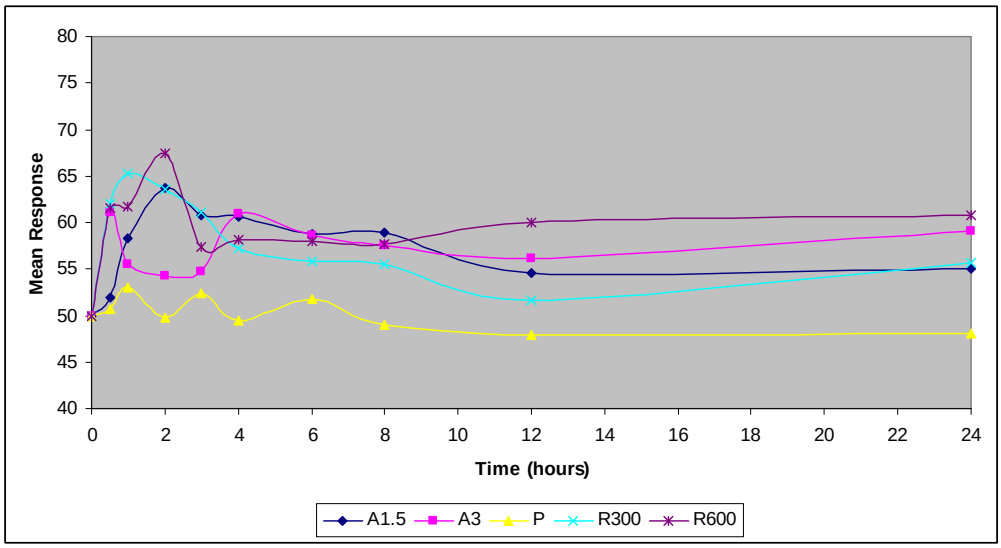


Figure 2 shows the mean time course profiles for Overall Drug Liking VAS. The data were collected at hours 6, 12, and 24 on this measure. R600 had very similar mean response to both A1.5 and A3 at hours 6, 12. At hour 24, the mean response to A3 was higher than that of R600. Although the mean response to R300 was not as large as R600, the mean response of R300 was higher than that of placebo.

Figure 2: Mean Time Course Profiles for Overall Drug Liking VAS

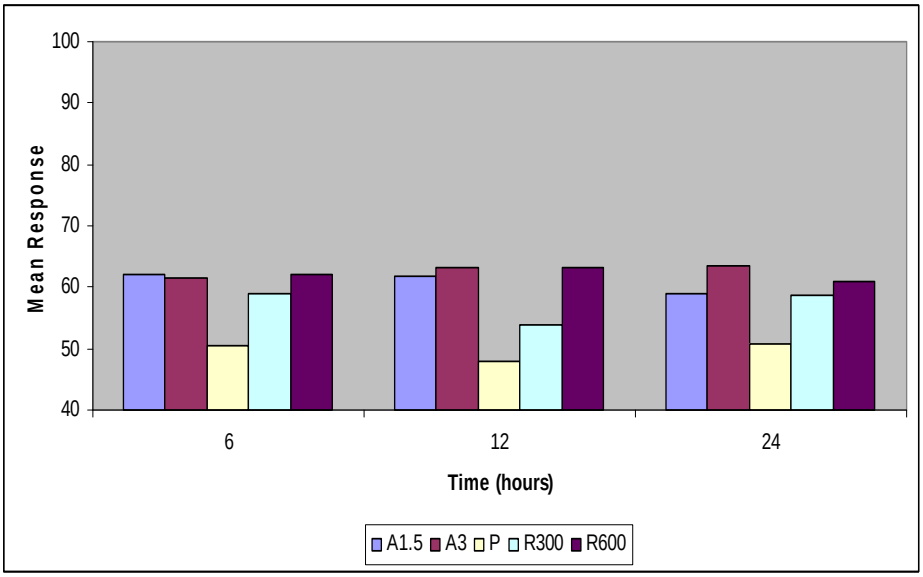


Figure 3 shows that the mean response of R600 on Take Drug Again VAS was higher than that of both A1.5 and A3 at hours 6 and 12. Although the mean response to R300 was less than both

doses of the positive control drug, the mean response of R300 was much greater than that of placebo.

Figure 3: Mean Time Course Profiles for Take Drug Again VAS

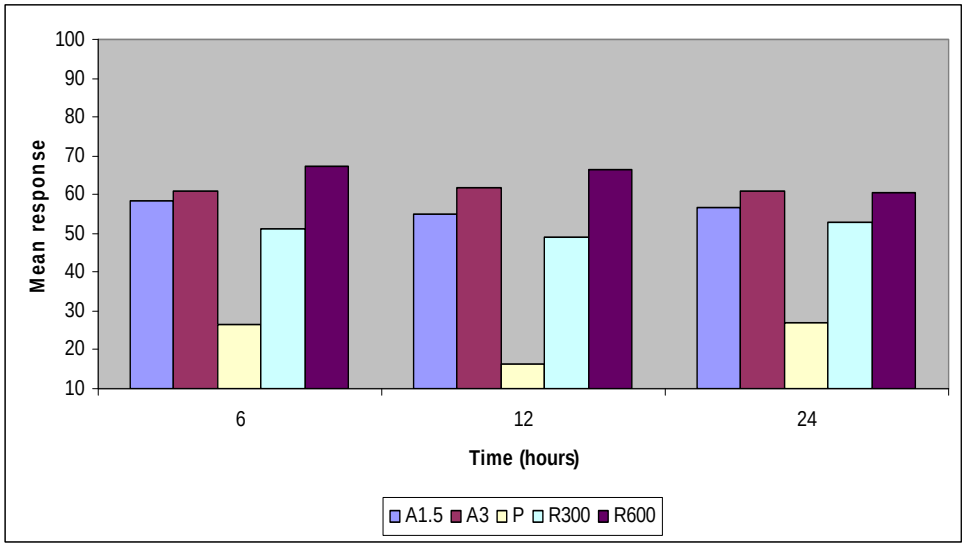
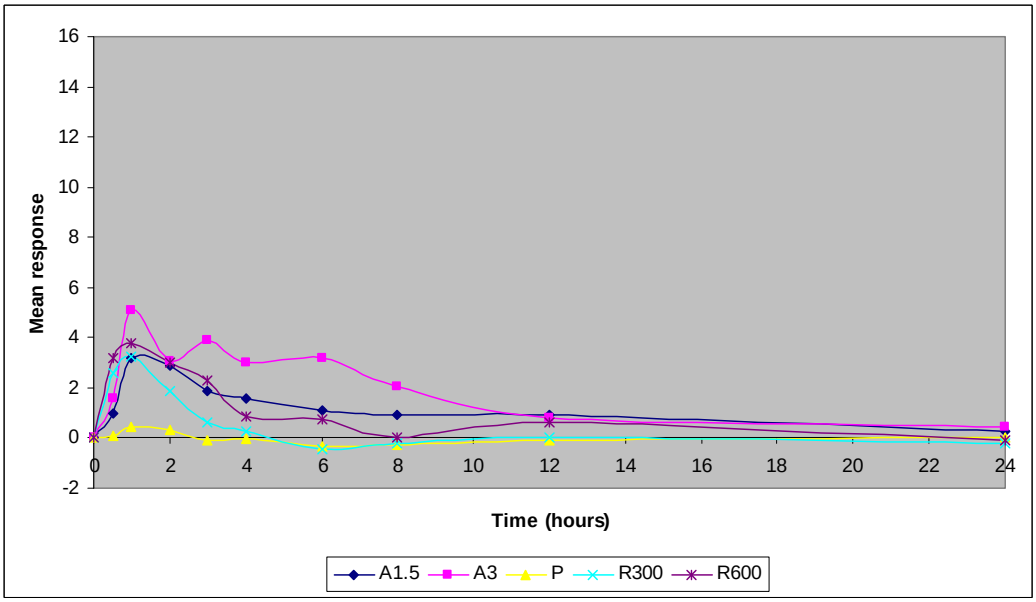


Figure 4 shows the mean time course profiles for ARCI MBG. The peak mean responses from A1.5, A3, R300 and R600 were all reached at hour 1. Although the peak mean responses of R300 and R600 were only different from the peak mean response of A3 by less than 2 units, the mean responses of R300 and R600 dropped down within 3-4 hours. However, the mean response of A3 remains between score 3 and 5 during hours 1 – 8, and were higher than any of the other treatments in this time period.

Figure 4: Mean Time Course Profiles for ARCI MBG



Notice that the summary statistics and the graphics did not take into account the possible effects due to treatment periods and sequences used in the crossover design study.

2.3.2 Statistical testing

2.3.2.1 Study model and contrasts of interest

The statistical model used in the reviewer's analysis includes sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. The model assumption of the normality of error terms was checked using the Shapiro-Wilk W-test on the residuals. If the normal assumption was not satisfied, the rank data (ranking within subject) were used to obtain the p-value of the test for difference in medians between two treatments.

2.3.2.2 Results

Table 2 lists the least square mean and corresponding standard error of responses to each primary measure, and each treatment in this study.

Table 2: Estimation for Mean of Emax on Primary Measures for Individual Treatments

Abuse potential Measure	TRT	N	LSmean	StdErr
Drug Liking VAS	A1.5	26	74.70	3.50
	A3	26	78.79	3.32
	P	26	54.73	3.68
	R300	26	70.79	3.62
	R600	26	77.03	3.38
ARCI MBG	A1.5	26	5.80	0.87
	A3	26	6.58	0.83
	P	26	1.03	0.92
	R300	26	4.57	0.90
	R600	26	5.70	0.85
Overall Drug Liking VAS	A1.5	26	67.16	4.40
	A3	26	71.57	4.19
	P	26	52.74	4.62
	R300	26	62.63	4.54
	R600	26	70.20	4.26
Take Drug Again VAS	A1.5	26	66.22	6.76
	A3	26	67.97	6.46
	P	26	35.93	7.07
	R300	26	57.06	6.96
	R600	26	69.09	6.56

Table 3 gives the W test statistic and the p-value of the W test for normality of the residual.

Table 3: Normality Test Results on Residuals for the Primary Endpoints

Abuse Potential Measure	N	W Statistic	p-Value
ARCI MBG	26	0.99367	0.7364
Drug Liking VAS	26	0.99534	0.9059
Overall Drug Liking VAS	26	0.97196	0.0029
Take Drug Again VAS	26	0.97101	0.0023

Tables 4 and 5 list the results from this reviewer's statistical analysis for the primary endpoints. Because p-values of the W- test were 0.0029 and 0.0023 for Overall Drug Liking VAS and Take Drug Again VAS, a rank analysis was performed by this reviewer for these two primary measures. For these two primary measures the difference of the least square means and standard error in the original scale, and p-value from the rank-test are listed in Table 5.

Table 4: Treatment Comparisons for ARCI MBG and Drug Liking VAS (Normality Assumption was Satisfied)

Abuse Potential Measure	TRT1	TRT2	LSmean Diff	StdErr	p-Value	95% CI	
						Lower	Upper
ARCI MBG	A1.5	P	4.76	1.02	<.0001	2.75	6.78
	A3	P	5.55	1.09	<.0001	3.39	7.72
	A1.5	R300	1.23	1.17	0.2958	-1.09	3.55
	A1.5	R600	0.10	1.08	0.9295	-2.05	2.24
	A3	R300	2.02	1.05	0.0564	-0.06	4.09
	A3	R600	0.88	1.02	0.387	-1.13	2.90
	P	R300	-3.53	1.25	0.0056	-6.01	-1.06
	P	R600	-4.67	1.12	<.0001	-6.88	-2.46
Drug Liking VAS	A1.5	P	19.97	4.15	<.0001	11.76	28.18
	A3	P	24.06	4.44	<.0001	15.26	32.85
	A1.5	R300	3.91	4.75	0.4123	-5.50	13.32
	A1.5	R600	-2.33	4.39	0.5961	-11.02	6.36
	A3	R300	8.00	4.26	0.0627	-0.43	16.43
	A3	R600	1.76	4.10	0.6691	-6.36	9.88
	P	R300	-16.06	4.95	<.0001	10.99	30.61
	P	R600	-22.30	4.11	0.2514	-3.40	12.89

Table 5: Treatment Comparisons for Overall Drug Liking VAS and Take Drug Again VAS (Normality Assumption was not Satisfied)

Abuse Potential Measure	TRT1	TRT2	LSmean Diff	StdErr	p-Value
Overall Drug Liking VAS	A1.5	P	14.42	5.05	<.0001
	A3	P	18.83	5.41	<.0001
	A1.5	R300	4.53	5.79	0.6018
	A1.5	R600	-3.03	5.35	0.2861
	A3	R300	8.94	5.19	0.172
	A3	R600	1.38	5.00	0.7443
	P	R300	-9.89	6.18	0.0025
	P	R600	-17.45	5.52	<.0001
Take Drug Again VAS	A1.5	P	30.29	7.49	<.0001
	A3	P	32.05	8.02	<.0001
	A1.5	R300	9.16	8.59	0.1594
	A1.5	R600	-2.87	7.93	0.8226
	A3	R300	10.91	7.69	0.1539
	A3	R600	-1.11	7.41	0.9291
	P	R300	-21.14	9.17	0.0079
	P	R600	-33.16	8.19	<.0001

From Tables 4 and 5, one may see that at α=0.05 (two-sided)

- Two doses of positive control drug, alprazolam 1.5 mg and 3 mg, had significantly higher mean (or median) response than placebo. That is, both doses of positive control drug validated the study;
- There was no significant difference in means (or medians) between both doses of retigabine and any dose of alprazolam;
- The means (medians) of both doses of retigabine were significantly higher than that of placebo.

2.4 Reviewer's Secondary analysis

The secondary analyses on other seven abuse potential measures Good Effects VAS, Bad Effects VAS, Any Drug Effects VAS, High VAS, ARCI Amphetamine (A), ARCI LSD and ARCI PCAG, were conducted using the same statistical methodologies as the primary analysis.

2.4.1 Descriptive statistics on the secondary measures

The descriptive statistics on Emaxs of the seven secondary abuse potential measures are presented in Table 6.

Table 6: Summary Statistics for the Secondary Abuse Potential Measures of Interest

Abuse Potential Measure	TRT	N	Mean	Std	Min	Q1	Med	Q3	Max
Any Drug Effects VAS	A1.5	26	84.81	20.08	11	75.5	89.5	100	100
	A3	26	92.62	11.04	65	88.5	99	100	100
	P	26	28.38	31.92	0	0	8	61.5	100
	R300	26	77.27	23.86	21	65	73.5	100	100
	R600	26	82.73	21.63	15	67.5	93	100	100
ARCI Amphetamine (A)	A1.5	26	3.19	2.71	0	1	2	5	11
	A3	26	3.85	2.99	0	1.75	3.5	6	10
	P	26	0.77	0.82	0	0	1	1.25	2
	R300	26	2.96	3.83	-1	0	1	6	11
	R600	26	3.28	2.70	0	1	2	5	11
ARCI LSD	A1.5	26	3.46	2.00	0	1.75	3.5	5.25	7
	A3	26	4.00	1.60	0	3	4	5	7
	P	26	1.23	1.66	-1	0	1	2	6
	R300	26	2.54	2.45	-1	0	2	4	8
	R600	26	4.08	2.69	1	1.5	4	6.5	10
ARCI Pent. Chlorpromazine Alcohol (PCAG)	A1.5	26	7.96	2.81	2	6	9	10	13
	A3	26	8.92	2.58	2	7	9	11	13
	P	26	1.08	1.26	0	0	1	2	4
	R300	26	5.23	3.30	0	3	5	8	11
	R600	26	5.60	3.38	1	2.5	5	9	12
Bad Drug Effects VAS	A1.5	26	45.27	31.00	0	9.75	50	65.25	100
	A3	26	65.65	25.41	1	50	71	84.25	100
	P	26	25.12	27.97	0	0	5	50.25	75
	R300	26	36.46	27.57	0	13.5	39	54.25	100
	R600	26	53.27	26.15	3	45.25	51	68.25	100
Good Drug Effects VAS	A1.5	26	73.73	25.82	3	64.5	78	90	100
	A3	26	81.35	19.85	36	66.75	88	100	100
	P	26	27.04	29.98	0	0.75	15	51.75	100
	R300	26	72.23	23.90	8	57.75	72	99.25	100
	R600	26	82.27	17.53	50	70	84.5	100	100
High VAS	A1.5	26	75.08	27.62	5	66.5	80.5	98	100
	A3	26	86.31	15.17	50	75.75	92.5	100	100
	P	26	18.96	26.84	0	0	4	49	90
	R300	26	66.77	28.46	0	55.25	68.5	86.5	100
	R600	26	80.08	20.53	48	60.75	83.5	100	100

2.4.2 Statistical testing

The least square means and corresponding standard errors of responses to each measure are listed in Table 7.

Table 7: Estimation of Mean of Emax on the Secondary Abuse Potential Measures for Individual Treatments

TRT	ARCI A		ARCI LSD		ARCI PCAG	
	LSmean	StdErr	LSmean	StdErr	LSmean	StdErr
A1.5	3.26	0.53	3.47	0.46	7.77	0.60
A3	3.67	0.51	3.99	0.43	8.94	0.56
P	0.95	0.56	1.18	0.48	0.64	0.63
R300	2.61	0.55	2.57	0.47	5.49	0.62
R600	3.26	0.52	4.12	0.45	5.42	0.58

TRT	Any Drug Effects		Bad Drug Effects		Good Drug Effects		High	
	LSmean	StdErr	LSmean	StdErr	LSmean	StdErr	LSmean	StdErr
A1.5	85.12	4.72	43.85	5.96	75.22	4.87	74.77	5.05
A3	93.30	4.41	66.95	5.62	81.19	4.61	86.48	4.75
P	29.15	5.03	22.63	6.30	29.51	5.14	19.91	5.35
R300	76.57	4.92	40.70	6.18	69.92	5.04	65.45	5.24
R600	82.55	4.50	55.23	5.73	82.10	4.69	80.24	4.84

Before conducting statistical testing, the Shapiro-Wilk W-test was performed for each endpoint. Table 8 lists the test results.

Table 8: Results from W-Test

Abuse Potential Measure	W Test Statistic	p-Value
ARCI Amphetamine (A)	0.98817	0.2149
ARCI LSD	0.96856	0.0013
ARCI Pent. Chlorpromazine Alcohol (PCAG)	0.9905	0.3851
Any Drug Effects VAS	0.96725	0.0009
Bad Drug Effects VAS	0.98689	0.1500
Good Drug Effects VAS	0.99114	0.4426
High VAS	0.98217	0.0415

Based on the results from Table 8, a rank-test was conducted on measures ARCI LSD, Any Drug Effects VAS, and High VAS in the comparisons among treatments. In these cases, least square means and standard errors are reported on the original scale.

Tables 9 and 10 are the analysis results for the secondary abuse potential measures of interest.

Table 9: Treatment Comparisons for Secondary Abuse Potential Measures of Interest (Normality Assumption was Satisfied)

Abuse Potential Measure	TRT1	TRT2	LSmean Diff	StdErr	p-Value	95% CI	
						Lower	Upper
ARCI Amphetamine (A)	A1.5	P	2.31	0.61	0.0002	1.10	3.52
	A3	P	2.72	0.65	<.0001	1.42	4.01
	A1.5	R300	0.65	0.70	0.357	-0.74	2.04
	A1.5	R600	0.00	0.65	0.9954	-1.28	1.29
	A3	R300	1.05	0.63	0.0955	-0.19	2.30
	A3	R600	0.41	0.61	0.5037	-0.80	1.62
	P	R300	-1.66	0.75	0.0286	-3.15	-0.18
	P	R600	-2.31	0.67	0.0008	-3.63	-0.98
ARCI Pent. Chlorpromazine Alcohol (PCAG)	A1.5	P	7.13	0.72	<.0001	5.71	8.54
	A3	P	8.29	0.77	<.0001	6.77	9.81
	A1.5	R300	2.29	0.82	0.0063	0.66	3.92
	A1.5	R600	2.36	0.76	0.0024	0.85	3.86
	A3	R300	3.45	0.74	<.0001	1.99	4.91
	A3	R600	3.52	0.71	<.0001	2.10	4.93
	P	R300	-4.84	0.88	<.0001	-6.58	-3.10
	P	R600	-4.77	0.78	<.0001	-6.33	-3.22
Bad Drug Effects VAS	A1.5	P	-3.18	0.54	0.005	6.54	35.89
	A3	P	-3.36	0.64	<.0001	28.59	60.04
	A1.5	R300	-1.14	0.62	0.7115	-13.68	19.98
	A1.5	R600	-1.06	0.57	0.1497	-26.92	4.16
	A3	R300	-1.32	0.60	0.0008	11.18	41.33
	A3	R600	-1.24	0.59	0.1125	-2.79	26.24
	P	R300	2.03	0.66	0.0488	-36.03	-0.09
	P	R600	2.12	0.58	0.0001	-48.64	-16.55
Good Drug Effects VAS	A1.5	P	45.71	5.92	<.0001	33.99	57.43
	A3	P	51.68	6.34	<.0001	39.12	64.23
	A1.5	R300	5.29	6.79	0.437	-8.14	18.73
	A1.5	R600	-6.88	6.27	0.2742	-19.29	5.52
	A3	R300	11.26	6.08	0.0664	-0.77	23.30
	A3	R600	-0.91	5.85	0.8763	-12.51	10.68
	P	R300	-40.42	7.25	<.0001	-54.76	-26.07
	P	R600	-52.59	6.47	<.0001	-65.40	-39.78

Table 10: Treatment Comparisons for Secondary Abuse Potential Measures of Interest (Normality Assumption was not Satisfied)

Abuse Potential Measure	TRT1	TRT2	LSmean Diff	StdErr	p-Value (Rank)
ARCI LSD	A1.5	P	2.29	0.57	0.0004
	A3	P	2.82	0.61	<.0001
	A1.5	R300	0.90	0.65	0.126
	A1.5	R600	-0.65	0.60	0.1688
	A3	R300	1.43	0.58	0.0009
	A3	R600	-0.13	0.57	0.7924
	P	R300	-1.39	0.69	0.1245
	P	R600	-2.94	0.62	<.0001
Any Drug Effects VAS	A1.5	P	55.96	6.33	<.0001
	A3	P	64.15	6.78	<.0001
	A1.5	R300	8.55	7.25	0.0782
	A1.5	R600	2.57	6.70	0.9203
	A3	R300	16.73	6.50	0.0003
	A3	R600	10.75	6.26	0.099
	P	R300	-47.42	7.75	<.0001
	P	R600	-53.40	6.92	<.0001
High VAS	A1.5	P	54.86	6.43	<.0001
	A3	P	66.57	6.89	<.0001
	A1.5	R300	9.32	7.37	0.427
	A1.5	R600	-5.47	6.80	0.3118
	A3	R300	21.02	6.60	0.0012
	A3	R600	6.23	6.36	0.1508
	P	R300	-45.54	7.87	<.0001
	P	R600	-60.33	7.03	<.0001

From Tables 4 and 5, one may see that at α=0.05 (two-sided)

- Two doses of positive control drug alprazolam 1.5 mg and 3 mg had significantly higher mean (median) response than placebo for all abuse potential measures considered in this reviewer's secondary analysis. That is, the positive control drugs validated the study for the seven measures.

- Both doses of retigabine had significantly higher mean (or median) response than placebo except for the comparison of medians between retigabine 300 mg and placebo on ARCI LSD.

- There was no significant difference in mean (or median) response between retigabine 300 mg and alprazolam 3 mg on measures ARCI Amphetamine (A), and Good Drug Effects VAS.

- For Bad Drug Effects VAS, Any Drug Effects VAS, High VAS and ARCI LSD, alprazolam 3 mg had significantly higher mean (or median) response than retigabine 300 mg.

- Two doses of alprazolam had significantly higher mean response than any dose of retigabine on ARCI PCAG.

- There was no significant difference in mean (or median) between alprazolam 1.5 mg and any dose of retigabine, or between alprazolam 3 mg and retigabine 600 mg on any secondary measures in this reviewer's analysis except ARCI PCAG.

3. Conclusions

Total of 11 measures were used in the evaluation of human abuse potential of retigabine. Table 11 summarizes the analysis results.

Table 11: Summary for Comparisons among Treatments (α=0.05, two-sided)

Abuse Potential Measure	A1.5 vs P	A3 vs P	A1.5 vs R300	A1.5 vs R600	A3 vs R300	A3 vs R600	P vs R300	P vs R600	
Drug Liking VAS	S (>)	S (>)	NS	NS	NS	NS	S (<)	S (<)	Primary
Overall Drug Liking VAS	S (>)	S (>)	NS	NS	NS	NS	S (<)	S (<)	
Take Drug Again VAS	S (>)	S (>)	NS	NS	NS	NS	S (<)	S (<)	
ARCI MBG	S (>)	S (>)	NS	NS	NS	NS	S (<)	S (<)	
Any Drug Effects VAS	S (>)	S (>)	NS	NS	S (>)	NS	S (<)	S (<)	Secondary
Good Drug Effects VAS	S (>)	S (>)	NS	NS	NS	NS	S (<)	S (<)	
Bad Drug Effects VAS	S (>)	S (>)	NS	NS	S (>)	NS	S (<)	S (<)	
High VAS	S (>)	S (>)	NS	NS	S (>)	NS	S (<)	S (<)	
ARCI Amphetamine (A)	S (>)	S (>)	NS	NS	NS	NS	S (<)	S (<)	
ARCI LSD	S (>)	S (>)	NS	NS	S (>)	NS	NS	S (<)	
ARCI PCAG	S (>)	S (>)	S (>)	S (>)	S (>)	S (>)	S (<)	S (<)	

Note: S: significant; NS: not significant.

In comparison TRT 1vs TRT2, S (>) means that the mean (or median) of TRT1 is significantly higher than that of TRT2, and S (<) means that the mean (or median) of TRT1 is significantly less than that of TRT2.

Based on the study results, this reviewer concluded that the human abuse potential of the new drug, retigabine, appears similar to the positive control drug alprazolam.

Appendix:

Per pharmacologist Dr. Bonson's request, this reviewer also generated following three Tables. The interpretation of the results, please see Dr. Bonson's report.

Table 12: Estimation for Mean of Emax of Change from Predose Responses on Additional Measures for Individual Treatments

Abuse Potential Measure	TRT	LSMean	StdErr	Abuse Potential Measure	TRT	LSMean	StdErr
Dizziness	A1.5	57.62	5.75	CRT all options, all TRT mean msec	A1.5	241.85	28.96
	A3	78.19	5.47		A3	310.65	27.69
	P	12.50	6.05		P	56.74	30.28
	R300	42.48	5.94		R300	52.81	29.79
	R600	50.54	5.63		R600	72.36	28.43
Drowsy	A1.5	0.92	0.08	CRT all options, right TRT% correct	A1.5	1.66	0.85
	A3	0.92	0.07		A3	-1.46	0.80
	P	0.09	0.08		P	2.09	0.91
	R300	0.70	0.08		R300	0.25	0.89
	R600	0.71	0.08		R600	1.21	0.83
Floating	A1.5	65.88	5.57	Mean of 3 flights false alarms	A1.5	2.60	0.53
	A3	75.87	5.22		A3	3.83	0.51
	P	17.68	5.92		P	0.64	0.55
	R300	48.59	5.79		R300	1.47	0.54
	R600	56.23	5.42		R600	1.42	0.52
Pleasant Mental State	A1.5	13.69	3.42	Mean of 3 flights Hits	A1.5	-0.06	0.28
	A3	15.56	3.22		A3	-0.79	0.26
	P	14.74	3.62		P	0.56	0.30
	R300	14.98	3.54		R300	-0.06	0.30
	R600	19.50	3.33		R600	0.29	0.27
Pleasant Physical State	A1.5	15.53	3.29	Mean of 3 flights Misses	A1.5	6.32	0.52
	A3	12.21	3.08		A3	7.95	0.49
	P	11.08	3.50		P	1.29	0.55
	R300	13.32	3.42		R300	1.19	0.54
	R600	18.61	3.20		R600	1.17	0.51

Table 13: Treatment Comparisons for Additional VAS Measures of Interest on Emax of Change from Predose Response

Abuse Potential Measure	TRT1	TRT2	LSMean Diff	StdErr	p-Value
Dizziness	A1.5	P	45.12	6.68	<.0001
	A3	P	65.69	7.17	<.0001
	A1.5	R300	15.14	7.68	0.0509
	A1.5	R600	7.08	7.10	0.3208
	A3	R300	35.72	6.86	<.0001
	A3	R600	27.65	6.67	<.0001
	P	R300	-29.98	8.20	0.0004
	P	R600	-38.04	7.32	<.0001
Drowsy VAS	A1.5	P	0.82	0.10	<.0001
	A3	P	0.83	0.11	<.0001
	A1.5	R300	0.21	0.11	0.0445
	A1.5	R600	0.21	0.11	0.0335
	A3	R300	0.22	0.10	0.0243
	A3	R600	0.22	0.10	0.0231
	P	R300	-0.61	0.12	<.0001
	P	R600	-0.61	0.11	<.0001
Floating VAS	A1.5	P	48.20	7.23	<.0001
	A3	P	58.19	7.75	<.0001
	A1.5	R300	17.29	8.31	0.0748
	A1.5	R600	9.65	7.68	0.2468
	A3	R300	27.28	7.43	0.0011
	A3	R600	19.64	7.22	0.01
	P	R300	-30.91	8.87	0.0001
	P	R600	-38.55	7.92	<.0001
Pleasant Mental State VAS	A1.5	P	-1.04	4.30	0.9185
	A3	P	0.82	4.61	0.634
	A1.5	R300	-1.29	4.94	0.2829
	A1.5	R600	-5.80	4.57	0.4707
	A3	R300	0.58	4.41	0.5442
	A3	R600	-3.94	4.29	0.1683
	P	R300	-0.24	5.27	0.3563
	P	R600	-4.76	4.71	0.4281
Pleasant Physical State VAS	A1.5	P	4.44	4.27	0.2111
	A3	P	1.13	4.58	0.4632
	A1.5	R300	2.21	4.91	0.2312
	A1.5	R600	-3.08	4.54	0.506
	A3	R300	-1.10	4.39	0.3751
	A3	R600	-6.40	4.26	0.2407
	P	R300	-2.24	5.24	0.9187
	P	R600	-7.53	4.68	0.0754

Note: Only p-value on Dizziness VAS is from t-test. The other p-values are from rank test.

Table 14: Treatment Comparisons for CRT and AD Measures of Interest on Emax of Change from Predose Response

Abuse Potential Measure	TRT1	TRT2	LSMean Diff	StdErr	p-Value
CRT all options, all TRT mean msec	A1.5	P	185.11	31.6792	<.0001
	A3	P	253.92	33.9827	<.0001
	A1.5	R300	189.04	36.411	<.0001
	A1.5	R600	169.49	33.6905	<.0001
	A3	R300	257.85	32.5551	<.0001
	A3	R600	238.3	31.6568	<.0001
	P	R300	3.9314	38.9014	0.7585
	P	R600	-15.6181	34.7409	0.2318
CRT all options, right TRT % correct	A1.5	P	-0.4302	1.1372	<.0001
	A3	P	-3.5501	1.2197	<.0001
	A1.5	R300	1.4085	1.3067	<.0001
	A1.5	R600	0.4443	1.2089	<.0001
	A3	R300	-1.7114	1.1685	<.0001
	A3	R600	-2.6756	1.1353	<.0001
	P	R300	1.8387	1.396	0.0075
	P	R600	0.8745	1.2467	0.1365
Mean of 3 flights False Alarms	A1.5	P	1.9676	0.5567	<.0001
	A3	P	3.1884	0.5973	<.0001
	A1.5	R300	1.1387	0.6401	<.0001
	A1.5	R600	1.1894	0.5922	<.0001
	A3	R300	2.3595	0.5721	<.0001
	A3	R600	2.4101	0.5564	<.0001
	P	R300	-0.8289	0.6838	0.1729
	P	R600	-0.7782	0.6106	0.1597
Mean of 3 flights Hits	A1.5	P	-0.6213	0.3791	<.0001
	A3	P	-1.3473	0.4067	<.0001
	A1.5	R300	-0.00651	0.4358	<.0001
	A1.5	R600	-0.3563	0.4031	<.0001
	A3	R300	-0.7324	0.3896	<.0001
	A3	R600	-1.0822	0.3785	<.0001
	P	R300	0.6148	0.4655	0.1654
	P	R600	0.265	0.4157	0.9197
Mean of 3 flights Misses	A1.5	P	5.0276	0.6794	<.0001
	A3	P	6.6578	0.7289	<.0001
	A1.5	R300	5.126	0.781	<.0001
	A1.5	R600	5.1458	0.7225	<.0001
	A3	R300	6.7561	0.6981	<.0001
	A3	R600	6.7759	0.6784	<.0001
	P	R300	0.09833	0.8343	0.1859
	P	R600	0.1181	0.745	0.9913

Note: All p-values are from rank test.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22345	ORIG-1	VALEANT PHARMACEUTICALS NORTH AMERICA	RETIGABINE

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/s/

LING CHEN
04/23/2010

STELLA G MACHADO
04/23/2010

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA 22-345
Drug Name:	POTIGA
Indication(s):	Partial seizures in adults
Applicant:	Valeant Pharmaceuticals North America
Date of Document:	October 30, 2009
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 1 (HFD-710)
Statistical Reviewer:	Ohidul Siddiqui, Ph.D
Medical Reviewer:	Steven Dinsmore, MD
Concurring Reviewers:	Kun Jin, Ph.D; James Hung, Ph.D
Medical Division:	HFD-120
Clinical Team:	Norman Hershkowitz MD, PhD
Project Manager:	Stephanie Keefe

Keywords: *NDA review, endpoint analysis/LOCF, multi-center*

Table of Contents

1. EXECUTIVE SUMMARY

The sponsor submitted findings of three adequate and well-controlled studies to demonstrate effectiveness of retigabine in treating patients with partial-onset epilepsy. Among the three studies, there are two Phase III studies (Studies 301 and 302) and one Phase IIB study (Study 205). All the three studies were international, multicenter, parallel-group randomized, and double-blind placebo-controlled studies.

1.1. Conclusions and Recommendations

With respect to the primary endpoint- percent change from baseline in 28-day total partial seizure frequency during the double-blind phase in the ITT double-blind population and also in the ITT Maintenance phase, retigabine demonstrated its significant efficacy in each of the three studies. In Study 205, retigabine at 900 mg/day and 1200 mg/day were statistically superior to placebo. The statistical significances of retigabine at 900 mg/day and 1200 mg/day were confirmed in Studies 301 and 302.

Although Retigabine 600 mg/day had a numerically greater median percent change from baseline than the change for placebo, it was not statistically significant from placebo in Study 205. However, retigabine 600 mg/day was statistically superior to placebo in Study 302.

There was also an evidence of increasing efficacy with retigabine doses in the cumulative distribution profile for percent change in total partial seizure frequency across the double-blind phase.

Retigabine at 600 mg/day and 900 mg/day (in Study 302) and 1200 mg/day (in Studies 205 and 301) also demonstrated its significant effects with respect to responder rate (the proportion of patients with a ≥50% reduction in 28-day total partial seizure frequency in the ITT maintenance population) during the maintenance phase.

The dropout rates during the double-blind phase in the three studies were relatively high (in a range from 17% to 42%). The sensitivity analyses indicate that the dropout rates have no impact on the efficacy of the doses. That is, the efficacy of each dose remained significant in the sensitivity analyses.

1.2. Brief Overview of Reviewed Clinical Studies

Pivotal Studies

Study 205 was a phase IIb, randomized, double-blind, placebo-controlled, multicenter, dose-ranging study of retigabine (600, 900 and 1200 mg/day) in patients (age 16 to 70 years) with partial-onset seizures. The study consisted of four phases: an 8-week prospective Baseline Phase during which patients were evaluated for seizure frequency, an 8-week Titration Phase to the final targeted randomized dose and an 8-week Maintenance Phase during which patients received

a fixed dose regimen. After completing the double-blind phase, patients could enroll in a long term, open-label, extension study, after a 5-week interim phase of dose adjustment.

Studies 301 and 302 were Phase III studies for assessing the efficacy and safety of retigabine in patients (aged 18 to 75 years) with refractory partial epilepsy. Both were randomized, double blind, placebo-controlled, multi-center, parallel-group studies with similar inclusion and exclusion criteria. Study 301 included assessment of retigabine (1200 mg/day; 400 mg TID) compared with placebo. Study 302 included assessment of retigabine 900 mg/day (300 mg TID) and retigabine 600 mg/day (200 mg TID) compared with placebo. There was an 8-week prospective Baseline Phase and patients were evaluated for seizure frequency, followed by a Titration Phase during which the retigabine dose was increased by 150 mg/week (50 mg TID) [up to 4 weeks in Study 302 and 6 weeks in Study 301]. At the end of the titration period, patients were maintained on a fixed dose for a 12-week Maintenance Period (Figures 2 and 3). In Study 301, patients had a single opportunity to down titrate to 1050 mg/day at the end of Week 7, if they were unable to tolerate the targeted retigabine dose (1200 mg/day). Patients who down-titrated were then to continue at 1050 mg/day for the remainder of the maintenance period. Efficacy data were reported based on the assigned randomized dose and not the actual dose received.

In each of the three studies, the primary endpoint was the percent change in the 28-day total partial seizure frequency occurring between baseline and the double-blind phase ((including all titration and maintenance phase data). The primary analysis was a non-parametric stratified rank analysis of covariance (ANCOVA) to compare the percent change in total partial seizure frequency of the retigabine and placebo treatment groups. Each of the studies demonstrated significant efficacy of retigabine in treating patients with partial-onset epilepsy.

1.3 Statistical Issues and Findings

There was no statistical issue in each of the three studies.

2. INTRODUCTION

2.1. Overview

In this submission, effectiveness of retigabine is claimed based on three adequate and well-controlled studies (N=1244) in patients with partial-onset epilepsy. Among the three studies, there are two Phase III studies (Studies 301 and 302) and one Phase IIB study (Study 205). All the three studies were international, multicenter, parallel-group randomized, double-blind, placebo-controlled studies.

Table 1 lists an overview of the submitted studies. The phase IIb study 205 was designed to assess the efficacy and safety of retigabine 600 mg/day (200 mg three times daily [TID]), 900 mg/day (300 mg TID), and 1200 mg/day (400 mg TID). The study also provides the primary dose-response data. The efficacy of 600 mg/day to 1200 mg/day was assessed in Phase III studies 301 (1200 mg/day) and 302 (600 mg/day and 900 mg/day). In the three studies, patients with partial onset seizures (simple partial seizures and/or complex partial seizures with or without secondary generalization) were recruited.

Table 1: Overview of the three studies.

	Study 205	**Study 301**	**Study 302**
Phase/Sponsor	IIb/Wyeth	III/Valeant	III/Valeant
Treatment Group	600, 900, 1200 mg/day, PBO	1200 mg/day, PBO	600, 900 mg/day, PBO
Dosage Forms Used	50 mg, 100 mg or 200 mg IR capsules (note: 600 mg dose = 2X100 mg capsule TID; 900 mg dose = 3X100 mg capsule TID; 1200 mg dose = 1X 200 mg and 2X 100 mg capsule TID)	50 mg, 100 mg, 300 mg IR tablets (note: 1200 mg dose = 1X 300 mg tablet and 2X 50 mg tablets TID)	50 mg and 100 mg IR tablets (note: 300 mg dose = 3X 100 mg tablets TID)
Duration of Double-blind	16 weeks	18 weeks	16 weeks
Duration of Titration	8 weeks	6 weeks	4 weeks
Duration of Maintenance	8 weeks	12 weeks	12 weeks
Countries	Australia, Belgium, Croatia, Czech Republic, Finland, France, Germany, Israel, Italy, Netherlands, New Zealand, Norway, Poland Portugal ,Slovakia, Spain, Sweden, UK, and US	Argentina, Brazil Canada, Mexico, and US	Australia, Belgium, France, Germany, Hungary, Israel, Poland, Russia, S Africa, Spain, UK Ukraine, and US

Source: Individual study reports

2.2. Data Sources

SAS data sets of the pivotal studies and study reports are available at \\Cdsesub1\evsprod\NDA022345\0000\.

3. STATISTICAL EVALUATION

3.1. Study reviewed

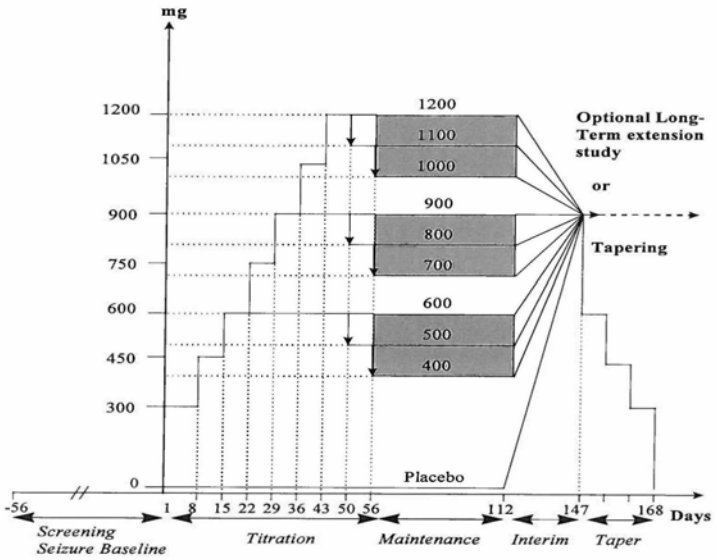
In this statistical review, the efficacy findings of the three studies (Studies 205, 301 and 302) are reviewed as follows.

3.1.1. Study 205

Study 205 was a phase IIb, randomized, double-blind, placebo-controlled, multicenter, dose-ranging study of retigabine (600, 900 and 1200 mg/day) in patients (age 16 to 70 years) with partial-onset seizures. The study consisted of four phases: an 8-week prospective Baseline Phase during which patients were evaluated for seizure frequency, an 8-week Titration Phase to the final targeted randomized dose and an 8-week Maintenance Phase during which patients received a fixed dose regimen. Figure 1 lists the design of the study. After completing the double-blind phase, patients could enroll in a long term, open-label, extension study, after a 5-week interim phase of dose adjustment.

The objectives of the study were to evaluate the efficacy and safety of retigabine 200 mg TID, 300 mg TID and 400 mg TID compared with placebo, when administered as add-on therapy in patients with partial epilepsy receiving one or two pre-specified AEDs.

Figure 1: Schematic design diagram of the study 205

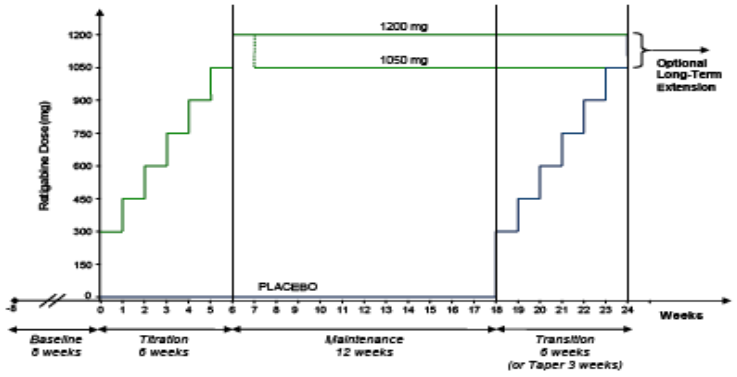


Source: Study report

3.1.2. Studies 301 and 302

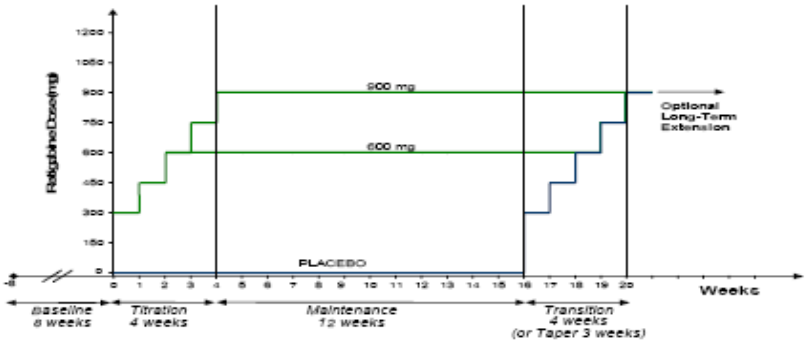
Studies 301 and 302 were Phase III studies for assessing the efficacy and safety of retigabine in patients (aged 18 to 75 years) with refractory partial epilepsy. Both were randomized, double blind, placebo-controlled, multi-center, parallel-group studies with similar inclusion and exclusion criteria. Study 301 included assessment of retigabine (1200 mg/day; 400 mg TID) compared with placebo. Study 302 included assessment of retigabine 900 mg/day (300 mg TID) and retigabine 600 mg/day (200 mg TID) compared with placebo. There was an 8-week prospective Baseline Phase during which patients were evaluated for seizure frequency, followed by a Titration Phase during which the retigabine dose was increased by 150 mg/week (50 mg TID) [up to 4 weeks in Study 302 and 6 weeks in Study 301]. At the end of the titration period, patients were maintained on a fixed dose for a 12-week Maintenance Period (Figures 2 and 3). In Study 301, patients had a single opportunity to down titrate to 1050 mg/day at the end of Week 7, if they were unable to tolerate the targeted retigabine dose (1200 mg/day). Patients who down-titrated were then to continue at 1050 mg/day for the remainder of the maintenance period. Efficacy data were reported based on the assigned randomized dose and not the actual dose received.

Figure 2. Study Design- Study 301



Source: Study report

Figure 3. Study Design- Study 302



Source: Study report

Primary and secondary efficacy variables in Studies (205, 301, 302**)**

In each of the three studies, the primary endpoint was the percent change in the 28-day total partial seizure frequency occurring between baseline and the double-blind phase (including all titration and maintenance phase data).

Secondary efficacy variables were (i) the distribution of change in seizure frequency from baseline by quartiles, (ii) the number of patients who achieve total freedom from seizures, (iii) time without seizures, (iv) potential exacerbation of pre-existing seizures or the development of new seizure types, (v) median percent change in 28-day total seizures in the maintenance phase, and (vi) responder rate in the double-blind phase.

Analysis Population and Primary Statistical Methods

The primary efficacy analysis population consisted of the patients who received at least one dose of study drug, had a baseline seizure evaluation, and at least one seizure evaluation on-therapy.

In the study 205, a rank analysis of covariance (ANCOVA) with the rank of the percentage change in monthly total partial seizure rate as a dependent measure and the rank of baseline monthly seizure rate as a covariate and treatment and center as factors in the model. The dose-response was studied by using appropriate contrasts in the ANCOVA according to a closed test procedure.

In studies 301 and 302, the primary analysis was a non-parametric stratified rank analysis of covariance (ANCOVA) to compare the percent change in total partial seizure frequency of the retigabine and placebo treatment groups. In both studies, the analysis was stratified by geographic region [Canada / United States versus Mexico / South America in study 301, and Central/Eastern Europe versus rest of the world in study 302] and baseline seizure frequency category ($8\leq$, >8] with primary ranks of percent change in seizure frequency for all patients as the response within each stratum and the standardized rank of continuous baseline seizure rate nested within the strata as a covariate. The standardized rank is the rank (regardless of treatment) for a patient within a stratum divided by the number of patients within that stratum, plus 1.

Additional analyses of percent change in total partial seizure frequency was stratified by geographic region only, and then stratified by baseline seizure rate category only. Responder rates for the retigabine group versus the placebo group were compared using logistic regression analysis / Fisher's Exact test.

Dealing with Missing Data in Studies 205, 301 and 302

In the Studies 205, 301 and 302, the rates of 28-day total partial seizure frequency in the double blind phase or maintenance phase were calculated based on the number of total partial seizures reported during that phase. For patients who discontinued treatment prematurely, the number of seizures reported up to the treatment discontinuation before entering the taper phase was used to calculate the 28-day seizure frequency. Patients who did not have any post baseline seizure data

were excluded from the primary analysis of percent change in 28-day total partial seizure frequency.

3.1.3 Sponsor's Findings:

Patient disposition and demographics

Table 2 lists the patient disposition of each study. Withdrawals for any reason were 15% to 22% in the placebo groups, 25% to 28% in the retigabine 600 mg/day groups, 32% to 34% in the 900 mg/day groups, and 37% to 43% in the 1200 mg/day groups. Withdrawals due to adverse events were 8% to 13% in the placebo groups, 14% to 21% in the retigabine 600 mg/day groups, 22% to 26% in the 900 mg/day groups, and 27% to 31% in the 1200 mg/day groups. Withdrawal due to lack of efficacy was not common (≤4% of patients in any treatment group) and there was no clear dose relationship.

Table 2. Patient Disposition during the Double-Blind Phase (Studies 205, 301 and 302)

	Number (%) of Patients								
	Study 205				**Study 301**		**Study 302**		
	Plb	**RTG 600 mg/day**	**RTG 900 mg/day**	**RTG 1200 mg/day**	**Plb**	**RTG 1200 mg/day**	**Plb**	**RTG 600 mg/day**	**RTG 900 mg/day**
Population									
Randomized	97	101	95	106	152	154	179	181	179
ITT	96	99	95	106	152	153	179	181	178
Completed	75 (77.3)	75 (74.3)	67 (70.5)	62 (58.5)	127 (83.6)	97 (63.0)	153 (85.5)	135 (74.6)	121 (67.6)
Discontinued	21 (21.9)	28 (28.0)	32 (33.7)	45 (42.5)	26 (17.1)	56 (36.6)	27 (15.1)	46 (25.4)	56 (31.5)
Reason for Discontinuation									
Adverse Event	12 (12.5)	21 (21.0)	21 (22.1)	33 (31.1)	13 (8.6)	41 (26.8)	14 (7.8)	26 (14.4)	46 (25.8)
Unsatisfactory response-efficacy	4 (4.2)	1 (1.0)	4 (4.2)	1 (0.9)	2 (1.3)	4 (2.6)	5 (2.8)	0	0
Lost to follow-up	0	0	1 (1.1)	0	2 (1.3)	1 (0.7)	2 (1.1)	4 (2.2)	1 (0.6)
Protocol violation	3 (3.1)	3 (3.0)	0	4 (3.9)	4 (2.6)	4 (2.6)	2 (1.1)	6 (3.3)	3 (1.7)
Unrelated to study	1 (1.0)	2 (2.0)	4 (4.2)	4 (3.9)	1 (0.7)	0	1 (0.6)	5 (2.8)	3 (1.7)
Other event	1 (1.0)	1 (1.0)	2 (2.1)	3 (2.8)	4 (2.6)	6 (3.9)	3 (1.7)	5 (2.8)	3 (1.7)

Source: Study Reports

Demographic and Baseline Characteristics

Table 3 lists the demographic characteristics of the randomized patients. There was no difference among treatment groups with respect to age or sex within each study. The majority of patients across all three studies were White/Caucasian. Study 301 included a greater percentage of Hispanic, Black and Other race patients than Studies 205 and 302. Median baseline seizure frequency ranged from 8 to 10 in Study 205, 11 to 12 in Study 301, and 9 to 10 in Study 302. Majority of patients were from non-US geographical regions. The US patients mainly consisted of patients in the retigabine 1200 mg/day group and corresponding placebo group (study 301).

Table 3. Demographic and Baseline Characteristics- Studies 205, 301 and 302

	Study 205				Study 301		Study 302		
	Plb N=96	RTG 600 mg/day N=100	RTG 900 mg/day N=95	RTG 1200 mg/day N=106	Plb N=152	RTG 1200 mg/dayN =153	Plb N=179	RTG 600 mg/day N=181	RTG 900 mg/day N=178
Age, years									
mean	34.5	36.8	37.0	38.3	36.7	37.7	37.7	37.5	37.7
Sex, n (%)									
Female	48 (50)	46 (46)	47 (49)	51 (48)	80 (52.6)	85 (55.6)	90 (50.3)	105 (58.0)	85 (47.8)
Race, n (%)									
Caucasian	89 (93)	98 (98)	92 (97)	103 (97)	78 (51.3)	90 (58.8)	169 (94.4)	173 (95.6)	170 (95.5)
Non-Caucasian	7 (7)	2 (2)	3 (3)	3 (3)	74 (49.7)	63 (41.2)	9 (5.6)	8 (4.4)	8 (4.5)
Baseline Seizure Frequency									
Median	8.5	8.5	7.9	10.4	11.3	12.1	9.3	9.5	10.3
Geographic region (US and Non-US), n (%)									
US	7 (7.3)	8 (8.0)	7 (7.4)	5 (4.7)	71 (46.7)	77 (50.3)	0	3 (1.7)	0
Non-US	89 (92.7)	92 (92.0)	88 (92.6)	101 (95.3)	81 (53.3)	76 (49.7)	179 (100)	178 (98.3)	178 (100)

Source: study reports

Primary efficacy findings

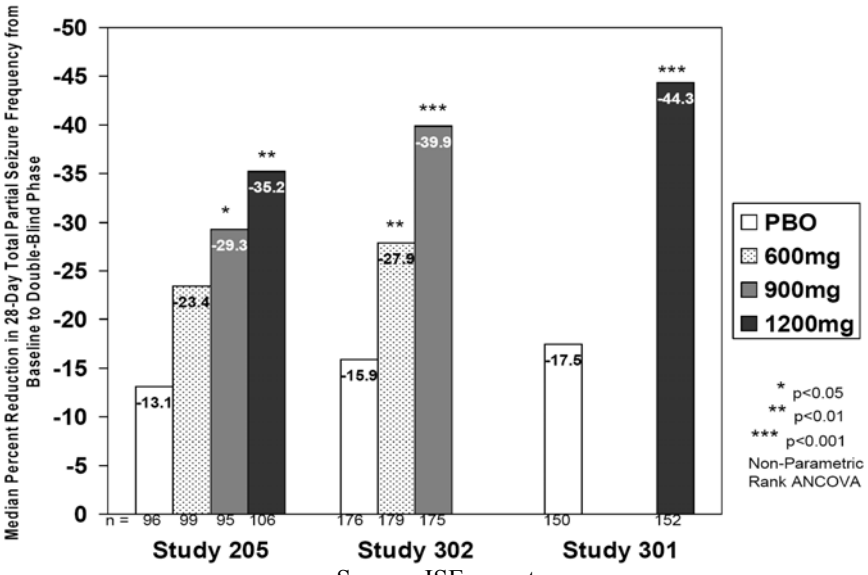
Table 4 and Figures 4-5 list the results of the primary efficacy endpoint- percent change in 28-day total partial seizure frequency from baseline to the double-blind treatment period (titration and maintenance phases combined) are summarized for the ITT double-blind population across Studies 205, 301 and 302. Retigabine 600 mg/day dose was statistically superior to placebo (p-value=0.007) in Study 302. The 900 mg/day dose was statistically superior to placebo (p-value <0.001) in Study 302. The 1200 mg/day dose was statistically superior to placebo (p-value<0.001) in Studies 205 and 301. Across the doses in Study 205, there was a numerical improvement trend (i.e. in Median percent changes) over placebo.

Table 4. Percent Change from Baseline in Total Partial Seizure Frequency ITT Double-Blind Population for Studies 205, 301 and 302

	Placebo	RTG 600 mg/day	RTG 900 mg/day	RTG 1200 mg/day
Study 205				
n	96	99	95	106
Median	-13.1	-23.4	-29.3	-35.2
Range	-100, 533	-100, 1703	-100, 298	-100, 375
P-value	-	0.199	0.043	<0.001
Study 301				
n	150	-	-	151
Median	-17.5	-	-	-44.3
Range	-90, 628	-	-	-100, 302
P-value	-	-	-	<0.001
Study 302				
n	176	179	175	-
Median	-15.9	-27.9	-39.9	-
Range	-100, 1712	-94, 250	-100, 226	-
P-value	-	0.007	<0.001	-

The p-values presented are from non-parametric rank ANCOVA models.
Source: Study reports

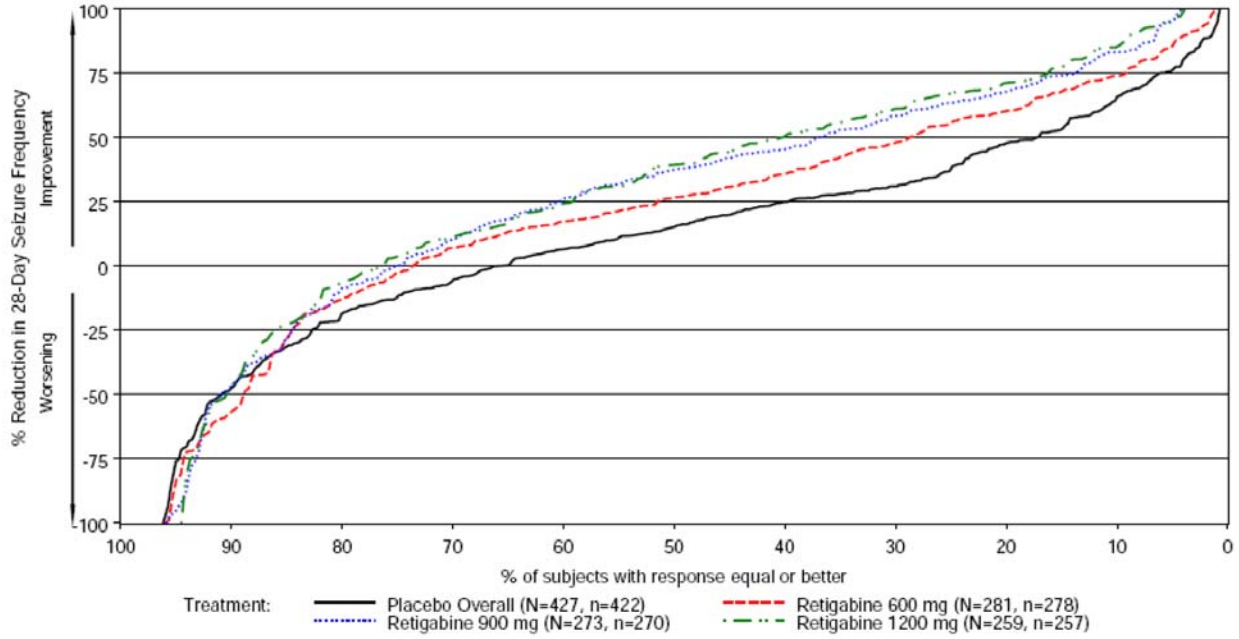
Figure 4. Percent Change from Baseline in Total Partial Seizure Frequency–ITT Double-Blind Population for Studies 205, 301 and 302



Source: ISE report

Figure 5 describes cumulative distribution profiles of the percentage of patients with a response equal to or better than the improvement or worsening of seizure frequency for each dose and placebo. The proportion of patients achieving a particular level of reduction in seizure frequency was consistently higher in the retigabine dose groups compared to placebo.

Figure 5. Distribution Profile of Total Partial Seizure Frequency (Double-Blind Phase) – ITT Double-Blind Population: Studies 205, 301 and 302



Source: ISE report

Sensitivity Analyses Excluding Data from Selected Study Sites in Study 205

The sponsor reported that multiple GCP compliance issues were identified at one site (site #021). In addition, the location/access to the investigator records has yet to be confirmed at another 5 (site #022, #052, #054, #070, #081) out of the 73 sites that participated in Study 205. Excluding these six sites, the sponsor conducted a sensitivity analysis on the primary endpoint (percent change in 28-day total partial seizure frequency from baseline to the double-blind phase) and secondary endpoint of responder rate in the maintenance phase. The magnitude of the treatment effect seen in each sensitivity analysis was similar to the original ITT population analysis.

Secondary Efficacy findings

Percent Change from Baseline in 28-Day Total Partial Seizure Frequency in the ITT Maintenance Population

Table 5 lists the median percent reduction from baseline in the 28-day total partial seizure frequency in the ITT maintenance population for the three studies. RTG 1200 mg/day was significant in Studies 205 and 301 (p-value<0.001), and RTG 600 mg/day and 900 mg/day were significant in Study 302 (p-value≤0.013). In Study 205, there were numerically larger

improvements observed in median percent change in seizure frequency at 600 mg and 900 mg, however, the results were not statistically significant (p-value=0.536 and p-value=0.170, respectively).

Table 5. Percent Change from Baseline in Total Partial Seizure Frequency (ITT-Maintenance Phase)- Studies 205, 301 and 302

	Placebo	RTG 600 mg/day	RTG 900 mg/day	RTG 1200 mg/day
Study 205				
n	78	83	74	68
Median	-22.9	-30.4	-35.8	-43.7
Range	-100, 200	-100, 1653	-100, 292	-100, 503
P-value [a]	-	0.536	0.170	0.008
Study 301				
n	137	-	-	119
Median	-18.9	-	-	-54.5
Range	-100, 1382	-	-	-100, 660
P-value [b]	-	-	-	<0.001
Study 302				
n	164	158	149	-
Median	-17.4	-35.3	-44.3	-
Range	-100, 1589	-100, 253	-100, 714	-
P-value [b]	-	0.002	<0.001	-

The p-values presented are from non-parametric rank ANCOVA models.
Source: ISE report

Responder Rate – ITT Maintenance Population

Table 6 and Figure 6 list the responder rates (defined as those experiencing a ≥50% reduction in 28-day total partial seizure frequency) from baseline to maintenance phase in each treatment group. The findings are consistent with the findings from the percent reduction analysis in the double-blind phase. The responder analysis results demonstrate that retigabine was statistically superior to placebo at all three tested doses in the Phase 3 studies ($p<0.001$ for all comparisons).

Percent Reduction in 28-Day Total Partial Seizure Frequency by Reduction Category - ITT maintenance phase

Table 7 lists the percent reduction in 28-Day Total Partial Seizure Frequency by reduction category in the ITT maintenance phase. The percent of retigabine patients in the ITT maintenance population with ≥75% reduction in seizure rate was greater than placebo, and increased with increasing dose. The proportions of patients with no change or an increase in seizure frequency were larger in the placebo groups than in the retigabine groups, with the exception of the 600 mg/day group in Study 205.

Table 5. Responder Rates – ITT Maintenance Population: Studies 205, 301 and 302

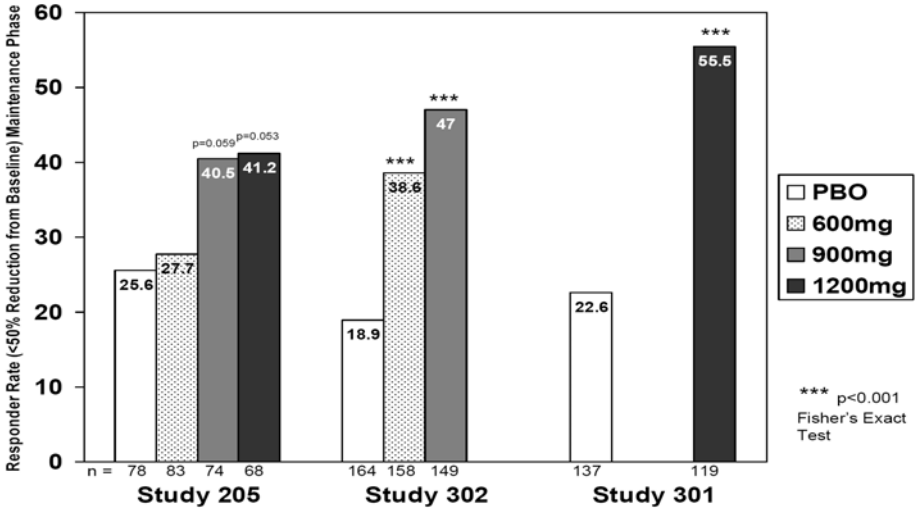
Number (%) of Responders were defined as patients with ≥50% reduction in 28-day total partial seizure frequency				
	Placebo	RTG 600 mg/day	RTG 900 mg/day	RTG 1200 mg/day
Study 205				
n	78	83	74	68
Responders	20 (25.6)	23 (27.7)	30 (40.5)	28 (41.2)
Non-responders	58 (74.4)	60 (72.3)	44 (59.5)	40 (58.8)
P-value [a]	-	0.845	0.057	0.010
Study 301				
n	137	-	-	119
Responders	31 (22.6)	-	-	66 (55.5)
Non-responders	106 (77.4)	-	-	53 (44.5)
P-value [b]	-	-	-	<0.001
Study 302				
n	164	158	149	-
Responders	31 (18.9)	61 (38.6)	70 (47.0)	-
Non-responders	133 (81.1)	97 (61.4)	79 (53.0)	-
P-value [b]	-	<0.001	<0.001	-

[a] The p-values presented are from logistic regression

[b] P-value from Fisher's Exact test.

Source: Study reports/ISE report

Figure 6. Responder Rate– ITT Maintenance Population: Studies 205, 301 and 302



Source: ISE reports

Table 7. Percent Reduction in 28-Day Total Partial Seizure Frequency by Reduction Category (Maintenance Phase) – ITT population: Studies 205, 301 and 302

	Number (%) of Patients			
	Placebo	RTG 600 mg/day	RTG 900 mg/day	RTG 1200 mg/day
Percent Increase/Reduction				
Study 205				
n	78	83	74	68
>75 to 100% decrease	7 (9)	10 (12)	12 (16)	15 (22)
50 to 75% decrease	13 (17)	13 (16)	18 (24)	13 (19)
>0 to <50% decrease	36 (46)	36 (43)	26 (35)	28 (41)
0 to 25% increase	11 (14)	12 (14)	4 (5)	3 (4)
>25% increase	11 (14)	12 (14)	14 (19)	9 (13)
P-value [a]		0.821	0.281	0.043
Study 301				
n	137	-	-	119
>75 to 100% decrease	13 (9)	-	-	37 (31)
50 to 75% decrease	18 (13)	-	-	29 (24)
>0 to <50% decrease	65 (47)	-	-	33 (28)
0 to 25% increase	20 (15)	-	-	4 (3)
>25% increase	21 (15)	-	-	16 (13)
P-value [a]				<0.001
Study 302				
n	164	158	149	-
>75 to 100% decrease	11 (7)	27 (17)	30 (20)	-
50 to 75% decrease	20 (12)	34 (22)	40 (27)	-
>0 to <50% decrease	83 (51)	60 (38)	49 (33)	-
0 to 25% increase	28 (17)	14 (9)	11 (7)	-
>25% increase	22 (13)	23 (15)	19 (13)	-
P-value [a]		0.005	<0.001	-

[a] P-value from CMH test
Source: Study reports

Investigator's judgment on Clinical Global Improvement

Table 8 lists a summary of the investigator's Clinical Global Improvement (CGI) scores at the end of the Maintenance Phase. The investigator's CGI scores indicated that the proportions of patients considered at least minimally improved at the end of the maintenance phase were higher for the retigabine groups than the placebo group within each of the three studies.

Table 8. Clinical Global Improvement at End of Maintenance Phase (ITT Population)- Studies 205, 301 and 302

	Study 205				Study 301		Study 302		
	Plb (N=78)	600mg (N=83)	900mg (N=74)	1200mg (N=68)	PlB (N=152)	1200mg (N=153)	PlB (N=179)	600mg (N=181)	900mg (N=178)
Very much improved	5.3%	9.5%	8.6%	12.5%	7%	14%	7%	8%	7%
Much improved	17.1%	29.7%	42.9%	29.7%	20%	30%	12%	27%	29%
Minimally improved	34.2%	35.1%	22.9%	29.7%	24%	16%	33%	28%	25%
No change	40.8%	23.0%	18.6%	23.4%	41%	28%	44%	31%	27%
Minimally worse	2.6%	2.7%	4.3%	4.7%	5%	5%	2%	3%	5%
Much worse	0	0	2.9%	0	2%	3%	1%	1%	4%
Very much worse	0	0	0	0	2%	3%	1%	0	1%

Source: Study reports

Effects of missing data--Sensitivity Analyses (Maintenance phase) across Studies 205, 301 and 302

The dropout rates during the double-blind phase in the three studies were relatively high (in a range from 17% to 42%). Therefore, two sensitivity analyses of percentage change from baseline in 28-day total partial seizure frequency were conducted across Studies 205, 301 and 302. In the first sensitivity analysis, seizure data from titration phase were used in the analysis for patients who dropped out during titration phase. In the second sensitivity analysis, it was assigned non-responder status for patients who dropped out of the titration phase. Table 9 lists the findings of the sensitivity analyses. The findings are consistent with the efficacy findings of the doses obtained from the protocol specified primary statistical analysis.

FDA Reviewer's Data Analyses and Comments

This reviewer re-analyzed the ITT data sets of the three studies and was able to reproduce the sponsor's reported findings on the primary and secondary efficacy measures. This reviewer did two sensitivity analyses on the primary efficacy measures of the studies. The sensitivity analyses include (i) Rank ANCOVA analysis on the observed total partial seizure frequency at post baseline; and (ii) ANCOVA on the log-transformed total partial seizure frequency at post baseline. Table 10 lists the p-values obtained from the sensitivity analyses. The p-values are similar to the p-values obtained from the protocol specified primary statistical analyses. All of the analyses consistently support the efficacy of retigabine doses. That is, Retigabine 200mg TID (in study 302), 300mg TID (in studies 205 and 302), and 400 mg TID (in study 301) were effective add-on therapy in the treatment of partial seizures in adult patients with refractory epilepsy.

This reviewer also reanalyzed the ITT data excluding the six irregularity sites in study 205, and confirmed the sponsor's findings.

Table 9. Sensitivity Analysis of Responder Rates in the Maintenance Phase – ITT Population for Study 205 and ITT Double-Blind Population for Studies 301 and 302

	Study 205				Study 301		Study 302		
	Plbo N=96	RTG 600 mg /day N=99	RTG 900 mg/day N=95	RTG 1200 mg/day N=106	Placebo N=152	RTG 1200 mg/day N=153	Placebo N=179	RTG 600 mg/day N=181	RTG 900 mg/day N=178
Sensitivity analysis: used titration data to calculate responder status for patients who dropped out of the titration phase									
Responders	24 (25)	27 (27.3)	36 (37.9)	42 (39.6)	32 (21.1)	76 (49.7)	35 (19.6)	63 (34.8)	78 (43.8)
Non-responders	72 (75)	72 (72.7)	59 (62.1)	64 (60.4)	120 (79.0)	77 (50.3)	144 (80.5)	118 (65.2)	100 (56.2)
P-value *	-	0.746	0.062	0.035	-	<0.001	-	0.001	<0.001
Sensitivity analysis: assumed non-responder status for patients who dropped out of the titration phase									
Responders	20 (20.8)	23 (23.2)	30 (31.6)	28 (26.4)	31 (20.4)	66 (43.1)	31 (17.3)	61 (33.7)	70 (39.3)
Non-responders	76 (79.2)	76 (76.8)	65 (68.4)	78 (73.6)	121 (79.6)	87 (56.9)	148 (82.7)	120 (66.3)	108 (60.7)
P-value *	-	0.731	0.101	0.409	-	<0.001	-	<0.001	<0.001

*The p-values are from Fisher's Exact test, Source study reports

Table 10. ANCOVA analyses on the total partial seizure frequency at post baseline-ITT Double-Blind Population for Studies 205, 301 and 302

	Study 205				Study 301		Study 302		
	Plbo N=96	RTG 600 mg /day N=99	RTG 900 mg/day N=95	RTG 1200 mg/day N=106	Plbo N=152	RTG 1200 mg/day N=153	Plbo N=179	RTG 600 mg/day N=181	RTG 900 mg/day N=178
Rank ANCOVA model on 28-day seizure frequency in the original scale									
P-Value	-	0.426	0.105	0.003	-	<0.001	-	0.039	<0.001
ANCOVA model on the log transformed 28-day seizure frequency									
P-Value	-	0.190	0.083	0.004	-	<0.001	-	0.025	<0.001

4. Subgroup Analyses

Subgroup Analyses – studies 205, 301 and 302

Within each study, subgroup analyses on the primary efficacy measure were performed to evaluate the uniformity of treatment effect within patient subgroups (gender, age group, and race). Table 11 lists the median seizure frequency per 28 days by gender and age groups. Within each study, subgroup analyses showed no substantial differences in efficacy of retigabine doses across the subgroups. The FDA reviewer also did the subgroup analyses on the studies. The reviewer's conclusions based on the findings were comparable with the sponsor's conclusions.

Table 11. Subgroup Analysis - Percent Change from Baseline in 28-Day Total Partial Seizure Frequency by Gender, Age Group and Race (Double-Blind Phase) –ITT Double-Blind Population: Studies 205, 301 and 302

	Study 205				**Study 301**		**Study 302**		
	Plb	**RTG 600 mg/day**	**RTG 900 mg/day**	**RTG 1200 mg/day**	**Plb**	**RTG 1200 mg/day**	**Plb**	**RTG 600 mg/day**	**RTG 900 mg/day**
Male									
n	48	54	48	55	71	67	88	75	91
Median	-17.0	-21.1	-31.9	-34.4	-19.8	-25.2	-21.2	-32.4	-34.6
Female									
n	48	45	47	51	79	84	88	104	84
Median	-11.9	-26.9	-26.9	-36.0	-14.8	-51.8	-7.7	-26.3	-44.4
≤44 years									
n	78	78	74	68	110	105	123	128	120
Median	-13.1	-20.7	-24.5	-31.2	-12.5	-39.2	-14.2	-29.1	-38.1
>44 years									
n	18	21	21	38	40	46	53	51	55
Median	-11.5	-35.0	-63.8	-41.9	-27.4	-51.5	-17.4	-26.6	-44.2
White/Caucasian									
n					77	89			
Median					-19.0	-38.5			
Hispanic									
n					47	39			
Median					-21.1	-51.6			
Other									
n					26	23			
Median					-3.4	-28.9			

Source: ISE report. The majority of patients in Studies 205 & 302 were White/Caucasian (>95%).

Table 12 lists subgroup analysis by geographic regions (US/Can=USA and Canada vs. Mex/Sam= Mexico and South America). The difference between treatment groups on the primary efficacy results for the ITT population favored retigabine in both geographic regions although a notably larger decrease in seizure frequency was observed in the Mex/Sam region; the median decrease for the retigabine-treated group was -29% in US/Can and -50% in Mex/Sam regions.

In studies 205 and 302, a few patients were randomized from USA (27 US patients out of 399 randomized patients in study 205; and 3 US patients out of 539 randomized patients in study 302). Therefore, no subgroup analyses were done in these two studies.

Table 12. Analyses of Percent Change in 28-day Total Partial Seizure Frequency From Baseline to Double-blind Phase Stratified by Geographic Region – ITT Population

Study 301	**Placebo (N=152)**		**RTG 400 mg TID (N=153)**	
Geographic region	**US/Can**	**Mex/SAm**	**US/Can**	**Mex/SAm**
Percent change from baseline	n=81	n=69	N=85	n=66
Median	-19.6	-11.7	-28.9	-50.4

Mex/SAm = Mexico and South America, n = number of evaluable patients, RTG = retigabine, US/Can = United State and Canada, Source: Study reports.

5. SUMMARY AND CONCLUSIONS

Collective Evidence of Efficacy in Studies 205, 301 and 302

With respect to the percent change from baseline in 28-day total partial seizure frequency during the double-blind phase in the ITT double-blind population and also in the ITT Maintenance phase, retigabine was able to demonstrate its significant efficacy in each of the three studies. In Study 205, retigabine at 900 mg/day and 1200 mg/day were statistically superior to placebo. The statistical significances of retigabine at 900 mg/day and 1200 mg/day were also confirmed in Studies 301 and 302.

Although Retigabine 600 mg/day had a numerically greater median percent change from baseline than the change for placebo, it was not statistically significant from placebo in Study 205. However, retigabine 600 mg/day was statistically superior to placebo in Study 302.

There was also an evidence of increasing efficacy with retigabine doses in the cumulative distribution profile for percent change in total partial seizure frequency across the double-blind phase.

Retigabine at 600 mg/day 900 mg/day in Study 302, and 1200 mg/day in Studies 205 and 301 also demonstrated its significant effects with respect to responder rate (the proportion of patients with a ≥50% reduction in 28-day total partial seizure frequency in the ITT maintenance population) during the maintenance phase.

The sensitivity analyses indicated that the dropout rates have no impact on the efficacy of the doses. That is, the sensitivity analyses also confirmed the efficacy findings for the doses.

Conclusions and Recommendations

The findings of the three studies confirmed that retigabine (600, 900, and 1200 mg/day) is an effective, add-on therapy in the treatment of partial seizures.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22345	ORIG-1	VALEANT PHARMACEUTICALS NORTH AMERICA	RETIGABINE

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/s/

OHIDUL I SIDDIQUI
07/06/2010

KUN JIN
07/06/2010
I concur with the review.

HSIEN MING J J HUNG
07/07/2010