CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211150Orig1s000

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 211150
Drug Name:	BF2.649
Indication:	Treatment of narcolepsy
Studies:	Carcinogenicity Studies in Rats for 104 Weeks and Mice for 26 Weeks
Applicant:	Sponsor: Bioprojet-Pharma 9 rue Rameau 75002 Paris, France Testing Facility for Rat Study: (b) (4)
Review Priority:	Standard
Biometrics Division:	Division of Biometrics - VI
Statistical Reviewer:	Hepei Chen
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Psychiatry Products
Reviewing Pharmacologist:	James Miller, Ph.D.
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. The objective of these studies was to evaluate the carcinogenic potential of the test item, BF2.649, a histamine H3 receptor antagonist/inverse agonist, following daily oral administration (gavage) to rats for 105/106 weeks and to mice for 26 weeks.

In this review the phrase "dose response relationship" refers to the linear component (trend) 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, one in male rats and one in female rats were conducted. As indicated in Table 1, in each of these two experiments there were three treated groups and one vehicle control group. Two hundred forty Sprague Dawley rats of each sex were assigned randomly in size of 60 rats per group. The dose levels for the three treated groups were 5, 15 or 30 mg/kg/day for both male and female rats. In this review these dose groups were referred to as the low (Group 2), mid (Group 3), and high (Group 4) dose groups, respectively. The rats in the vehicle control groups (Group 1) were administrated with sterile water, and handled for the same duration and in the same manner as the treated groups.

Table 1: Experimental Design in Rat Study

Group No.	No. of Animals		Test Material	Dosage Level (mg/kg/day)	
	Male	Female		Male	Female
1	60	60	Vehicle Control	0	0
2	60	60	BF2.649 Low	5	5
3	60	60	BF2.649 Mid	15	15
4	60	60	BF2.649 High	30	30

Each animal was checked for mortality and morbidity at least twice a day, including weekends and public holidays. Each animal (all groups) was observed at least once a day, at approximately the same time, for the recording of clinical signs. A particular attention was paid to the clinical observation of high-dose animals treated at 30 mg/kg/day (group 4). In addition, detailed clinical examinations were performed once a week until the end of the study. On completion of the treatment period, after at least 14 hours fasting and blood samplings all surviving animals were deeply anesthetized by an intraperitoneal injection of sodium pentobarbital and sacrificed by exsanguination. Any moribund animals were sacrificed in the same way. A microscopic examination was performed at the end of the study on all tissues listed in the Tissue Procedure Table for all principal animals sacrificed as scheduled, found dead or prematurely sacrificed.

2.1. Sponsor's analyses

2.1.1. Survival analysis

In the sponsor’s analysis, survival probability functions were estimated by the Kaplan-Meier technique. Survival curves were compared by the log-rank procedure, according to Peto’s method (Peto et al., 1980). Animals killed at the terminal sacrifice were considered as censored

observations in the statistical analysis. Other causes of death (i.e. natural death, moribund sacrifice or accidental death) were not considered as censored observations.

Sponsor's findings:

The sponsor's analysis showed that the numbers of rats surviving to their terminal necropsy were 32 (53%), 24 (40%), 26 (43%), and 22 (37%) in Groups 1, 2, 3, and 4 for male rats, respectively, and 26 (43%), 21 (35%), 22 (37%), and 18 (30%) for female rats respectively. The sponsor reported that there were no statistically significant differences in the survival curves between all groups in both male and female rats (log-rank test p-value = 0.1428 and 0.4721, respectively), indicating no apparent effect of treatment in survival for groups given the test item in both male and female rats.

2.1.2. Tumor data analysis

In the sponsor's report, statistical analysis of the incidence of tumors was based on the principles outlined by Peto et al. (1980). Peto's method corrects for longevity (and hence for the period of time at risk) and applies a statistical approach appropriate to the cause of death ("context of observation"). The results are split into time-intervals based on time-of-death or time-to-tumor-detection. The expected frequency of each tumor is calculated using death-rate calculations (for fatal tumors) and prevalence calculations (for non-fatal "incidental" tumors). The final test statistics for each type of tumor combine trend scores across the fatal and non-fatal categories. For each tumor type encountered in the study; where appropriate, tumors were also grouped for analysis, following the principles outlined by McConnell et al. (1986),

A one-tailed exact test was used to analyze any tumor type for which there are 12 or less tumor-bearing animals (over all groups). Trend test statistics were conducted on neoplastic findings according to Peto et al. (1980).

Adjustment for multiple testing:

In the sponsor's report, a decision rule was applied as follows (FDA, 2001):
- for common tumors, a result was considered significant if $p<0.005$,
- for rare tumors (those which are found in less than 1% of control animals), a result was considered significant if $p<0.025$.

Sponsor's findings:

In the sponsor's report, there was an apparent increase in incidence of hepatocellular adenomas in mid-dose male rats. However, since this was not statistically significant with the exact Peto's test ($p = 0.0281$), this increase in mid-dose male rats only was considered to be fortuitous and not to be related to the test item administration. No statistically significant trends for common tumors, and no statistically significant differences between control and treated groups in rare tumors were observed in both male and female rats.

2.2. Reviewer's analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing

toxicologist, this reviewer independently performed the survival and tumor data analyses using the data provided by the sponsor electronically.

2.2.1. Survival analysis

In the reviewer's analysis, the survival distributions of rats in all four groups (Groups 1, 2, 3, and 4) were estimated using the Kaplan-Meier product limit method. The dose response relationship was tested across Groups 2, 3, and 4 using the likelihood ratio test, and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for all five groups in male and female rats, respectively. The intercurrent mortality data of all four groups and the results of the tests for dose response relationship and homogeneity of survivals for Groups 2, 3, and 4 are given in Tables 1A and 1B in the appendix for male and female rats, respectively.

Reviewer's findings:

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy were 32 (53%), 24 (40%), 26 (43%), and 22 (37%) in Groups 1, 2, 3, and 4 for male rats, respectively, and 26 (43%), 21 (35%), 22 (37%), and 18 (30%) for female rats respectively. The reviewer's analysis also showed a statistically significant increase in mortality in the high dose group when comparing to the vehicle control group (p-value = 0.0282) in male rats. No other significant findings were noted in survival for male and female rats.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships across Groups 1, 2, 3, and 4, and pairwise comparisons of each of the three treated groups (Groups 2, 3, and 4) against the vehicle control group (Group 1), using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993).

In the ploy-k method, the adjustment for differences in mortality among treatment groups is made by modifying the number of animals at risk in the denominators in the calculations of overall tumor rates in the Cochran-Armitage test to reflect less-than-whole-animal contributions for animals that die without tumor before the end of the study (Bailer and Portier 1988). The modification is made by defining a new number of animals at risk for each treatment group. The number of animals at risk for the *i*-th treatment group R^* i is defined as $R^*_i = \sum W_{ij}$ where w_{ij} is the weight for the *j*-th animal in the *i*-th treatment group, and the sum is over all animals in the group.

Bailer and Portier (1988) proposed the weight w_{ij} as follows:

$w_{ij} = 1$ to animals dying with the tumor, and

$w_{ij} = (t_{ij} / tsacr)^3$ to animals dying without the tumor,

where t_{ij} is the time of death of the *j*-th animal in the *i*-th treatment group, and tsacr is the planned (or intended) time of terminal sacrifice. The above formulas imply that animals living up to the end of the planned terminal sacrifice date without developing any tumor will also be assigned $w_{ij} = 1$ since t_{ij} = tsacr. Also animals developed the tumor type being tested before the end of the study will be assigned as $w_{ij} = 1$.

Certain treatment groups of a study or the entire study may be terminated earlier than the planned (or intended) time of terminal sacrifice due to excessive mortalities. However, based on the principle of the Intention-to-treat (ITT) analysis in randomized trials, the tsacr should not be affected by the unplanned early terminations. The tsacr should always be equal to the planned (or intended) time of terminal sacrifice. For those animals that were sacrificed later than tsacr, regardless their actual terminal sacrifice time, tsacr was used as their time of terminal sacrifice in the analysis.

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.

Multiple testing adjustment:

For the adjustment of multiple testing, this reviewer used the methodologies suggested in the draft FDA guidance for statistical design and analysis of carcinogenicity studies (2015). For a submission with one two-year study in one species and one short-term study with another species, significance levels are 0.005 and 0.025 for common and rare tumors, respectively, in dose response relationship (trend) tests, and significance levels are 0.01 and 0.05 for common and rare tumors, respectively, in pairwise comparisons.

A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. However, if the background information for the common or rare tumor is not available, the number of animals bearing tumors in the vehicle control group in the present study was used to determine the common or rare tumor status in the review report. That is, if the number of animals bearing tumors in the vehicle control group is 0, then this tumor is considered as the rare tumor; otherwise, if the number of animals bearing tumors in the control group is greater than or equal to 1, then this tumor is considered as the common tumor.

Reviewer's findings:

The tumor rates and the p-values of the tested tumor types are listed in Tables 2A and 2B in the appendix for male and female rats, respectively. The tumor types with p-values less than or equal to 0.05 for dose response relationship and/or pairwise comparisons of treated groups and vehicle control are reported in Table 2.

As noted in Table 2, based on the criteria of adjustment for multiple testing discussed above, a statistically significant increase for the incidence of adenoma hepatocellular in liver was noted in the mid dose group when compared with the vehicle control group (p-value = 0.0401) in male rats if this tumor was considered to be rare. No other statistically significant findings were noted in tumor data for both male and female rats.

Table 2: Summary Table of Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Vehicle Control Group in Male Rats

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	5 mg Low (L) P - C vs. L	15 mg Mid (M) P - C vs. M	30 mg High (H) P - C vs. H
Male					
Liver	Adenoma, Hepatocellular	0/60 (50)	0/60 (42)	4/60 (42)	0/60 (41)
		0.3355	NC	0.0401 $	NC
Female					
Mammary Glands Are	Adenocarcinoma	5/60 (44)	12/60 (46)	6/60 (44)	13/60 (45)
		0.0807	0.0640	0.5000	0.0353 @
	Adenocarcinoma Arising In Fibroadenoma	4/60 (44)	7/60 (44)	5/60 (43)	3/60 (40)
		0.7128	0.2605	0.4852	0.4461
	Adenocarcinoma/Adenocarcinoma Arising In Fibroadenoma	8/60 (45)	17/60 (48)	10/60 (45)	14/60 (45)
		0.2502	0.0454 @	0.3964	0.1098
Thyroid Glands	Adenoma, C Cell	1/60 (43)	7/60 (43)	4/60 (44)	1/60 (40)
		0.7816	0.0288 @	0.1874	0.7346
	Carcinoma, C Cell	1/60 (43)	1/60 (43)	0/60 (42)	0/60 (39)
		0.8015	NC	0.4941	0.4756
	Adenoma, C Cell/ Carcinoma, C Cell	2/60 (43)	8/60 (44)	4/60 (44)	1/60 (40)
		0.8844	0.0482 @	0.3492	0.4726

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;

$ = Statistically significant at 0.05 level in rare tumor for test of pairwise comparison;

@ = Not statistically significant at 0.01 level in common tumor for test of pairwise comparison;

3. Mouse Study

Two separate experiments, one in male mice and one in female mice were conducted. As indicated in Table 3, in each of these two experiments there were three treated groups, one positive control group, and one vehicle control group. One hundred and twenty five transgenic CB6F1-TgrasH2 mice of each sex were assigned randomly in size of 25 mice per group. The dose levels for the three treated groups were 15, 30 or 75 mg/kg/day for both male and female mice, respectively. In this review these dose groups were referred to as the low (Group 2), mid (Group 3), and high (Group 4) dose groups, respectively. The mice in the vehicle control group and the positive control group were administrated with the vehicle (water for injection) and MNU (N-methyl-N-nitrosourea), respectively, and handled for the same duration and in the same manner as the treated groups.

Table 3: Experimental Design in Mouse Study

Group No.	No. of Animals		Test Material	Dosage Level (mg/kg/day)	
	Male	Female		Male	Female
1	25	25	Vehicle Control	0	0
2	25	25	BF2.649 Low	15	15
3	25	25	BF2.649 Mid	30	30
4	25	25	BF2.649 High	75	75
5	25	25	Positive Control MNU	0	0

The animals were observed for general health/mortality and moribundity twice daily, once in the morning and once in the afternoon, throughout the study. Cage side observations were performed once daily, beginning Week -1, throughout the dosing phase; the observations were performed 1

to 3 hours postdose during the dosing phase. The animals were removed from the cage and a detailed clinical observation was performed at least once weekly, beginning Week -1. For carcinogenicity group animals that died on study, a macroscopic examination was conducted and specified tissues were saved. Carcinogenicity group animals surviving until scheduled euthanasia were weighed and the animals were euthanized by isoflurane inhalation, followed by exsanguination.

3.1. Sponsor's analyses

3.1.1. Survival analysis

In the sponsor's report, survival probability functions were estimated by the Kaplan-Meier technique. Survival curves were compared using the log-rank test between vehicle and positive control groups (groups 1 and 5) and between vehicle and test item treated groups (groups 1 to 4). Animals sacrificed at the terminal sacrifice were included in the statistical analysis and considered as being censured data. Other causes of death (i.e. natural death, moribund sacrifice or accidental death) were also included.

Sponsor's findings:

The sponsor's analysis showed that the numbers of mice surviving to their terminal necropsy were 24 (96%), 24 (96%), 25 (100%), 25 (100%), and 3 (12%) in the vehicle control, low, mid, high, and positive control groups for male mice, respectively, and 25 (100%), 23 (92%), 25 (100%), 25 (100%), and 7 (28%) for female mice, respectively. The sponsor's analysis showed no statistically significant differences between survival curves of vehicle treated group and test item treated groups in male mice (log-rank test p-value=0.5681) and female mice (logrank test p-value=0.1058).

3.1.2. Tumor data analysis

In the sponsor's report, statistical analysis of the incidence of tumors based on the principles outlined by Peto et al (1980) are not applied in short-term studies due to the low mortality compared to a 2-year carcinogenicity study.

Analysis of tumor incidences was performed by comparison between vehicle group (group 1) and positive control group (group 5) using a one-tailed Fisher's exact test and comparison between vehicle (group 1) and each test item treated groups (groups 2 to 4) using a one-tailed Fisher's exact test. A one-tailed Cochran-Armitage test for trend was performed to investigate the relationship between the increasing dosage of the test item and the tumor incidences.

Multiple testing adjustment:

No adjustment for multiple testing was descripted or discussed for the mouse study in the sponsor's report.

Sponsor's findings:

In the sponsor's report, a dose-dependent higher tumor incidence of the lung bronchi-alveolar carcinoma was observed (0/25, 0/25, 0/25 and 2/25 with a p-value=0.0276, from group 1 to 4).

However, this increase in incidence was not statistically significant as the incidence was within the range of historical control data in the literature. It was considered not to be related to the test item administration. No statistically significant associations were observed between each test item treated group and the vehicle group for both male and female mice.

3.2. Reviewer's analyses

Similar to the rat study, this reviewer independently performed survival and tumor data analyses of mouse data to verify sponsor's analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

For the analysis of both the survival data and the tumor data in mice, this reviewer used similar methodologies that were used for the analyses of the rat survival and tumor data.

3.2.1. Survival analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data, and the results of the tests for dose response relationship and homogeneity of survivals for the vehicle control, low, mid, and high dose groups were given in Tables 3A and 3B in the appendix for male and female mice, respectively.

Reviewer's findings:

The reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 24 (96%), 24 (96%), 25 (100%), 25 (100%), and 3 (12%) in the vehicle control, low, mid, high, and positive control groups for male mice, respectively, and 25 (100%), 23 (92%), 25 (100%), 25 (100%), and 7 (28%) for female mice, respectively. No statistically significant findings were noted in mortality for male and female mice.

3.2.2. Tumor data analysis

Reviewer's findings:

The tumor rates and the p-values of the tested tumor types are listed in Tables 4A and Table 4B in the appendix for male and female mice, respectively. No statistically significant tumor findings were noted for male and female mice.

4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. The objective of these studies was to evaluate the carcinogenic potential of the test item, BF2.649, a histamine H3 receptor antagonist/inverse agonist, following daily oral administration (gavage) to rats for 105/106 weeks and to mice for 26 weeks.

Rat Study:

Two separate experiments, one in male rats and one in female rats were conducted. In each of these two experiments there were three treated groups and one vehicle control group. Two

hundred forty Sprague Dawley rats of each sex were assigned randomly in size of 60 rats per group. The dose levels for the three treated groups were 5, 15 or 30 mg/kg/day for both male and female rats.

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy were 32 (53%), 24 (40%), 26 (43%), and 22 (37%) in Groups 1, 2, 3, and 4 for male rats, respectively, and 26 (43%), 21 (35%), 22 (37%), and 18 (30%) for female rats respectively. The reviewer's analysis also showed a statistically significant increase in mortality in the high dose group when comparing to the vehicle control group (p-value = 0.0282) in male rats. No other significant findings were noted in survival for male and female rats.

Based on the criteria of adjustment for multiple testing discussed above, a statistically significant increase for the incidence of adenoma hepatocellular in liver was noted in the mid dose group when compared with the vehicle control group (p-value = 0.0401) in male rats if this tumor was considered to be rare. No other statistically significant findings were noted in tumor data for both male and female rats.

Mouse Study:

Two separate experiments, one in male mice and one in female mice were conducted. In each of these two experiments there were three treated groups, one positive control group, and one vehicle control group. One hundred and twenty five transgenic CB6F1-TgrasH2 mice of each sex were assigned randomly in size of 25 mice per group. The dose levels for the three treated groups were 15, 30 or 75 mg/kg/day for both male and female mice, respectively.

The reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 24 (96%), 24 (96%), 25 (100%), 25 (100%), and 3 (12%) in the vehicle control, low, mid, high, and positive control groups for male mice, respectively, and 25 (100%), 23 (92%), 25 (100%), 25 (100%), and 7 (28%) for female mice, respectively. No statistically significant findings were noted in mortality for male and female mice.

No statistically significant tumor findings were noted for male and female mice.

Hepei Chen.
Mathematical Statistician

Concur: Karl Lin, Ph.D.
Team Leader, DBVI

Cc: Archival NDA 211150

Dr. James Miller
Dr. Lillian Patrician

5. Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

	Vehicle Control		Low		Mid		High	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	2	3.33	4	6.67	5	8.33	4	6.67
53 - 78	5	11.67	11	25.00	12	28.33	13	28.33
79 - 91	5	20.00	9	40.00	6	38.33	9	43.33
92 - 105	16	46.67	12	60.00	11	56.67	12	63.33
Terminal sacrifice	32	53.33	24	40.00	26	43.33	22	36.67
Total	60		60		60		60	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.0823	0.0521	0.1212	0.0282
Homogeneity (Log-Rank)	0.1413	0.0488	0.1166	0.0262

#All Cum. % Cumulative Percentage except for Terminal sacrifice;
* = Significant at 5% level; ** = Significant at 1% level.

Table 1B: Intercurrent Mortality Rate in Female Rats

	Vehicle Control		Low		Mid		High	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	3	5.00			1	1.67	2	3.33
53 - 78	12	25.00	11	18.33	11	20.00	15	28.33
79 - 91	7	36.67	18	48.33	16	46.67	18	58.33
92 - 105	12	56.67	10	65.00	10	63.33	7	70.00
Terminal sacrifice	26	43.33	21	35.00	22	36.67	18	30.00
Total	60		60		60		60	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.1562	0.4687	0.5307	0.1442
Homogeneity (Log-Rank)	0.4781	0.4631	0.5272	0.1397

#All Cum. % Cumulative Percentage except for Terminal sacrifice;
** = Significant at 1% level.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	5 mg Low (L) P - C vs. L	15 mg Mid (M) P - C vs. M	30 mg High (H) P - C vs. H
Adrenal Cortices	Adenoma, Cortical Cell	0/60 (50)	0/60 (42)	0/60 (42)	1/60 (41)
		0.2343	NC	NC	0.4505
	Carcinoma, Cortical Cell	1/60 (50)	0/60 (42)	0/60 (42)	1/60 (41)
		0.4713	0.4565	0.4565	0.7009
	Adenoma, Cortical Cell/ Carcinoma, Cortical Cell	1/60 (50)	0/60 (42)	0/60 (42)	2/60 (41)
		0.1775	0.4565	0.4565	0.4252
Adrenal Medullas	Pheochromocytoma, Benign	7/60 (51)	7/59 (42)	0/60 (42)	5/59 (40)
		0.7604	0.4564	0.9878	0.4407
	Pheochromocytoma, Malignant	1/60 (50)	2/59 (41)	0/60 (42)	0/59 (40)
		0.8693	0.4252	0.4565	0.4444
	Pheochromocytoma, Benign/ Pheochromocytoma, Maligna	7/60 (51)	9/59 (42)	0/60 (42)	5/59 (40)
		0.8304	0.2404	0.9878	0.4407
Brain	Astrocytoma, Malignant	2/60 (50)	1/60 (42)	0/60 (42)	1/60 (41)
		0.6333	0.4342	0.7074	0.4252
	Granular Cell Tumor, Benign	1/60 (50)	0/60 (42)	2/60 (43)	0/60 (41)
		0.5511	0.4565	0.4430	0.4505
	Granular Cell Tumor, Malignant	0/60 (50)	0/60 (42)	0/60 (42)	1/60 (41)
		0.2343	NC	NC	0.4505
	Granular Cell Tumor, Benign/ Granular Cell Tumor, Malignant	1/60 (50)	0/60 (42)	2/60 (43)	1/60 (41)
		0.3363	0.4565	0.4430	0.7009
Eyes	Carcinoma, Squamous Cell	0/59 (50)	0/60 (42)	0/60 (42)	1/60 (41)
		0.2343	NC	NC	0.4505
Harderian Glands	Adenocarcinoma	0/59 (50)	1/60 (43)	0/60 (42)	0/60 (41)
		0.4716	0.4624	NC	NC
Heart	Rhabdomyosarcoma	0/60 (50)	1/60 (42)	0/60 (42)	0/60 (41)
		0.4743	0.4565	NC	NC
Hemolymphoret. Sys	Leukemia, Granulocytic	2/60 (51)	1/60 (42)	0/60 (42)	2/60 (41)
		0.4383	0.4269	0.7020	0.6050
	Lymphoma, Malignant	1/60 (51)	3/60 (44)	2/60 (43)	0/60 (41)
		0.7890	0.2548	0.4356	0.4457
	Sarcoma, Histiocytic	0/60 (50)	1/60 (42)	2/60 (43)	1/60 (41)
		0.2592	0.4565	0.2111	0.4505

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	5 mg Low (L) P - C vs. L	15 mg Mid (M) P - C vs. M	30 mg High (H) P - C vs. H
Kidneys	Liposarcoma	1/60 (50)	0/60 (42)	0/60 (42)	0/60 (41)
		0.7143	0.4565	0.4565	0.4505
	Renal Mesenchymal Tumor, Malignant	0/60 (50)	1/60 (42)	0/60 (42)	0/60 (41)
		0.4743	0.4565	NC	NC
Liver	Adenoma, Hepatocellular	0/60 (50)	0/60 (42)	4/60 (42)	0/60 (41)
		0.3355	NC	0.0401 $	NC
	Carcinoma, Hepatocellular	2/60 (50)	1/60 (42)	1/60 (43)	1/60 (41)
		0.5759	0.4342	0.4430	0.4252
	Adenoma, Hepatocellular/ Carcinoma, Hepatocellular	2/60 (50)	1/60 (42)	5/60 (43)	1/60 (41)
		0.4791	0.4342	0.1600	0.4252
Lungs	Adenoma, Bronchio-Alveolar	1/60 (50)	0/60 (42)	0/60 (42)	0/60 (41)
		0.7143	0.4565	0.4565	0.4505
	Locally Invasive Tumor	0/60 (50)	1/60 (43)	0/60 (42)	0/60 (41)
		0.4716	0.4624	NC	NC
Mammary Glands Are	Adenocarcinoma	0/2 (2)	0/1 (1)	1/1 (1)	0/2 (2)
		0.5000	NC	0.3333	NC
	Fibroadenoma	2/2 (2)	0/1 (1)	0/1 (1)	0/2 (2)
		0.9333	0.6667	0.6667	0.8333
Mesent. Lymph Node	Hemangioma	1/59 (50)	1/60 (42)	0/60 (42)	0/56 (39)
		0.7765	0.7074	0.4565	0.4382
Pancreas	Adenocarcinoma, Acinar Cell	0/60 (50)	0/60 (42)	1/60 (42)	0/60 (41)
		0.4743	NC	0.4565	NC
	Adenoma, Acinar-Islet Cell	1/60 (50)	0/60 (42)	0/60 (42)	0/60 (41)
		0.7143	0.4565	0.4565	0.4505
	Adenocarcinoma, Acinar Cell/ Adenoma, Acinar-Islet	1/60 (50)	0/60 (42)	1/60 (42)	0/60 (41)
		0.5871	0.4565	0.7074	0.4505
	Adenoma, Islet Cell	3/60 (50)	3/60 (42)	3/60 (43)	6/60 (41)
		0.0828	0.5748	0.5868	0.1541
	Carcinoma, Islet Cell	1/60 (50)	1/60 (42)	2/60 (42)	0/60 (41)
		0.6333	0.7074	0.4342	0.4505
	Adenoma, Islet Cell/ Carcinoma, Islet Cell	4/60 (50)	4/60 (42)	5/60 (43)	6/60 (41)
		0.1585	0.5409	0.4039	0.2508
Parathyroid Glands	Adenoma	0/57 (49)	0/57 (41)	0/55 (40)	1/58 (40)
		0.2353	NC	NC	0.4494

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	5 mg Low (L) P - C vs. L	15 mg Mid (M) P - C vs. M	30 mg High (H) P - C vs. H
Pituitary Gland	Adenoma, Pars Distalis	30/60 (53)	19/59 (45)	18/59 (45)	21/60 (45)
		0.7595	0.8881	0.9247	0.7818
	Adenoma, Pars Intermedia	1/60 (50)	0/59 (41)	0/59 (41)	0/60 (41)
		0.7110	0.4505	0.4505	0.4505
	Adenoma, Pars Distalis/ Adenoma, Pars Intermedia	31/60 (53)	19/59 (45)	18/59 (45)	21/60 (45)
		0.8041	0.9198	0.9478	0.8329
Preputial Glands	Adenocarcinoma	0/60 (50)	0/58 (42)	1/60 (43)	0/60 (41)
		0.4773	NC	0.4624	NC
	Carcinoma, Squamous Cell	0/60 (50)	1/58 (42)	0/60 (42)	2/60 (41)
		0.0906	0.4565	NC	0.2002
Prostate	Schwannoma, Malignant	0/60 (50)	1/60 (43)	0/60 (42)	0/60 (41)
		0.4716	0.4624	NC	NC
Skeletal Muscle	Rhabdomyosarcoma	0/60 (50)	0/60 (42)	1/60 (43)	0/60 (41)
		0.4773	NC	0.4624	NC
Skin	Basal Cell Tumor, Benign	0/60 (50)	1/60 (42)	0/60 (42)	1/60 (41)
		0.2801	0.4565	NC	0.4505
	Basal Cell Tumor, Malignant	0/60 (50)	0/60 (42)	0/60 (42)	1/60 (41)
		0.2343	NC	NC	0.4505
	Basal Cell Tumor, Benign/ Basal Cell Tumor, Malignant	0/60 (50)	1/60 (42)	0/60 (42)	2/60 (41)
		0.0906	0.4565	NC	0.2002
	Hair Follicle Tumor, Benign	0/60 (50)	1/60 (42)	0/60 (42)	1/60 (41)
		0.2801	0.4565	NC	0.4505
	Keratoacanthoma	0/60 (50)	2/60 (42)	0/60 (42)	1/60 (41)
		0.4112	0.2057	NC	0.4505
	Papilloma, Squamous Cell	0/60 (50)	1/60 (42)	2/60 (42)	2/60 (42)
		0.1092	0.4565	0.2057	0.2057
	Carcinoma, Squamous Cell	0/60 (50)	0/60 (42)	1/60 (43)	0/60 (41)
		0.4773	NC	0.4624	NC
	Carcinoma, Squamous Cell/ Papilloma, Squamous Cell/	0/60 (50)	3/60 (42)	3/60 (43)	3/60 (42)
		0.1202	0.0914	0.0951	0.0914
Spleen	Hemangiosarcoma	0/60 (50)	1/60 (42)	1/60 (42)	0/60 (41)
		0.4713	0.4565	0.4565	NC
	Sarcoma, Not Otherwise Specified	1/60 (50)	0/60 (42)	0/60 (42)	0/60 (41)
		0.7143	0.4565	0.4565	0.4505

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	5 mg Low (L) P - C vs. L	15 mg Mid (M) P - C vs. M	30 mg High (H) P - C vs. H
Subcutaneous Tissu	Fibroma	7/12 (11)	6/9 (8)	5/10 (9)	2/7 (5)
		0.8374	0.4938	0.4650	0.6346
	Fibrosarcoma	0/12 (11)	0/9 (7)	1/10 (9)	1/7 (4)
		0.0903	NC	0.4500	0.2667
	Fibroma/Fibrosarcoma	7/12 (11)	6/9 (8)	6/10 (9)	3/7 (5)
		0.5609	0.4938	0.6300	0.3462
	Histiocytoma, Fibrous, Malignant	1/12 (11)	2/9 (8)	0/10 (9)	0/7 (4)
		0.8159	0.3756	0.4500	0.2667
	Lipoma	0/12 (11)	0/9 (7)	1/10 (9)	1/7 (5)
		0.1109	NC	0.4500	0.3125
	Osteosarcoma	1/12 (11)	0/9 (7)	0/10 (9)	0/7 (4)
		0.6452	0.3889	0.4500	0.2667
	Sarcoma, Not Otherwise Specified	0/12 (11)	1/9 (8)	0/10 (9)	0/7 (4)
		0.4062	0.4211	NC	NC
Testes	Adenoma, Leydig Cell	1/59 (49)	0/60 (42)	2/60 (42)	0/60 (41)
		0.5551	0.4615	0.4418	0.4556
Thymus	Thymoma, Malignant	0/60 (50)	0/60 (42)	0/60 (42)	1/60 (41)
		0.2343	NC	NC	0.4505
Thyroid Glands	Adenoma, C Cell	12/60 (51)	6/60 (43)	8/58 (42)	5/60 (41)
		0.8530	0.8188	0.6044	0.8695
	Carcinoma, C Cell	0/60 (50)	1/60 (42)	0/58 (42)	0/60 (41)
		0.4743	0.4565	NC	NC
	Adenoma, C Cell/ Carcinoma, C Cell	12/60 (51)	7/60 (43)	8/58 (42)	5/60 (41)
		0.8757	0.7291	0.6044	0.8695
	Adenoma, Follicular Cell	1/60 (50)	1/60 (42)	1/58 (42)	3/60 (41)
		0.1035	0.7074	0.7074	0.2373
	Carcinoma, Follicular Cell	1/60 (50)	1/60 (42)	1/58 (42)	0/60 (41)
		0.6979	0.7074	0.7074	0.4505
	Adenoma, Follicular Cell/ Carcinoma, Follicular Cell	2/60 (50)	1/60 (42)	2/58 (42)	3/60 (41)
		0.1951	0.4342	0.6230	0.4058
Tongue	Sarcoma, Not Otherwise Specified	0/59 (50)	0/59 (42)	0/58 (42)	1/60 (42)
		0.2386	NC	NC	0.4565

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	5 mg Low (L) P - L vs. C	15 mg Mid (M) P - M vs. C	30 mg High (H) P - H vs. C
Adrenal Cortices	Adenoma, Cortical Cell	2/60 (44)	2/60 (43)	1/60 (43)	1/60 (39)
		0.6851	0.6832	0.4913	0.4543
Adrenal Medullas	Pheochromocytoma, Benign	0/55 (42)	1/54 (40)	0/58 (40)	1/54 (37)
		0.2887	0.4878	NC	0.4684
Brain	Granular Cell Tumor, Malignant	0/60 (43)	1/60 (43)	0/60 (42)	0/60 (39)
		0.4850	0.5000	NC	NC
Clitoral Glands	Carcinoma, Squamous Cell	2/59 (44)	1/58 (41)	0/58 (41)	0/59 (38)
		0.9279	0.4732	0.7350	0.7151
Eyes	Melanoma	0/60 (43)	0/59 (42)	0/60 (42)	1/60 (40)
		0.2395	NC	NC	0.4819
Forestomach	Papilloma, Squamous Cell	0/60 (43)	0/60 (42)	1/60 (43)	0/60 (39)
		0.4910	NC	0.5000	NC
Harderian Glands	Adenocarcinoma	1/60 (44)	0/59 (42)	0/60 (42)	0/60 (39)
		0.7365	0.4884	0.4884	0.4699
Hemolymphoret. Sys	Lymphoma, Malignant	3/60 (45)	1/60 (42)	1/60 (43)	2/60 (39)
		0.5040	0.6653	0.6744	0.4316
	Sarcoma, Histiocytic	0/60 (43)	0/60 (42)	0/60 (42)	1/60 (40)
		0.2395	NC	NC	0.4819
Kidneys	Lipoma	1/60 (43)	0/60 (42)	1/60 (43)	0/60 (39)
		0.6090	0.4941	NC	0.4756
	Nephroblastoma, Malignant	1/60 (44)	0/60 (42)	0/60 (42)	0/60 (39)
		0.7365	0.4884	0.4884	0.4699
Liver	Hemangiosarcoma	1/60 (43)	0/60 (42)	0/60 (42)	0/60 (39)
		0.7410	0.4941	0.4941	0.4756

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	5 mg Low (L) P - L vs. C	15 mg Mid (M) P - M vs. C	30 mg High (H) P - H vs. C
Mammary Glands Are	Adenocarcinoma	5/60 (44)	12/60 (46)	6/60 (44)	13/60 (45)
		0.0807	0.0640	0.5000	0.0353
	Adenocarcinoma Arising In Fibroadenoma	4/60 (44)	7/60 (44)	5/60 (43)	3/60 (40)
		0.7128	0.2605	0.4852	0.4461
	Adenocarcinoma/Adenocarcinoma Arising In Fibroadenoma	8/60 (45)	17/60 (48)	10/60 (45)	14/60 (45)
		0.2502	0.0454	0.3964	0.1098
	Adenoma	1/60 (43)	5/60 (43)	3/60 (43)	0/60 (39)
		0.8624	0.1010	0.3080	0.4756
	Fibroadenoma	29/60 (49)	28/60 (48)	31/60 (52)	27/60 (47)
		0.5428	0.4519	0.5628	0.4863
	Tumor, Mixed, Benign	0/60 (43)	0/60 (42)	1/60 (42)	0/60 (39)
		0.4880	NC	0.4941	NC
Ovaries	Tumor, Granulosa Cell, Benign	0/60 (43)	0/60 (42)	1/60 (42)	1/60 (39)
		0.1737	NC	0.4941	0.4756
	Tumor, Granulosa Cell, Malignant	1/60 (43)	0/60 (42)	0/60 (42)	0/60 (39)
		0.7410	0.4941	0.4941	0.4756
	Tumor, Granulosa Cell, Benign/ Tumor, Granulosa Cell, Malignant	1/60 (43)	0/60 (42)	1/60 (42)	1/60 (39)
		0.3841	0.4941	0.7471	0.7281
	Tumor, Sex Cord Stromal, Mixed, Benign	0/60 (43)	0/60 (42)	0/60 (42)	1/60 (39)
		0.2349	NC	NC	0.4756
Pancreas	Adenocarcinoma, Acinar Cell	1/60 (43)	0/59 (42)	0/60 (42)	0/60 (39)
		0.7410	0.4941	0.4941	0.4756
	Adenoma, Islet Cell	1/60 (43)	3/59 (43)	1/60 (42)	1/60 (39)
		0.6301	0.3080	0.7471	0.7281
	Carcinoma, Islet Cell	0/60 (43)	1/59 (42)	0/60 (42)	0/60 (39)
		0.4880	0.4941	NC	NC
	Adenoma, Islet Cell/ Carcinoma, Islet Cell	1/60 (43)	4/59 (43)	1/60 (42)	1/60 (39)
		0.7067	0.1800	0.7471	0.7281
Parathyroid Glands	Adenoma	1/56 (41)	1/56 (40)	0/58 (42)	0/56 (38)
		0.8090	0.7469	0.5060	0.4810
	Carcinoma	0/56 (41)	0/56 (40)	0/58 (42)	1/56 (38)
		0.2360	NC	NC	0.4810
	Adenoma/Carcinoma	1/56 (41)	1/56 (40)	0/58 (42)	1/56 (38)
		0.4366	0.7469	0.5060	0.7339

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	5 mg Low (L) P - L vs. C	15 mg Mid (M) P - M vs. C	30 mg High (H) P - H vs. C
Pituitary Gland	Adenoma, Pars Distalis	42/60 (55)	44/60 (55)	47/60 (56)	43/60 (53)
		0.2847	0.4089	0.2234	0.3563
	Adenoma, Pars Intermedia	0/60 (43)	0/60 (42)	1/60 (42)	0/60 (39)
		0.4880	NC	0.4941	NC
	Adenoma, Pars Distalis/ Adenoma, Pars Intermedia	42/60 (55)	44/60 (55)	48/60 (56)	43/60 (53)
		0.2695	0.4089	0.1550	0.3563
Skeletal Muscle	Rhabdomyosarcoma	1/60 (44)	0/60 (42)	0/60 (42)	0/60 (39)
		0.7365	0.4884	0.4884	0.4699
Skin	Carcinoma, Squamous Cell	0/60 (43)	0/59 (42)	0/59 (42)	1/60 (40)
		0.2395	NC	NC	0.4819
	Keratoacanthoma	1/60 (43)	0/59 (42)	1/59 (42)	0/60 (39)
		0.6074	0.4941	0.7471	0.4756
	Carcinoma, Squamous Cell/ Keratoacanthoma	1/60 (43)	0/59 (42)	1/59 (42)	1/60 (40)
		0.3904	0.4941	0.7471	0.7346
Spinal Cord	Astrocytoma, Malignant	0/60 (43)	0/60 (42)	0/60 (42)	1/60 (39)
		0.2349	NC	NC	0.4756
Spleen	Hemangiosarcoma	0/60 (43)	1/60 (43)	0/60 (42)	0/60 (39)
		0.4850	0.5000	NC	NC
Subcutaneous Tissu	Fibroma	0/4 (3)	0/4 (2)	0/1 (0)	2/6 (3)
		0.1071	NC	NC	0.2000
	Fibrosarcoma	1/4 (3)	1/4 (3)	0/1 (0)	1/6 (4)
		0.4333	NC	NC	0.2857
	Fibroma/Fibrosarcoma	1/4 (3)	1/4 (3)	0/1 (0)	3/6 (4)
		0.2143	NC	NC	0.3714
	Hemangioma	0/4 (3)	1/4 (2)	0/1 (0)	0/6 (3)
		0.3750	0.4000	NC	NC
	Lipoma	2/4 (3)	0/4 (2)	0/1 (0)	1/6 (4)
		0.7381	0.7000	NC	0.6286
	Sarcoma, Not Otherwise Specified	1/4 (3)	0/4 (2)	1/1 (1)	1/6 (4)
		0.5000	0.4000	0.5000	0.2857
	Schwannoma, Malignant	0/4 (3)	1/4 (3)	0/1 (0)	0/6 (3)
		0.3333	0.5000	NC	NC
Thymus	Thymoma, Benign	0/60 (43)	1/60 (42)	1/60 (43)	0/60 (39)
		0.4788	0.4941	0.5000	NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	5 mg Low (L) P - L vs. C	15 mg Mid (M) P - M vs. C	30 mg High (H) P - H vs. C
Thyroid Glands	Adenoma, C Cell	1/60 (43)	7/60 (43)	4/60 (44)	1/60 (40)
		0.7816	0.0288	0.1874	0.7346
	Carcinoma, C Cell	1/60 (43)	1/60 (43)	0/60 (42)	0/60 (39)
		0.8015	NC	0.4941	0.4756
	Adenoma, C Cell/ Carcinoma, C Cell	2/60 (43)	8/60 (44)	4/60 (44)	1/60 (40)
		0.8844	0.0482	0.3492	0.4726
	Adenoma, Follicular Cell	1/60 (43)	1/60 (43)	1/60 (43)	1/60 (39)
		0.5046	NC	NC	0.7281
	Carcinoma, Follicular Cell	0/60 (43)	2/60 (43)	1/60 (43)	0/60 (39)
		0.6657	0.2471	0.5000	NC
	Adenoma, Follicular Cell/ Carcinoma, Follicular Cell	1/60 (43)	3/60 (43)	2/60 (43)	1/60 (39)
		0.5836	0.3080	0.5000	0.7281
Urinary Bladder	Carcinoma, Squamous Cell	0/60 (43)	1/59 (42)	0/60 (42)	0/60 (39)
		0.4880	0.4941	NC	NC
Uterus	Adenocarcinoma, Endometrial	1/60 (43)	3/60 (43)	2/60 (43)	0/60 (39)
		0.8161	0.3080	0.5000	0.4756
	Adenoma, Endometrial	0/60 (43)	1/60 (42)	0/60 (42)	0/60 (39)
		0.4880	0.4941	NC	NC
	Adenocarcinoma, Endometrial/ Adenoma, Endometrial	1/60 (43)	4/60 (43)	2/60 (43)	0/60 (39)
		0.8618	0.1800	0.5000	0.4756
	Polyp, Endometrial Stroma	7/60 (45)	2/60 (43)	8/60 (43)	5/60 (41)
		0.4142	0.9105	0.4611	0.5530
	Sarcoma, Endometrial Stromal	0/60 (43)	0/60 (42)	2/60 (42)	2/60 (40)
		0.0646	NC	0.2412	0.2292
	Sarcoma, Endometrial Stromal/ Polyp, Endometrial Stromal	7/60 (45)	2/60 (43)	10/60 (43)	7/60 (42)
		0.1824	0.9105	0.2598	0.5588
	Adenocarcinoma, Endometrial/ Adenoma, Endometrial/ Sarcoma, Endometrial Stromal/ Polyp, Endometrial Stromal	8/60 (45)	6/60 (44)	11/60 (43)	7/60 (42)
		0.4169	0.5962	0.2645	0.4410
	Carcinoma, Squamous Cell	1/60 (44)	2/60 (43)	0/60 (42)	0/60 (39)
		0.8793	0.4913	0.4884	0.4699
	Granular Cell Tumor, Benign	0/60 (43)	0/60 (42)	1/60 (43)	0/60 (39)
		0.4910	NC	0.5000	NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	5 mg Low (L) P - L vs. C	15 mg Mid (M) P - M vs. C	30 mg High (H) P - H vs. C
Uterus/Vagina	Granular Cell Tumor, Benign	2/60 (43)	4/60 (42)	5/60 (43)	3/59 (39)
		0.3705	0.3267	0.2166	0.4532
Vagina	Granular Cell Tumor, Benign	2/60 (43)	3/60 (42)	4/60 (42)	3/59 (39)
		0.3202	0.4887	0.3267	0.4532
	Granular Cell Tumor, Malignant	0/60 (43)	1/60 (42)	0/60 (42)	0/59 (39)
		0.4880	0.4941	NC	NC
	Granular Cell Tumor, Benign/ Granular Cell Tumor, Malignant	2/60 (43)	4/60 (42)	4/60 (42)	3/59 (39)
		0.3914	0.3267	0.3267	0.4532
	Polyp, Stromal	0/60 (43)	1/60 (43)	0/60 (42)	0/59 (39)
		0.4850	0.5000	NC	NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 3A: Intercurrent Mortality Rate in Male Mice

	Vehicle Control		Low		Mid		High		Positive Control	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 13									2	8.00
14 - 27	1	4.00	1	4.00					20	88.00
Terminal sacrifice	24	96.00	24	96.00	25	100.00	25	100.00	3	12.00
Total	25		25		25		25		25	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.1671	0.9885	0.2390	0.2390
Homogeneity (Log-Rank)	0.5681	0.9885	0.3173	0.3173

Table 3B: Intercurrent Mortality Rate in Female Mice

	Vehicle Control		Low		Mid		High		Positive Control	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 13									2	8.00
14 - 27			2	8.00					16	72.00
Terminal sacrifice	25	100.00	23	92.00	25	100.00	25	100.00	7	28.00
Total	25		25		25		25		25	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.4040	0.0935	NC	NC
Homogeneity (Log-Rank)	0.1058	0.1531	NC	NC

Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 15 mg P - VC vs. L	Mid (M) 30 mg P - VC vs. M	High (H) 75 mg P - VC vs. H	Water (WC) 0 mg P - VC vs. WC
Forestomach	Carcinoma, Squamous Cell	0/25 (24)	0/25 (24)	0/25 (25)	0/25 (25)	3/25 (12)
		NC	NC	NC	NC	0.0308 $
	Papilloma, Squamous Cell	0/25 (24)	0/25 (24)	0/25 (25)	0/25 (25)	16/25 (19)
		NC	NC	NC	NC	0.0000 $
	Carcinoma, Squamous Cell/ Papilloma, Squamous Cell	0/25 (24)	0/25 (24)	0/25 (25)	0/25 (25)	19/25 (21)
		NC	NC	NC	NC	1.0000
Harderian Glands	Adenoma	1/25 (24)	0/25 (24)	0/25 (25)	0/25 (25)	2/25 (10)
		1.0000	1.0000	1.0000	1.0000	0.2005
Hemolymphoret. Sys	Lymphoma, Malignant	0/25 (24)	0/25 (24)	0/25 (25)	0/25 (25)	22/25 (24)
		NC	NC	NC	NC	0.0000 $
Kidneys	Carcinoma, Transitional Cell	0/25 (24)	1/25 (24)	0/25 (25)	0/25 (25)	
		0.7551	0.5000	NC	NC	
Liver	Adenoma, Hepatocellular	0/25 (24)	1/25 (24)	0/25 (25)	0/25 (25)	
		0.7551	0.5000	NC	NC	
Lungs	Adenoma, Bronchio-Alveolar	0/25 (24)	1/25 (24)	1/25 (25)	0/25 (25)	
		0.6364	0.5000	0.5102	NC	
Skin	Papilloma, Squamous Cell	0/25 (24)	0/25 (24)	0/25 (25)	0/25 (25)	8/25 (15)
		NC	NC	NC	NC	0.0001 $
Whole body	Hemangiosarcoma	2/22 (25)	0/25 (25)	1/24 (25)	1/24 (25)	
		0.4844	1	NC	0.6493	
Spleen	Hemangioma	0/25 (24)	0/25 (24)	0/25 (25)	1/25 (25)	
		0.2551	NC	NC	0.5102	
	Hemangiosarcoma	1/25 (25)	1/25 (24)	0/25 (25)	1/25 (25)	
		0.5536	0.7449	1.0000	NC	
	Hemangioma/Hemangiosarcoma	1/25 (25)	1/25 (24)	0/25 (25)	2/25 (25)	
		0.2552	0.7449	0.5000	0.5000	
Thymus	Benign Thymoma	0/24 (23)	0/25 (24)	0/24 (24)	1/25 (25)	
		0.2604	NC	NC	0.5208	

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 15 mg P - VC vs. L	Mid (M) 30 mg P - VC vs. M	High (H) 75 mg P - VC vs. H	Positive (PC) 0 mg P - VC vs. PC
Forestomach	Carcinoma, Squamous Cell	0/25 (25)	0/25 (24)	0/25 (25)	0/25 (25)	2/25 (14)
		NC	NC	NC	NC	0.1228
	Papilloma, Squamous Cell	0/25 (25)	0/25 (24)	0/25 (25)	0/25 (25)	19/25 (21)
		NC	NC	NC	NC	0.0000 $
	Carcinoma, Squamous Cell/ Papilloma, Squamous Cell	0/25 (25)	0/25 (24)	0/25 (25)	0/25 (25)	21/25 (22)
		NC	NC	NC	NC	0.0000 $
Harderian Glands	Adenoma	0/25 (25)	1/25 (24)	1/25 (25)	0/25 (25)	2/25 (14)
		0.6287	0.4898	0.5000	NC	0.1228
Hemolymphoret. Sys	Lymphoma, Malignant	0/25 (25)	3/25 (24)	0/25 (25)	0/25 (25)	18/25 (23)
		0.8476	0.1099	NC	NC	0.0000 $
Lungs	Carcinoma, Bronchio-Alveolar	0/25 (25)	0/25 (24)	0/25 (25)	2/25 (25)	
		0.0618	NC	NC	0.2449	
Skin	Papilloma, Squamous Cell	1/25 (25)	0/25 (24)	0/25 (25)	0/25 (25)	7/25 (16)
		1.0000	1.0000	1.0000	1.0000	0.0031#
Spleen	Hemangiosarcoma	0/25 (25)	1/25 (24)	1/25 (25)	1/25 (25)	
		0.2997	0.4898	0.5000	0.5000	
Urinary Bladder	Hemangiosarcoma	0/25 (25)	0/25 (24)	0/25 (25)	1/25 (25)	
		0.2525	NC	NC	0.5000	

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

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

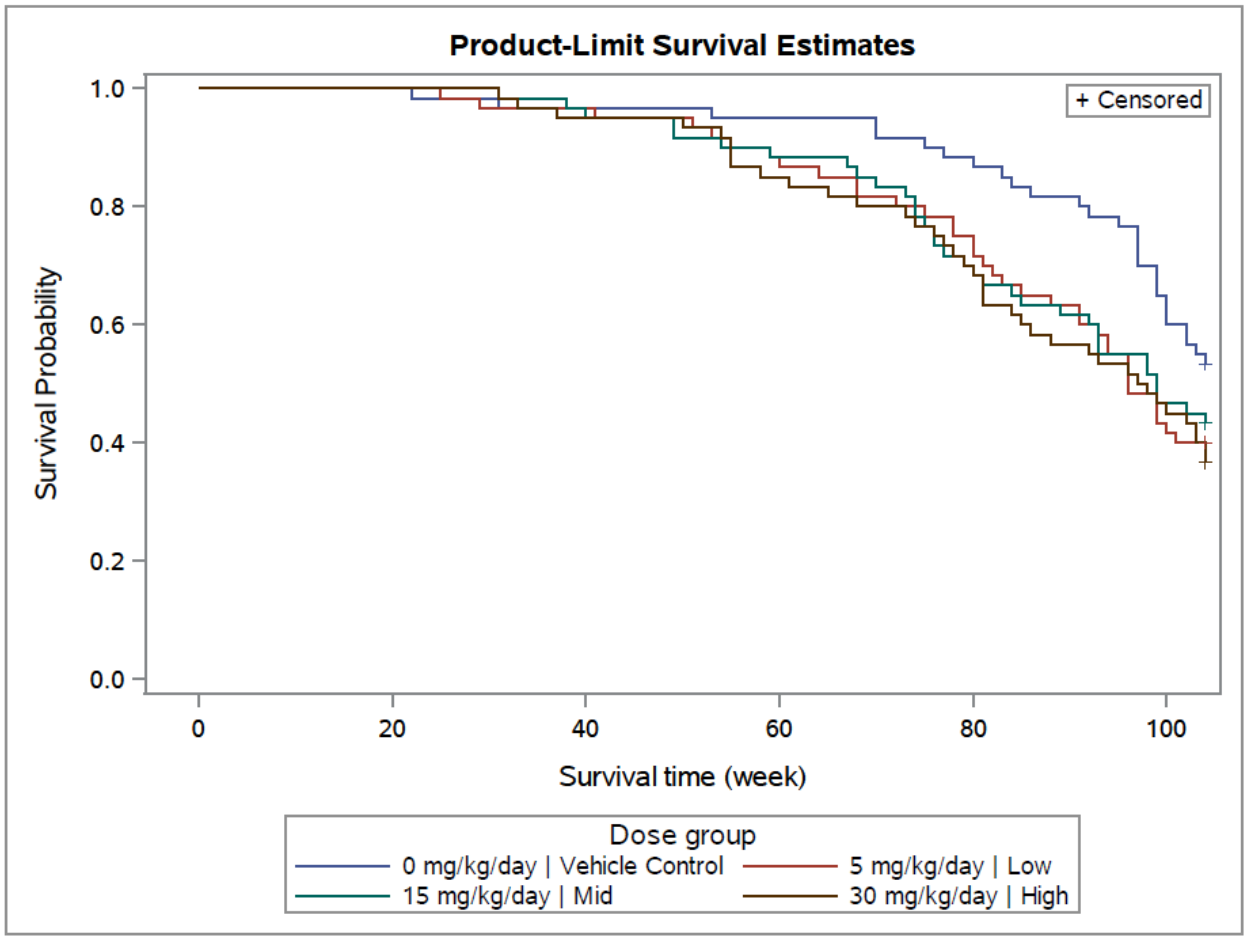


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

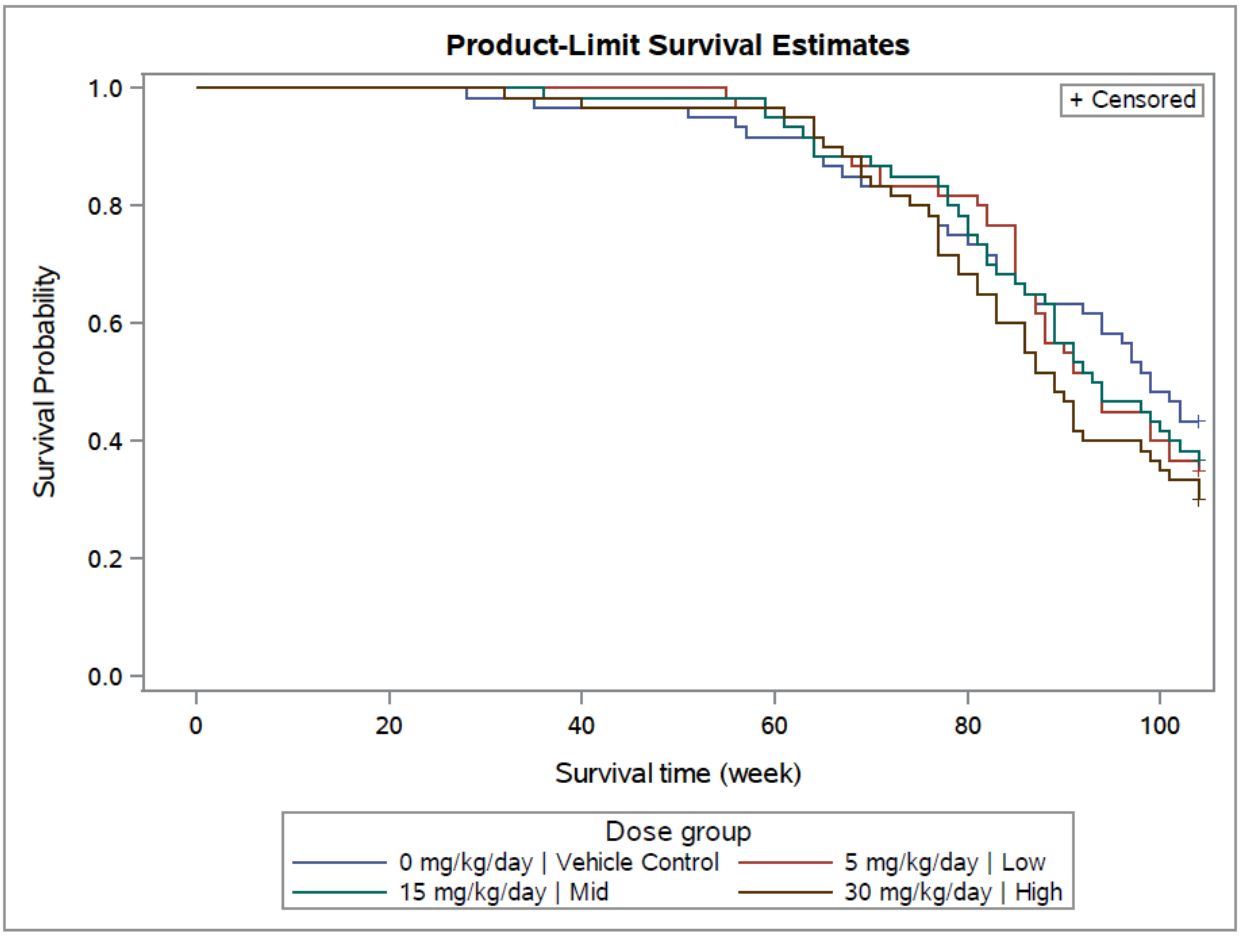


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

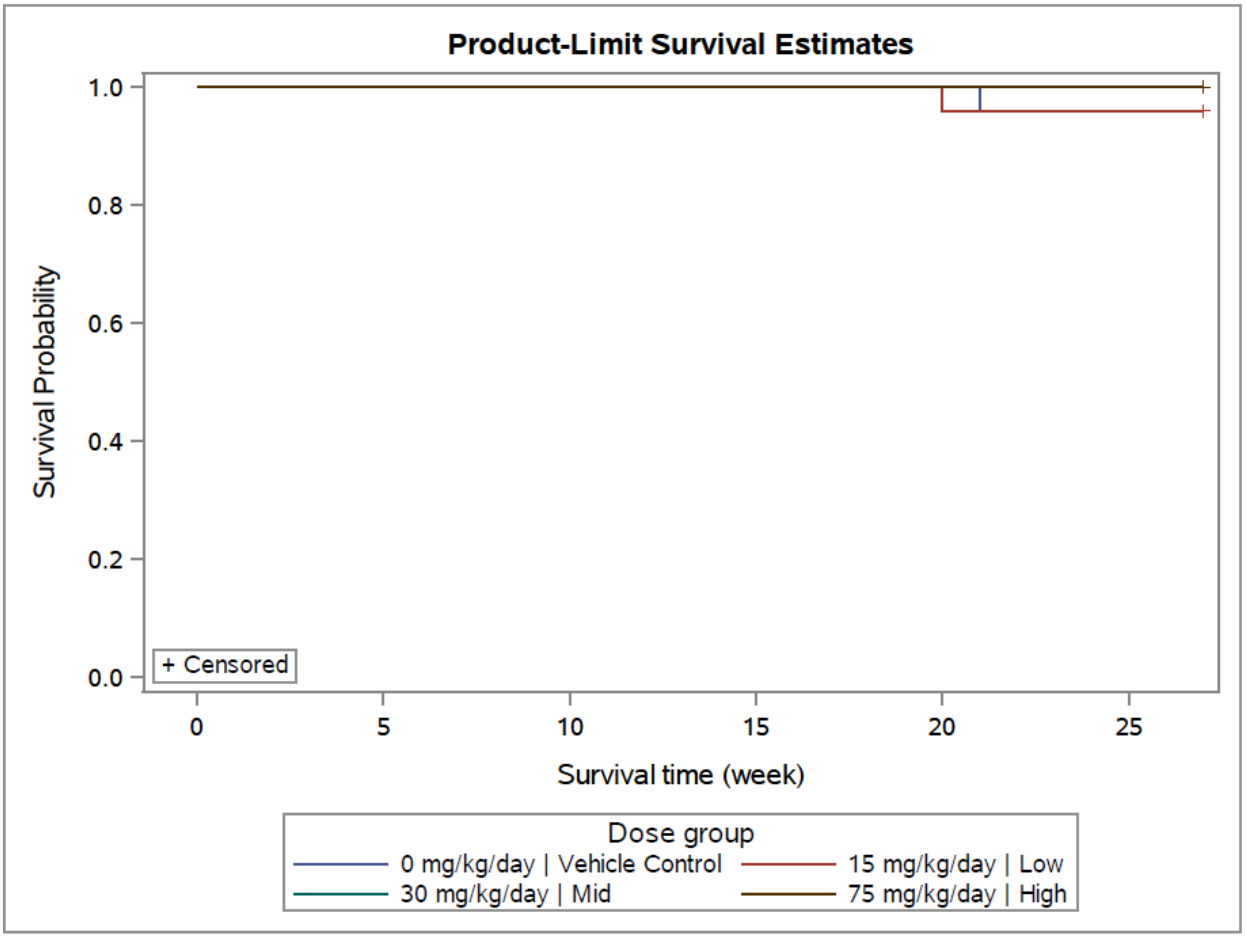
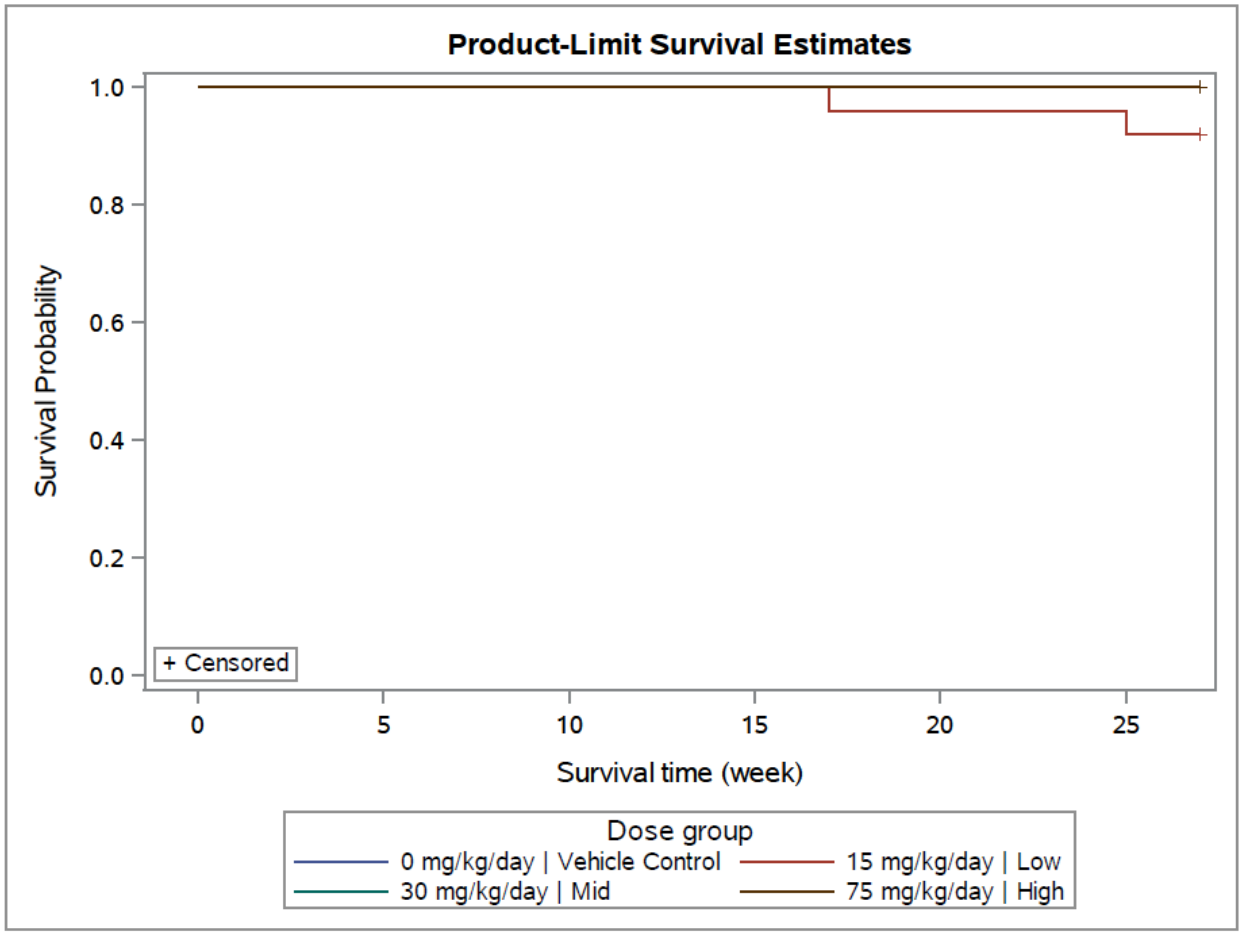


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



6. References

Bailer, A.J, Portier, C.J. (1988). “Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples.” *Biometrics*, 44, 417-431.

Bieler, G.S. and Williams, R.L. (1993). “Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity”. *Biometrics* 49, 793-801.

Guidance for Industry. Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Statues of Pharmaceuticals (Draft Guidance). U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). May 2015.

Mantel N. (1980). Assessing laboratory evidence for neoplastic activity. *Biometrics*. 36: 381-399.

Heyse J.F., Rom D. (1988). Adjusting for Multiplicity of Statistical Tests in the Analysis of Carcinogenicity Studies. *Biometrical Journal*. 30: 883-896.

Harter H.I. (1957). Error Rates and Sample Sizes for Range Tests in Multiple Comparisons. *Biomtrics*. 13: 511-536.

Haseman, J. (1983). “A re-examination of false-positive rates for carcinogenesis studies”, *Fundamental and Applied Toxicology*, 3: 334-339.

Lin KK (2000) Carcinogenicity Studies of Pharmaceuticals. In: *Encyclopedia of Biopharmaceutical Statistics*, ed. Shein-Chung Chow, Marcel Dekker, New York.

Lin K.K. and Rahman A.M. (1998). ” Overall false positive rates in tests for linear trend in tumor incidence in animal carcinogenicity studies of new drugs”, *Journal of Biopharmaceutical Statistics*, 8(1), 1-15.

Peto, R., M.C. Pike, N.E. Day, R.G. Gray, P.N. Lee, S. Parish, J. Peto, Richards, and J.Wahrendorf. (1980) “Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments”, Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, *Annex to supplement, World Health Organization, Geneva*, 311-426.

Rahman, A.M., and Lin, K.K. (2008), "A Comparison of False Positive Rates of Peto and Poly-3 Methods for Long-Term Carcinogenicity Data Analysis Using Multiple Comparison Adjustment Method Suggested by Lin and Rahman", *Journal of Biopharmaceutical Statistics*, 18:5, 849-858.

Rahman, A.M., and Lin, K.K. (2009), "Design and Analysis of Chronic Carcinogenicity Studies of Pharmaceuticals in Rodents", in “Design and Analysis of Clinical Trials with Time-to-Event Endpoints", K.E Peace, Editor, Chapman & Hall/CRC, Taylor & Francis Group, LLC, Boca Raton, FL, London, and New York.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HEPEI CHEN
07/31/2019 02:46:25 PM

KARL K LIN
08/01/2019 10:29:16 AM
Concur with review.

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	211150/Original-1
Drug Name:	Pitolisant
Indication:	Excessive daytime sleepiness (EDS) in adults with narcolepsy, Cataplexy in adults with narcolepsy
Applicant:	Bioprojet Pharma
Date(s):	Submission Date: 12/14/2018 PDUFA Date: 08/14/2019
Review Priority:	Priority
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Semhar Ogbagaber, Ph.D.
Concurring Reviewers:	Jinglin Zhong, Ph.D., HM James Hung, Ph.D.
Medical Division:	Division of Psychiatry Products
Clinical Team:	Martine Solages, M.D.
Project Manager:	Brendan Muoio, Pharm. D.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

Bioprojet Pharma submitted three primary efficacy studies (HARMONY 1, HARMONY 1BIS and HARMONY CTP) under NDA 211150 to investigate WAKIX (pitolisant) for two indications: 1) the treatment of excessive daytime sleepiness (EDS) in adults with narcolepsy (supported by HARMONY 1, HARMONY 1BIS); 2) the treatment of cataplexy in adults with narcolepsy [redacted] (b) (4) Narcolepsy is a serious, chronic, rare neurologic disorder characterized by excessive daytime sleepiness, cataplexy (sudden loss of muscle tone) and sleep paralysis. Pitolisant was approved by EMA (European Medicines Agency) for one indication, excessive daytime sleepiness in narcolepsy with or without cataplexy on March 31, 2016. [redacted] (b) (4)

The three studies evaluated flexible doses (as determined by investigators) of pitolisant versus placebo, that is, HARMONY 1 (10, 20, 40 mg/day), HARMONY CTP (5, 10, 20, 40 mg/day) and HARMONY 1BIS (5, 10, 20 mg/day).

Pitolisant treatment group showed statistically significant improvement in the primary efficacy endpoint, ESS (Epworth Sleepiness Scale) compared to placebo, in HARMONY 1 (LS mean difference = -3.10; $p = 0.02$) and HARMONY 1BIS (LS mean difference = -2.19; $p = 0.03$). The replicated efficacy results showed improved daytime sleepiness which supports the indication of EDS.

[redacted] (b) (4)

All the studies were conducted outside of U.S. [HARMONY 1: mostly in Western Europe and 1 country in Central Europe; HARMONY CTP: Russia, Southeast, Central and Eastern Europe; HARMONY 1BIS: mostly Western Europe, 1 country in South America, 1 country in Central Europe].

2 INTRODUCTION

2.1 Overview

Pitolisant was approved by EMA (European Medicines Agency) for excessive daytime sleepiness and cataplexy associated with narcolepsy on March 31, 2016. The Applicant seeks to claim indication for excessive daytime sleepiness and cataplexy in patients with narcolepsy.

All the studies were conducted outside of US, in support of this NDA to evaluate the effect of pitolisant for treatment of excessive daytime sleepiness and cataplexy associated with narcolepsy.

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
P07-03 (HARMONY 1)	Phase 3, multicenter, randomized, double-blind, placebo and comparator-controlled, parallel group study to evaluate BF2.649, for treatment of excessive daytime sleepiness (EDS) in narcoleptic patients with or without cataplexy	BF2.649 (10 to 40 mg/day) (31) Modafinil (100 to 400 mg/day) (33) Placebo (30)	Primary: Change from baseline to week 8 in Epworth Sleepiness Scale (ESS) total score. Note: Step-down approach was used to control for multiple comparisons of treatments: test superiority (BF2.649 > placebo) and non-inferiority (BF2.649 vs modafinil) on a fixed non-inferiority margin.	Primary: BF2.649 versus placebo is significant (p = 0.022). But, BF2.649 versus modafinil is not significant where 95% CI = (-2.11, 2.30) (p=0.932**). **Non-inferiority test couldn't be concluded, the 95% CI lower bound, -2.11 < non-inferiority margin NI=2).
[redacted]				

(b) (4)

				(b) (4)
P09-15 (HARMONY 1BIS)	Phase 3, multicenter, randomized, double-blind, placebo and comparator-controlled, parallel group study to evaluate BF2.649, in the treatment of excessive daytime sleepiness (EDS) in narcolepsy	BF2.649 (5, 10, 20 mg/day) (66) Modafinil (100, 200, 400 mg/day) (65) Placebo (32)	Primary: Change from baseline to week 8 in Epworth Sleepiness Scale (ESS) total score. Note: Step-down approach was used to control for multiple comparisons of treatments: test superiority (BF2.649 > placebo) and non-inferiority (BF2.649 vs modafinil) on a fixed non-inferiority margin.	Primary: BF2.649 versus placebo is significant (p = 0.03). But, BF2.649 versus modafinil is not significant where 95% CI = (1.02, 4.48) (p=0.002**). **Non-inferiority test couldn't be concluded, the 95% CI lower bound, 1.02 < non-inferiority margin NI=2).

Source: Reviewer (there were no prospectively pre-specified key secondary endpoints in all three trials)

2.2 Data Sources

The sponsor's submitted data and SAS program listings for the two pivotal studies are available in the following directory of the CDER' electronic document room (EDR): \\Cdsesub1\evsprod\NDA211150\0005

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The reviewer found the quality and integrity of the submitted data satisfactory and acceptable for the review analysis.

3.2 Evaluation of Efficacy

The objective of these confirmatory studies was to provide evidence of efficacy of pitolisant for excessive daytime sleepiness and cataplexy in adult patients with narcolepsy.

3.2.1 Study Design and Endpoints

3.2.1.1 HARMONY 1

Study Design

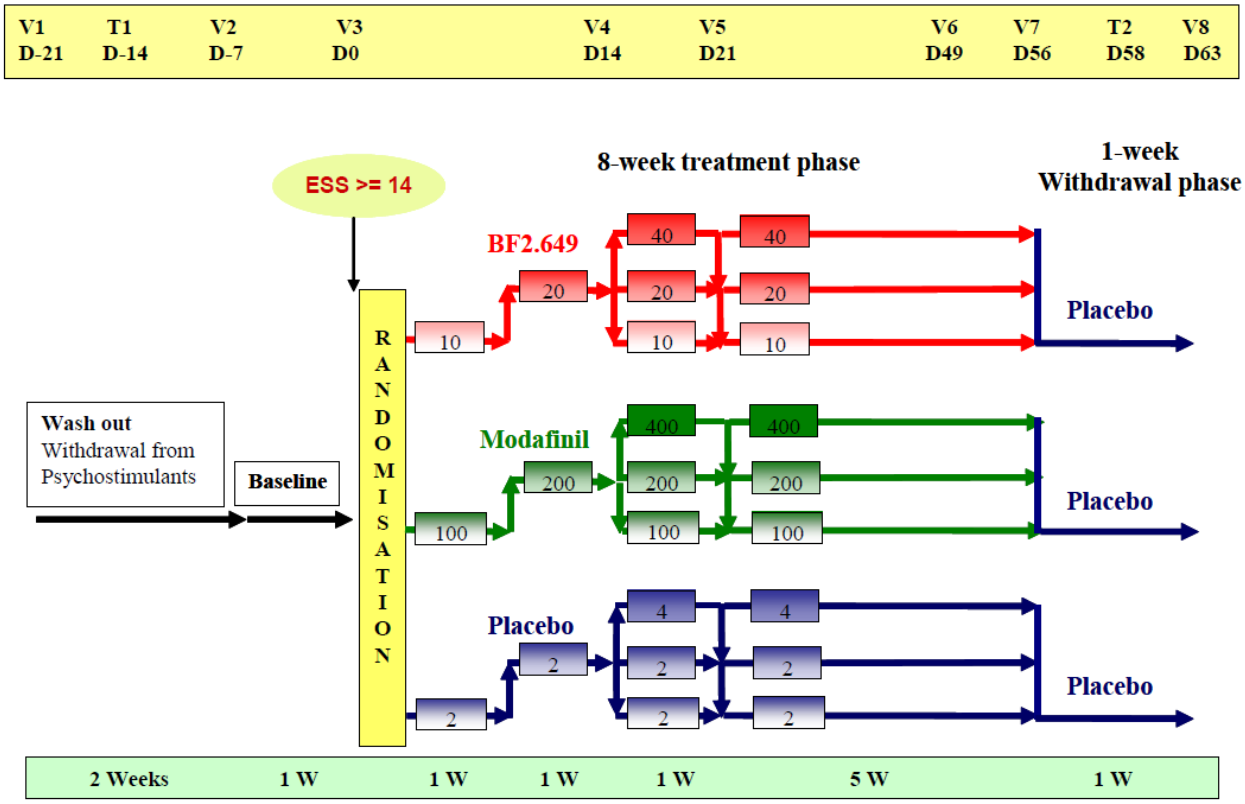
This is a phase 3, multicenter, randomized, double-blind, placebo and active-controlled (Modafinil), parallel group, flexible dose study. The study compares pitolis//ant (escalating doses of 10mg, 20mg or 40 mg) and Modafinil (escalating doses of 100mg, 200mg, or 400 mg) and placebo.

This study enrolled subjects at 24 centers in 5 countries: France, Germany, Hungary, the Netherlands and Switzerland. The first subject was enrolled on 26 May 2009 and the last subject's visit was on 30 June 2010. Subjects were 18 years of age or over and meet international classification of sleep for both new and previously diagnosed patients with narcolepsy with or without cataplexy.

If screened to enroll into the study, subjects would discontinue taking medications for EDS (such as modafinil, amphetamine or any other medications for treatment of EDS) during a washout period of at least 14 days prior to the baseline visit. If patients never used stimulants, they would enter the baseline period. However, cataplexy patients were allowed to remain on stable doses of anticataleptic medications (sodium oxybate, antidepressant such as SSRI) throughout the trial. Tricyclic antidepressants are prohibited.

During the baseline period, which lasted 7 days, patients were not allowed to take prohibited medications. Subjects who fulfilled the inclusion criteria (such as ESS at baseline ≥ 14) were randomized 1:1:1 to pitolisant, modafinil and placebo groups and enrolled in an 8-week double-blind treatment period. Randomized patients received flexible doses of pitolisant (10mg, 20mg, 40mg per day) and modafinil (100mg, 200mg, 400mg per day) with 3-week individual dose-titration period. Investigators were able to monitor and adjust doses during treatment period at days 0, 14, 21 based on individual response and tolerability. Subjects who completed the treatment period entered a 1-week withdrawal period during which all subjects received only placebo. The overall study period was 12 weeks.

Figure 1: Overall Study Schema-HARMONY 1



Source: Figure 1 of Sponsor's Clinical Study Report (Page 24)

Study Endpoints (Primary and secondary efficacy)

The primary efficacy outcome was the mean at the end of study ([V7+V6]/2) in ESS† (Epworth Somnolence Scale) total score between pitolisant and placebo. Higher scores of ESS total indicate increased sleepiness. The maximum total score is 24. Baseline ESS value (ESSBL) is measured at baseline visits, (V2 and V3). Final ESS value (ESSFINAL) is calculated as the arithmetic mean of V6 and V7, or the last visit for premature withdrawals (ESS*). ESS* is the value last observation carried forward. If no post-baseline value is available, then ESSFINAL = ESSBL.
Missing Baseline ESS: when ESS at V2 is missing then ESSBL will be calculated as the average at V1 and V3.

† ESS: *is a self-administered questionnaire which evaluates chances of dozing in eight different situations often encountered in daily life. Dozing probability ratings are "would never doze" (0 points), "slight chance of dozing" (1 point), moderate chance of dozing" (2 points), and "high chance of dozing" (3 points) in eight hypothetical situations often encountered in the daily life (CSR, page 36).*

Secondary endpoints: ESS responder rate (ESSF ≤ 10 or ESSF-ESSBL ≥ 3), Maintenance of Wakefulness Test (MWT), Daily Cataplexy Rate (DRC) and Sustained Attention to Response Task (SART).

The original protocol was issued on December 15, 2011, and was amended once on October, 2018.

(b) (4)

Reviewer's Note 2: The sponsor conducted futility analysis "to avoid useless continuation of a trial" but the interim analysis had no impact on the overall trial plan.

(b) (4)

3.2.1.3 HARMONY 1BIS

Study Design

This is a randomized, double-blind, placebo and Modafinil controlled, parallel group, multicenter trial assessing the effects of pitolisant in the treatment of excessive daytime sleepiness in narcolepsy. The study compares pitolisant (escalating doses of 5mg, 10mg or 20 mg) and Modafinil (escalating doses of 100mg, 200mg, or 400 mg) and placebo.

This study was multinational and multicenter in scope: 32 study sites and 8 countries: Argentina (2 sites), Austria (1 site), Finland (1 site), France (8 sites), Germany (4 sites), Hungary (4 sites), Italy (6 sites), Spain (6 sites). The first subject was enrolled on 25 October 2010 and the last subject's visit was on 24 July 2012.

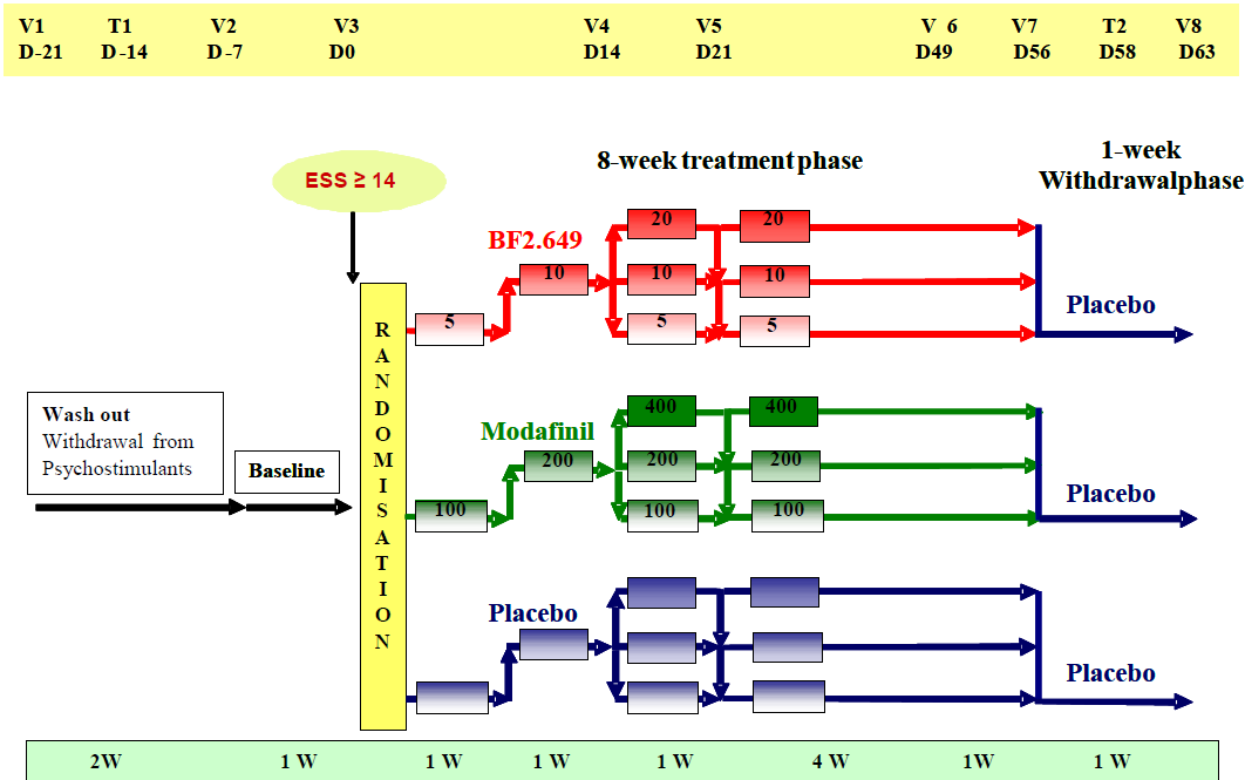
Diagnosis and Main Criteria for Inclusion: Subjects were 18 years of age or over; male or female; diagnosed with narcolepsy with or without cataplexy and meet the International Classification of Sleep Disorders (ICSD-2) criteria.

After 2 weeks of washout period during which they discontinue taking prohibited medications such as psychostimulants, baseline measures were taken during the 1-week baseline period. If patients never used stimulants, they would enter the baseline period. Total duration of the trial, from screening visit (V1) to final visit (V8), was 12 weeks: a 2-week washout period (V1 to V2), 1-week baseline period (V2-V3), an 8-week treatment period (V3-V7) and a 1-week withdrawal phase (V7-V8).

Subjects who fulfilled the inclusion criteria (such as ESS at baseline $\geq$ 14) were randomized* 2:2:1 to pitolisant, modafinil and placebo groups and enrolled in an 8-week double-blind treatment period. From D1 to D7, patients received BF2.649 5 mg/d or modafinil 100 mg/d or placebo. From D8 to D14, doses were increased to pitolisant (10 mg/day), modafinil (200 mg/day) or placebo. At D15, doses could be adjusted according to individual benefit/risk ratio (5, 10 or 20 mg/day for pitolisant; 100, 200 or 400 mg/day for modafinil; placebo). At D21, an individual dose adjustment could be performed again, but no dose increase was allowed. Dose remained stable for a five-week period and all patients received placebo in the subsequent 1-week withdrawal period (D56 to D63).

*Unequal Randomization: According to applicant's stated rationale, the choice of unequal randomization was for two reasons: to test for both superiority and inferiority, and safety. That is, *"The choice of an initial 1:2:2 randomization ratio was: a) this was together a superiority test (Placebo><verum), and a non-inferiority test (verum><modafinil). However the non-inferiority test obviously requires more patients, thus the size of the placebo arm might be reduced, b) the decision to increase the two verum arms was for safety purposes."* (CSR, page 26)

Figure 3: Overall Study Schema-HARMONY 1BIS



Source: Figure 1 of Sponsor's Clinical Study Report (Page 24)

Study Endpoints (Primary and secondary efficacy)

The primary efficacy outcome was the mean difference of ESS total score at final visit ([V7+V6]/2) between pitolisant and placebo. Higher scores of ESS total indicate increased sleepiness. The maximum total score is 24. Baseline ESS value (ESSBL) is measured at baseline visits, (V2 and V3). Final ESS value (ESSFINAL) is calculated as the arithmetic mean of V6 and V7, or the last visit for premature withdrawals (ESS*). ESS* is the summary mean of the two last observation carried forward values. If no post-baseline value is available, then ESSFINAL = ESSBL.

Missing Baseline ESS: when ESS at V2 is missing then ESSBL will be calculated as the average at V1 and V3.

Secondary endpoints: ESS responder rate (ESSF $\leq$ 10 or ESSF-ESSBL $\geq$ 3), daily cataplexy rate, MWT, SART.

The original protocol which was issued on 30 April 2010 and all changes including a sample size increase was amended on 26 April 2011.

3.2.2 Statistical Methodologies

The following statistical methodologies were pre-specified in the sponsor's statistical analysis plan.

3.2.2.1 HARMONY 1

The primary analysis for the primary and other secondary efficacy endpoints was carried out on the intention to treat (ITT). The ITT population included all randomized patients who received at least 1 dose of study medication and provided at least 1 post-baseline value.

Efficacy Analyses Methods (Primary Efficacy)

The comparison between potosilant and placebo for ESS final score (ESSF) was analyzed using analysis of covariance with linear mixed effect model, adjusted for ESS baseline score (ESSBL), treatment (fixed effect) and center (random effect). The final visit scores were imputed using last observation carried forward (LOCF). The difference in ESS final scores between pitolisant and modafinil was assessed if there was a statistically significant difference between pitolisant and placebo groups.

Multiple Comparisons: step-down approach was conducted to control type 1 error rate. The 2 hypotheses, superiority (pitolisant > placebo) and non-inferiority (pitolisant vs modafinil) on a fixed non-inferiority margin (NIM), were tested on the same alpha level (0.025). That is,
Step 1: H_{01}: pitolisant $\leq$ placebo must be rejected at $\alpha = 0.025$. Proceed to test H_{02} when H_{01} was rejected.
Step 2: H_{02}: pitolisant $\leq$ modafinil $- \theta$ (where θ=2 is the NIM) must be rejected at $\alpha = 0.025$.

Efficacy Analyses Methods (Other Efficacy Endpoints)

The effect of pitolisant group was assessed based on ESS responder rate (logistic regression); geometric mean ratio based on pooled Student t-test for Maintenance of Wakefulness Test (MWT) Sustained Attention to Response Task (SART) and Daily Cataplectic Rate. The last observed value is imputed in a similar manner as the primary efficacy endpoint.

Both MWT and SART were administered, in four sessions, at visit 3 and end of treatment period (visit 8). During a 40-minute session, MWT measures ability to stay awake in minutes. The SART (a complete assessment takes 4 min, 20 sec), used to quantify vigilance and attention in narcolepsy patients, consists of 3 error measurement scores: "the number of times a key is pressed when 3 is presented" ("NO GO"), "the number of times when no key is pressed when it should have been" ("GO"), and the sum of the two components.

Multiplicity: In testing the secondary endpoints, there were no corrections made for multiplicity to control the overall type I error rate.

Reviewer's Note: According to sponsor's SAP (November 28, 2010), the secondary endpoints, MWT and SART, were to be assessed according to a non-parametric Mann-Whitney test since they were not assumed to follow normal distribution. But this non-parametric method was not utilized in the final data analysis.

In response to FDA Information Request on 27 March 2019, the Applicant conducted analyses based on Mann-Whitney test for the secondary endpoint: MWT. See Reviewer Comment 1 in Section 3.2.2.1 whether the specified confirmatory results for MWT remained consistent.

Sensitivity Analyses

- Primary efficacy analysis on PP (per-protocol) population.

Supportive Analyses

A few ANCOVA without center effect were computed:

1. ESSF adjusted on ESSBL
2. ESSF not adjusted on ESSBL

3.2.2.3 HARMONY 1BIS

The primary efficacy was conducted on the FAS population. The FAS includes subjects who were randomized, received at least 1 dose of study drug, and had at least 1 valid post-baseline value for assessment of primary efficacy.

Efficacy Analyses Methods (Primary Efficacy)

The primary analysis method for the final ESS score (ESSF) was a linear mixed effect model (LME), which included baseline ESS score (ESSBL), treatment as a fixed effect and center as a

random effect. The hypothesis testing involved a superiority (vs. placebo) and non-inferiority (vs. modafinil) test of pitolisant. The non-inferiority test was based on the non-inferiority margin of -2.

Efficacy Analyses Methods (Other Efficacy Endpoints)
Logistic regression for ESS responder rate*; linear fixed effect model for Maintenance of Wakefulness Test (MWT) and Sustained Attention to Response Task (SART); quasi-Poisson regression model for daily cataplexy rates (DCR).

* ESS responder rate: defined as the absolute value of ESSF $\leq$ 10 at study end or ESSF – ESSBL > 3.

Multiplicity: In testing the secondary endpoints, there were no corrections made for multiplicity to control the overall type I error rate.

However, a step-down approach was used to test superiority (pitolisant > placebo) and non-inferiority (pitolisant vs modafinil) on a fixed non-inferiority margin (NIM).

Sensitivity Analyses

- Primary efficacy analysis on PP (per-protocol) population.

Supportive Analyses

A few ANCOVA without center effect were computed:

3. ESSF adjusted on ESSBL
4. ESSF not adjusted on ESSBL

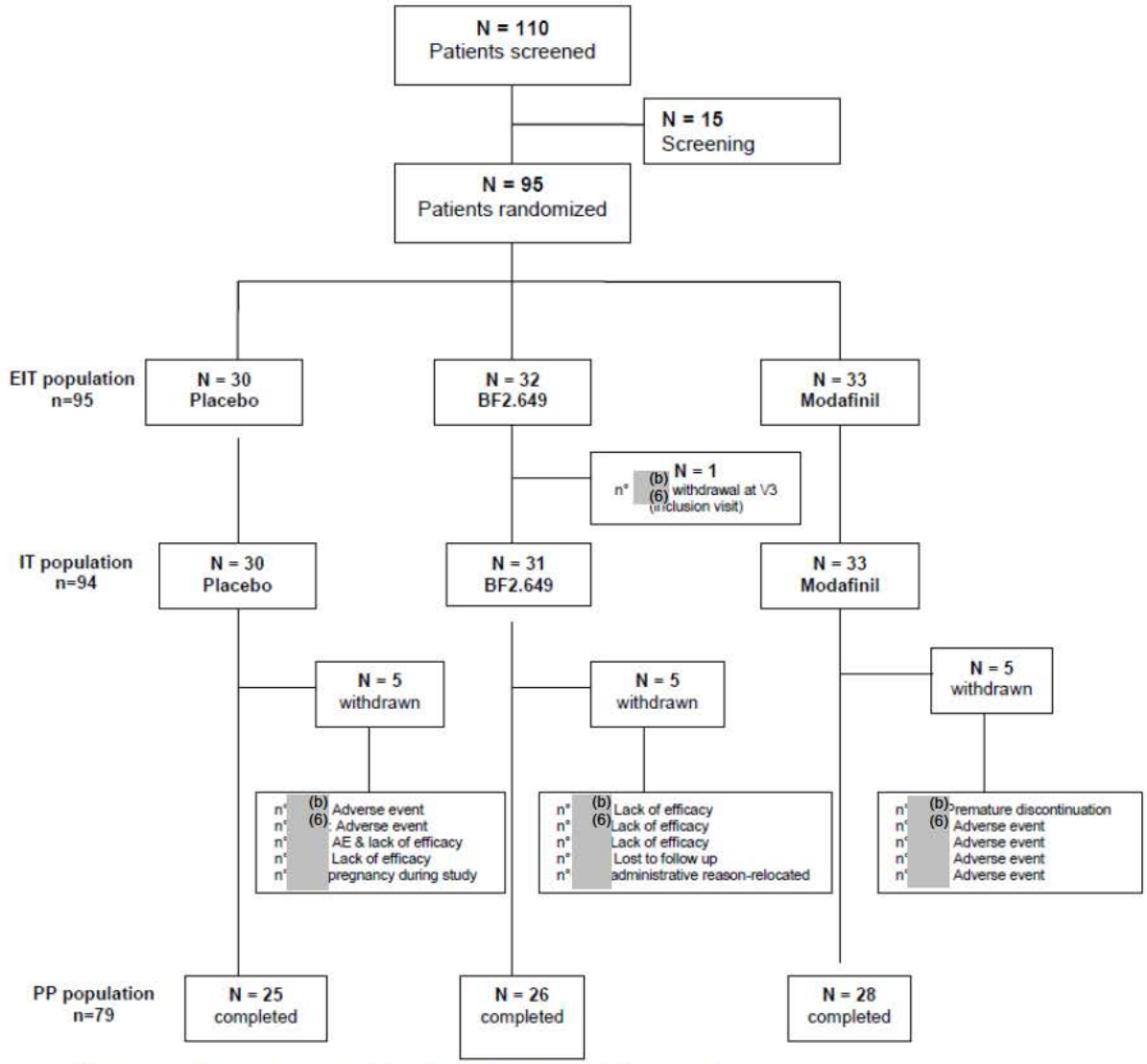
3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 HARMONY 1

Of the 110 patients screened, 95 subjects met the eligibility criteria and were randomized placebo (30), pitolisant (32), or modafinil (33). The ITT included 94 patients since one subject has no post-baseline measurements.

Table 1 and Figure 4 display overall subject dispositions, including the percentage of discontinuation for all randomized subjects in the 3 treatment groups due to major or premature withdrawals: placebo (16.7%), pitolisant (16.1%), modafinil (15.2%), which was similar across treatment groups. Overall discontinuation rate was 15.2%. The frequent discontinuation reasons included adverse events (8.5%) and lack of efficacy (4.3%).

Figure 4: Patient Disposition-HARMONY 1



Source: Figure 3 of Sponsor's Clinical Study Report (Page 53)

Table 2: Disposition of Patients-HARMONY 1 [n (%)] (All Patients)

	PLACEBO	BF2.649	MODAFINIL	ALL
Selected	-	-	-	110
Randomized / Extended Intent-to-treat (EIT)	30	32	33	95 (100%)
Randomized / Intent-to-treat (IT)	30 (31.9%)	31 (33%) *	33 (35.1%)	94 (100%)
Major deviations or Premature Withdrawals	5 (16.7%)	5 (16.1%)	5 (15.2%)	15 (16%)
Per Protocol (PP)	25 (31.6%)	26 (32.9%)	28 (35.4%)	79 (100%)
Completed	25 (31.6%)	26 (32.9%)	28 (35.4%)	79 (100%)
Premature Withdrawals	5 (16.7%)	5 (16.1%)	5 (15.2%)	15 (16%)
Minor deviations	25 (83.3%)	29 (93.5%)	24 (72.7%)	78 (83%)
** Patient (b) (6) was excluded from IT population due to consent withdrawal.*				
Analysis was conducted on ADSL and ADDV datasets				

Source: Table 14.1.1.1 in Appendix 14 of Sponsor's Clinical Study Report (Page 6)

Baseline demographic characteristics were balanced across the randomized population as summarized in Table 2. The average age of patients was 39 years ranging from 18 to 75 years; majority of participants were whites (94.7%). Also, the baseline narcolepsy characteristics were similar across the three treatment groups (Table 3).

Table 3: Summary of Demographic Characteristics-HARMONY 1 (ITT Population)

	PLACEBO (N=30)		BF2.649 (N=31)		MODAFINIL (N=33)		p-value
Parameter	**N**	**Value[1]**	**N**	**Value[1]**	**N**	**Value[1]**	
Age (yr)	30	39.5 [30.0; 52.0]	31	33.0 [21.0; 49.0]	33	40.0 [2.05; 48.0]	0.335
Weight (kg)	30	81.0 ± 20.7	31	90.9 ± 21.0	33	81.0 ± 16.3	0.073
Height (cm)	30	168.8 ± 10.4	31	173.9 ± 9.8	33	171.0 ± 8.5	0.122
BMI (kg/m²)	30	28.2 ± 6.0	31	30.4 ± 8.3	33	27.7 ± 5.3	0.250
Gender (Males)	30	43.3 (13)	31	64.5 (20)	33	54.5 (18)	0.274
2 yrs Post-Menopause or Sterilized	17	35.3 (6)	11	27.3 (3)	15	26.7 (4)	0.916
Mode of Contraception[2]	11		8		11		
Bill Control Pill		18.2 (2)		37.5 (3)		18.2 (2)	0.880
IUD		27.3 (3)		12.5 (1)		18.2 (2)	
Other Method		54.5 (6)		50.0 (4)		63.6 (7)	
Race	30		31		33		
White		93.3 (28)		93.5 (29)		97.0 (32)	0.736
Black or African American		6.7 (2)		6.5 (2)		3.0 (1)	

Source: Table 6 of Sponsor's Clinical Study Report (Ref. 14.1.2.1, Page 56)

[1]Data are expressed as Mean ± SD for weight, height, BMI; as % (n) for gender, contraception, race; as Median [25th%; 75th%] for age.

[2] Patient (b) (6) birth control method by vaginal route equivalent to 0.03 mg ethinyl estradiol by oral route; Patients (b) (6) and (b) (6) were using oral estroprogestative as birth control method with a dose different to 0.05 mg of ethinylestradiol. These three deviations were considered minor.

Table 4: Summary of Baseline Narcolepsy Characteristics-HARMONY 1 (ITT Population)

	PLACEBO (N=30)		BF2.649 (N=31)		MODAFINIL (N=33)		p-value[2]
Parameter	**N**	**Value[1]**	**N**	**Value[1]**	**N**	**Value[1]**	
Duration of Narcolepsy (yrs)	30	15.2 [9.2; 25.3]	31	11.1 [8.2; 18.0]	33	12.2 [5.7; 20.3]	0.459
Multiple Sleep Latency Test (min)	18	5.4 ± 2	20	3.7 ± 2.6	20	4.9 ± 2.4	0.080
History of Drug Abuse or Dependence Disorder	30	0.0 (0)	31	0.0 (0)	33	0.0 (0)	.
History of Cataplexy		80.0 (24)		80.6 (25)		81.8 (27)	1.000
History of Associated Symptoms							
Sleep paralysis		50.0 (15)		48.4 (15)		66.7 (22)	0.282
Hallucinations		63.3 (19)		58.1 (18)		63.6 (21)	0.896
Automatic behavior		30.0 (9)		48.4 (15)		48.5 (16)	0.259
Dyssomnia		46.7 (14)		58.1 (18)		60.6 (20)	0.551
Baseline ESS (V2 + V3)/2	30	18.9 ± 2.5	31	17.8 ± 2.5	33	18.5 ± 2.7	0.246
Baseline CGIS (Scale 1=EDS)	30	5.3 ± 0.8	31	5.2 ± 0.9	33	5.2 ± 1.2	0.903
Baseline CGIS (Scale 2=cataplexy)	30	3.1 ± 1.9	31	3.6 ± 1.7	33	3.0 ± 1.9	0.440
Baseline EQ-5D	29	64 ± 19.2	31	65.3 ± 21.3	32	58.7 ± 19.4	0.390
Baseline SART-NOGO	30	8.0	30	9.1	33	9.0	0.692
Baseline SART-GO	30	3.5	30	3.6	33	3.3	0.808
Baseline SART-TOTAL	30	11.4	30	12.5	33	11.4	0.995
Baseline MWT	30	8.4	31	7.4	33	8.8	0.639

Source: Table 7 of Sponsor's Clinical Study Report (Ref: Table 14.1.2.1, Page 57)

[1] Data are expressed as Mean ± SD except for narcolepsy characteristics (expressed as % (n)), duration of narcolepsy (expressed as Median [25th%; 75th%]) and MWT, SART (Geometric Mean)

[2] Details on the statistical tests used to compare groups are provided in section 9.7.1.

(b) (4)

3 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

3.2.3.3 HARMONY 1BIS

Of the 183 patients who were selected, 166 were randomized of which 163 were included in the ITT population: placebo (32), pitolisant (66), or modanifil (65). Three (3) patients were excluded from the randomized population which formed the ITT for the following reasons: never took the study drug (modafinil), diagnosis of narcolepsy was not confirmed (placebo), only took one dose of treatment (pitolisant).

Table 8: Disposition of Patients-HARMONY 1BIS [% (n)]

Patient Status	PLACEBO % (n)	BF2.649 % (n)	MODAFINIL % (n)	TOTAL N
Selected	-	-	-	**183**
Randomized	**19.9 (33)**	**40.4 (67)**	**39.8 (66)**	**166**
Safety[1]	**20.0 (33)**	**40.6 (67)**	**39.4 (65)**	**165**
Extended Intent-to-Treat (EIT)[2]	**19.5 (32)**	**40.9 (67)**	**39.6 (65)**	**164**
Intent-to-Treat (ITT)[3]	**19.6 (32)**	**40.5 (66)**	**39.9 (65)**	**163**
Major Deviations	0.0 (0)	0.0 (0)	1.5% (1)	1
Per Protocol (PP)[4]	**19.7 (30)**	**39.5 (60)**	**40.8 (62)**	**152**
Completed	20.3 (31)	39.2 (60)	40.5 (62)	153
Premature Withdrawals[5]	16.7 (2)	58.3 (7)	25.0 (3)	12
Minor Deviations	44.4 (4)	44.4 (4)	11.1 (1)	9

[1] Patient (b) (6) was prematurely withdrawn after randomization before first treatment intake and was excluded from Safety Population.

[2] Patient (b) (6) did not meet criteria for a diagnosis of narcolepsy and was excluded from the efficacy analysis but taken into account for the analysis of safety as he/she had received the study treatment; this patient prematurely discontinued the study treatment but was not prematurely withdrawn from the trial and was considered as completed the study.

[3] Patient (b) (6) had premature withdrawal at D14 after only one treatment intake and was excluded from ITT population.

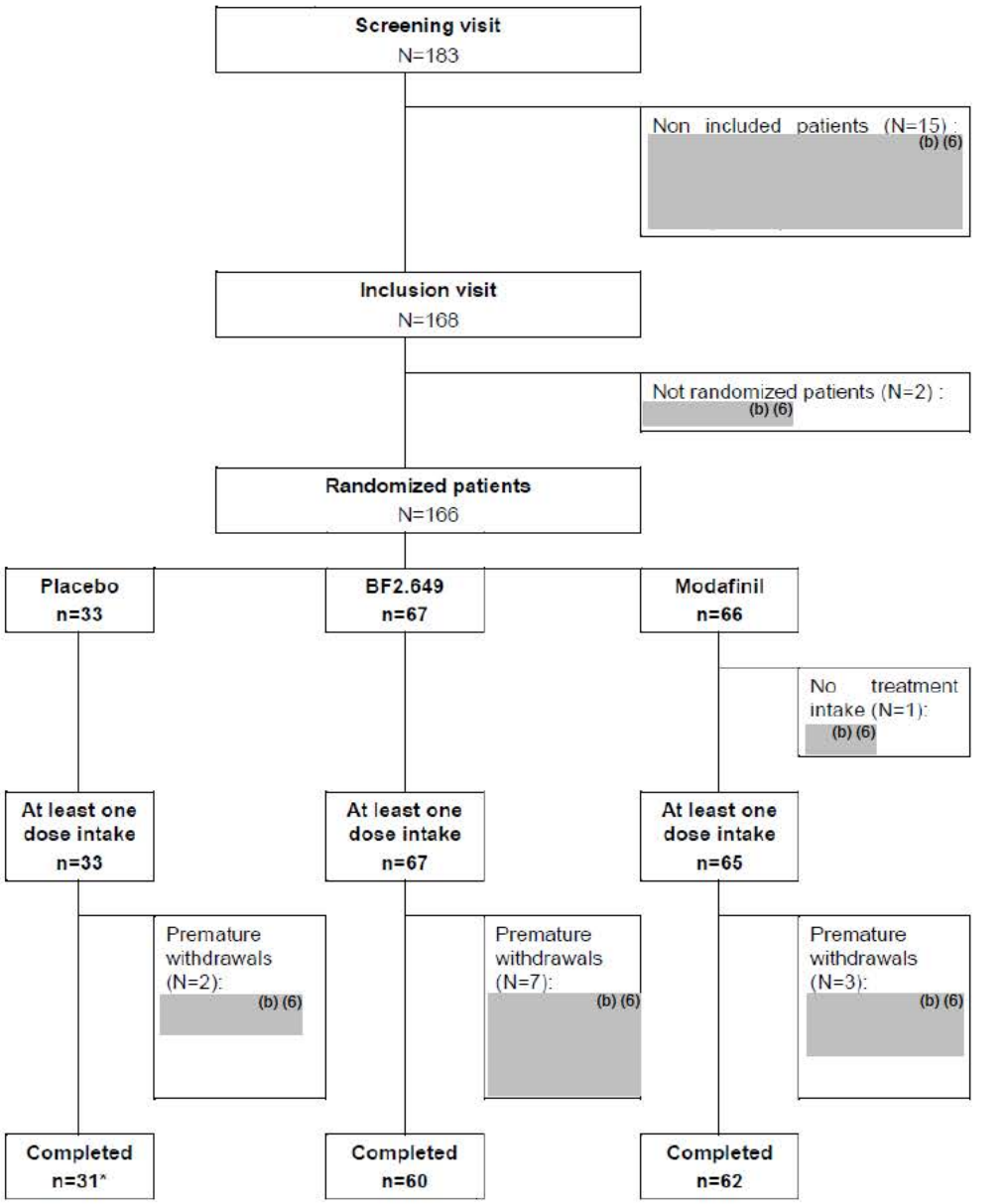
[4] Eleven patients of ITT population with premature withdrawal were excluded from the PP population: patients (b) (6) (b) (6) (major deviation), (b) (6)

[5] Premature withdrawals among patients who took at least one dose of study drug, i.e. excluding patient (b) (6) who was prematurely withdrawn without having any dose.

Source: Table 5 of Sponsor's Clinical Study Report (Page 63)

Figure 6 describes patient disposition that shows excluded patients for various reasons. The overall completion rate was 92.7% and corresponding rates for all randomized subjects are: placebo (94.0%), pitolisant (89.5%), modafinil (95.4%), and showing similarity across treatment groups. Dropouts by treatment groups were: 2 (3.1%) in placebo; 6 (9.1%) in pitolisant; 3 (4.6%) in modafinil. There were 12 (7.3%) premature withdrawals. The frequent reasons for premature withdrawal were: adverse events (50%) and/or patient decision (33.3%).

Figure 6: Patient Disposition-HARMONY 1BIS



* Including patient (b) (6) (placebo) who was not taken into account for the efficacy analysis because the diagnosis of narcolepsy was not confirmed. This patient was considered for safety analysis as he/she took the study drug (Section 11.1).
Source: Figure 3 of Sponsor's Clinical Study Report (Page 65)

Baseline demographic characteristics in all randomized population were similar. The median age of patients was between 29 to 58 years. Clear majority of participants were whites except 1 (1.4%) American Indian/Alaskan Native in pitolisant group, 1 (1.5%) African American/Black in modafinil and 1 (1.5%) Asian in modafinil.

Table 9: Summary of Demographic and Baseline Characteristics-HARMONY 1BIS (EIT Population)

Parameter	PLACEBO (N=32)	BF2.649 (N=67)	MODAFINIL (N=65)	p-value
Age [yr], median (range)	42.5 (29; 55)	37 (29; 52)	43 (32; 58)	0.405
Weight [kg], mean ± SD	80.7 ± 16.1	79.9 ± 19.5	78.5 ± 17.6	0.828
Height [cm], mean ± SD	167.6 ± 10.7	170.4 ± 9.5	168.5 ± 10.5	0.369
BMI [kg/m²], mean ± SD	28.8 ± 5.7	27.4 ± 5.6	27.6 ± 5.3	0.438
Gender [Males], % (n)	46.9 (15)	47.8 (32)	46.2 (30)	0.983
2 yrs Post-Menopause or Sterilized females, % (n)	47.1 (8/17)	31.4 (11/35)	48.6 (17/35)	0.301
Mode of Contraception				
Bill Control Pill, % (n)	44.4 (4/9)	29.2 (7/24)	27.8 (5/18)	0.792
IUD, % (n)	22.2 (2/9)	20.8 (5/24)	33.3 (6/18)	
Other Method, % (n)	33.3 (3/9)	50.0 (12/24)	38.9 (7/18)	
Ethnicity				
White, % (n)	87.5 (28)	89.6 (60)	83.1 (54)	0.722
Black or African American, % (n)	0.0 (0)	0.0 (0)	1.5 (1)	
Asian, % (n)	0.0 (0)	0.0 (0)	1.5 (1)	
American Indian or Alaska Native, % (n)	0.0 (0)	1.4 (1)	0.0 (0)	
Missing, % (n)	12.5 (4)	9.0 (6)	13.9 (9)	
History of Drug Abuse or Dependence Disorder, % (n)	0.0 (0)	1.5 (1)	0.0 (0)	0.483

Source: Table 9 of Sponsor's Clinical Study Report (Page 71)

SD=standard deviation; EIT=Extended-Intent-to-Treat: randomized pts regardless if treatment was initiated and irrespective of their outcome.

Table 10: Summary of Baseline Narcolepsy Characteristics and Efficacy Variables-HARMONY 1BIS (EIT Population)

	PLACEBO (N=32)		BF2.649 (N=67)		MODAFINIL (N=65)		p-value
Parameter	**N**		**N**		**N**		
Duration of Narcolepsy [yrs], median (range)	31	11 [0; 62]	66	15 [0; 47]	63	10 [0; 59]	0.715
Multiple Sleep Latency Test (min), mean ± SD	23	5.1 ± 4	51	4.7 ± 3	55	5.3 ± 4.7	0.725
History of Cataplexy, % (n)		81.3 (26)		74.6 (50)		76.9 (50)	0.766
History of Associated Symptoms							
Sleep paralysis, % (n)		68.8 (22)		44.8 (30)		52.3 (34)	0.082
Hallucinations, % (n)		62.5 (20)		52.2 (35)		55.4 (36)	0.630
Automatic behavior, % (n)		40.6 (13)		34.3 (23)		32.3 (21)	0.718
Dyssomnia, % (n)		31.3 (10)		40.3 (27)		24.6 (16)	0.155
Baseline ESS (V2 +V3)/2, Mean ± SD	32	18.2 ± 2.3	67	18.2 ± 2.4	65	18.1 ± 2.8	0.979
Median (range)		18.5 [15; 23]		18.5 [14; 24]		17.5 [12; 24]	
Baseline MWT, gMean*	32	8.3	67	7.4	65	7.0	0.928
Median (range)		8.4 [1 ; 40]		6.5 [1 ; 40]		8.0 [0 ; 40]	
Baseline SART-NOGO, gMean*	32	7.5	67	8.2	64	8.9	0.593
Median (range)		8.4 [1; 22]		8.3 [2; 23]		10.4 [2; 22]	
Baseline SART-GO, gMean*	32	3.05	67	3.22	64	2.94	0.886
Median (range)		2.1 [1; 27.8]		2.8 [1; 38.8]		2.3 [1; 54.8]	
Baseline SART-TOTAL, gMean*	32	10.54	67	11.08	64	11.71	0.764
Median (range)		12.4 [1.3; 37.3]		10.8 [2.5; 49.5]		13 [1.8; 61]	
Baseline EQ-5D VAS, Mean ± SD	31	66.2 ± 23	67	65.1 ± 23.2	64	71.5 ± 18.3	0.208
Median (range)		74 [7.8; 100]		70 [4; 99]		75 [8; 100]	
Baseline Beck Score, Mean ± SD	32	4.5 ± 4.2	67	5 ± 4.1	65	3.5 ± 3.3	0.074
Median (range)		4 [0; 15]		4 [0; 14]		3 [0; 14]	

* gMean = geometric mean; The geometric mean was used as the data were of a log-normal distribution; which enabled avoidance of spurious influence from extreme values seen in log-normal data.
SD = standard deviation

Source: Table 10 of Sponsor's Clinical Study Report (Page 73)

3.2.4 Results and Conclusions

3.2.4.1 HARMONY 1

Primary Endpoint

The reviewer confirmed sponsor's efficacy findings (Table 10) based on imputation for the baseline or final visit scores using last observation carried forward (LOCF). The least square mean at week 8 on ESS showed a mean of 12.39 for pitolisant and 15.48 for placebo showing a statistically significantly treatment difference of -3.10 (p-value = 0.022). Patients on pitolisant group have less chance of dozing compared to patients on placebo. A total of 94 patients were included in the ITT population.

Table 11: Adjusted ESS Final Total Score at Week 8-HARMONY 1 (ITT; LME)

Visit	Placebo N=30	Pitolisant N=31
Baseline (BL)*		
N	30	31
Mean ± SD	18.9 ±2.5	17.8 ±2.5
Final (F)** at Week 8		
N	30	31
LS Mean ± SE	15.48±1.03	12.39 ±1.01
p-value		0.022
LS mean differences ± SE		-3.10 ±1.30
95% CI for differences		(-5.73, -0.46)

Source: Table 11 of Sponsor's Clinical Study Report (Page 62)
(BL)* = ESS (V2+V3)/2; Final (F)** = ESS (sum of the last two available values post-baseline)/2; CI = confidence interval; LS = least-squares; LME = linear mixed effect mode; SE = standard error; ITT = Intention to Treat; SD= Standard Deviation
Note: Increase in ESST total score indicates increased chance of dozing.

Table 11 shows the trial failed to establish non-inferiority of pitosilant relative to modafinil (p = 0.948) since 2.17 > NIM = 2.

Table 12: Adjusted ESS Final Total Score at Week 8-HARMONY 1 (ITT; LME)

Visit	Modafinil N=33	Pitolisant N=31
Baseline (BL)*		
N	33	31
Mean ± SD	18.5 ±2.7	17.8 ±2.5
Final (F)** at Week 8		
N	33	31
LS Mean ± SE	13.07 ±1.16	13.15 ±1.18
p-value		0.95
LS mean differences ± SE		0.07 ±1.11
95% CI for differences		(-2.17, 2.32)

Source: Table 13 of Sponsor's Clinical Study Report (Page 62)
(BL)* = ESS (V2+V3)/2; Final (F)** = ESS (sum of the last two available values post-baseline)/2; CI = confidence interval; LS = least-squares; LME = linear mixed effect model; SE = standard error; SD= Standard Deviation

Note: Increase in ESST total score indicates increased chance of dozing.

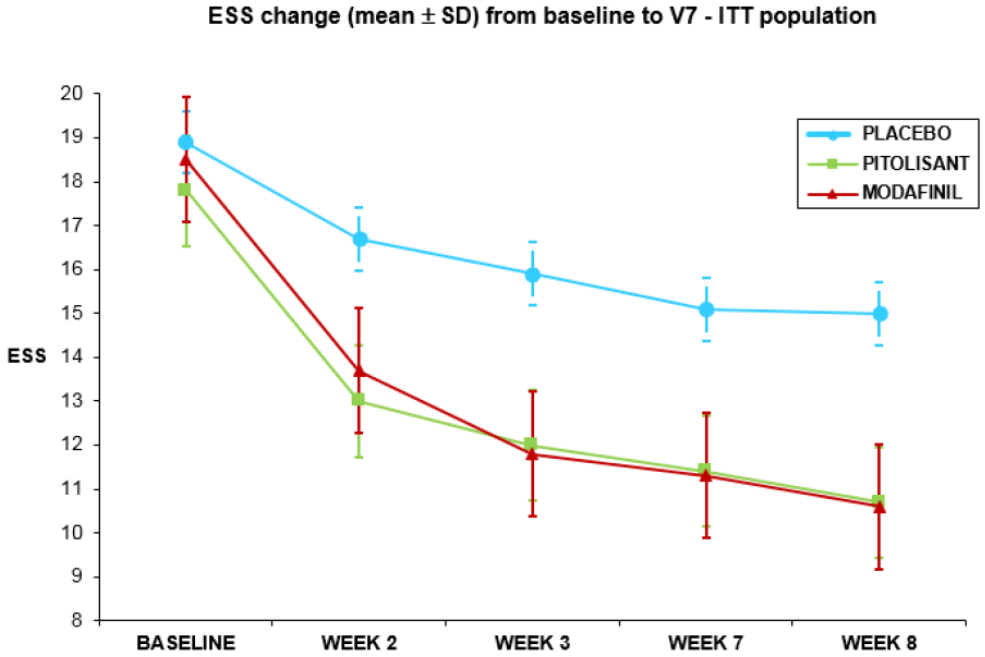
Table 13: Summary of ESS Scores [Mean +/- SD] by Visit and Treatment Group-HARMONY 1 (ITT Population)

ITT (N=94)						
	PLACEBO (N=30)		BF2.649 (N=31)		MODAFINIL (N=33)	
Visit	N	MN ± SD	n	MN ± SD	N	MN ± SD
Visit 1	30	18.1 ± 2.9	31	15.7 ± 4.4	33	17.1 ± 3.5
Visit 2	15	19.6 ± 2.7	18	17.4 ± 2.2	16	19.2 ± 2.8
Visit 3	30	19.2 ± 2.6	31	17.6 ± 2.9	33	18.4 ± 3.0
Baseline (BL)*	30	18.9 ± 2.5	31	17.8 ± 2.5	33	18.5 ± 2.7
Visit 4	30	16.7 ± 4.1	30	13.0 ± 4.8	31	13.7 ± 5.4
Visit 5	29	15.9 ± 4.1	30	12.0 ± 5.9	31	11.8 ± 6.3
Visit 6	27	15.1 ± 4.8	27	11.4 ± 5.8	29	11.3 ± 6.5
Visit 7	25	15.0 ± 4.6	26	10.7 ± 6.6	28	10.6 ± 5.6
Final (F) **	30	15.6 ± 4.7	31	11.8 ± 6.1	33	11.6 ± 6.0
Final (F) °	30	15.6 ± 4.7	31	12.0 ± 6.2	33	11.6 ± 6.0
F**-BL	30	-3.3 ± 4.1	31	-6.0 ± 6.1	33	-6.9 ± 6.1
F°-BL	30	-3.4 ± 4.2	31	-5.8 ± 6.2	33	-6.9 ± 6.2
(F**-BL)/BL (%)	30	-17.8 ± 22.4	31	-33.4 ± 32.2	33	-36.7 ± 31.4
(F°-BL)/BL (%)	30	-17.9 ± 22.4	31	-32.4 ± 33.4	33	-36.8 ± 31.6
Mean‡	30	16.0 ± 4.2	30	12.0 ± 5.5	31	12.1 ± 5.7
Mean‡‡	30	16.0 ± 4.2	31	12.3 ± 5.6	33	12.2 ± 5.5
Responders‡‡‡		% (n)		% (n)		% (n)
ESS ≤ 10	30	13.3 (4)	31	45.2 (14)	33	45.5 (15)

Source: Table 10 of Sponsor's Clinical Study Report (Page 61)

* Baseline = ESS (V2 + V3)/2.
** Final = ESS (sum of the last two available values post-baseline)/2
° Final (F) = ESS (last available value post-baseline).
‡ Mean = Arithmetic mean of all ESS values from Baseline through Final (LOCF last 2 values) visit.
‡‡ Mean = Arithmetic mean of all ESS values from Baseline through Final (LOCF last value) visit.
‡‡‡ Treatment Responders are patients with ESS Final ≤ 10

Figure 7: ESS Total Score by Visit-HARMONY 1 (ITT)



Source: Figure 4 of Sponsor's Clinical Study Report (Page 60)

The average ESS total score over time shows a general decrease in chance of sleepiness in all treatment groups. Specifically, a clear differentiation between pitolisant and placebo exists at the end of treatment as well as weeks 2, 3 and 7.

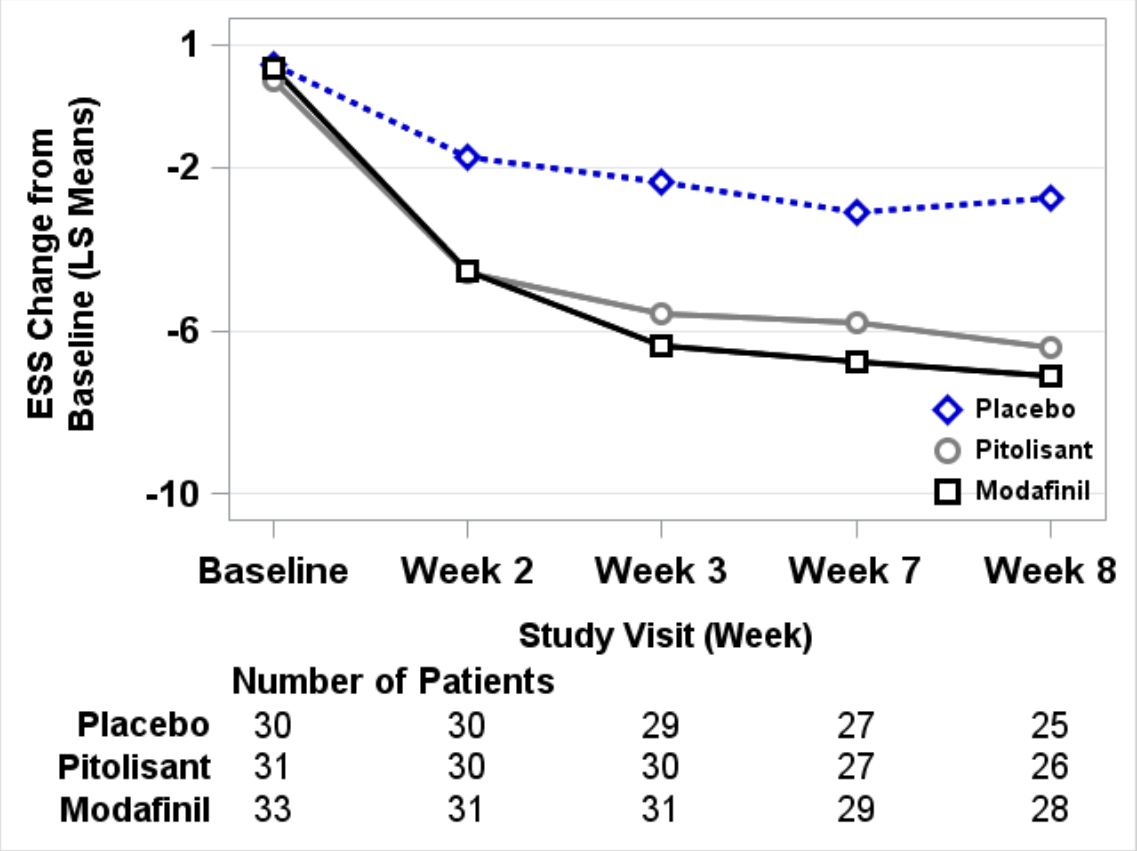
Reviewer's Additional Analysis 1: as an alternative analysis this reviewer conducted a mixed model repeated measures (MMRM; with AR (1) variance covariance structure) to confirm if Applicant's primary efficacy analysis is consistent. The model was adjusted for baseline, treatment, visit and treatment-by-visit; center as random effect; ESS values were observed at each week and not LOCF imputed.

Table 14: Adjusted Change from Baseline to Week 8 in ESS Total Score-HARMONY 1 (ITT; MMRM)

Visit	Placebo N=30	Pitolisant N=31	Modafinil N=33	Pitolisant v. Modafinil
Baseline (BL)*				
N	30	31	33	
Mean ± SD	18.9 ±2.5	17.8 ±2.5	17.8 ±2.5	
Change at Week 8				
N	25	26	28	
LS Mean ± SE	-2.73±0.90	-6.41 ±0.88	-7.09 ±0.86	
p-value		0.002	0.0002	0.55
LS mean differences ± SE		-3.68±1.16	-4.36±1.14	0.68 ±1.14
95% CI for differences		(-5.96, -1.39)	(-6.59, -2.12)	(-1.56, 2.92)

Source: Reviewer

Figure 8: Change in ESS Total Score by Visit-HARMONY 1 (ITT)



Number of Patients					
Placebo	30	30	29	27	25
Pitolisant	31	30	30	27	26
Modafinil	33	31	31	29	28

Source: Reviewer

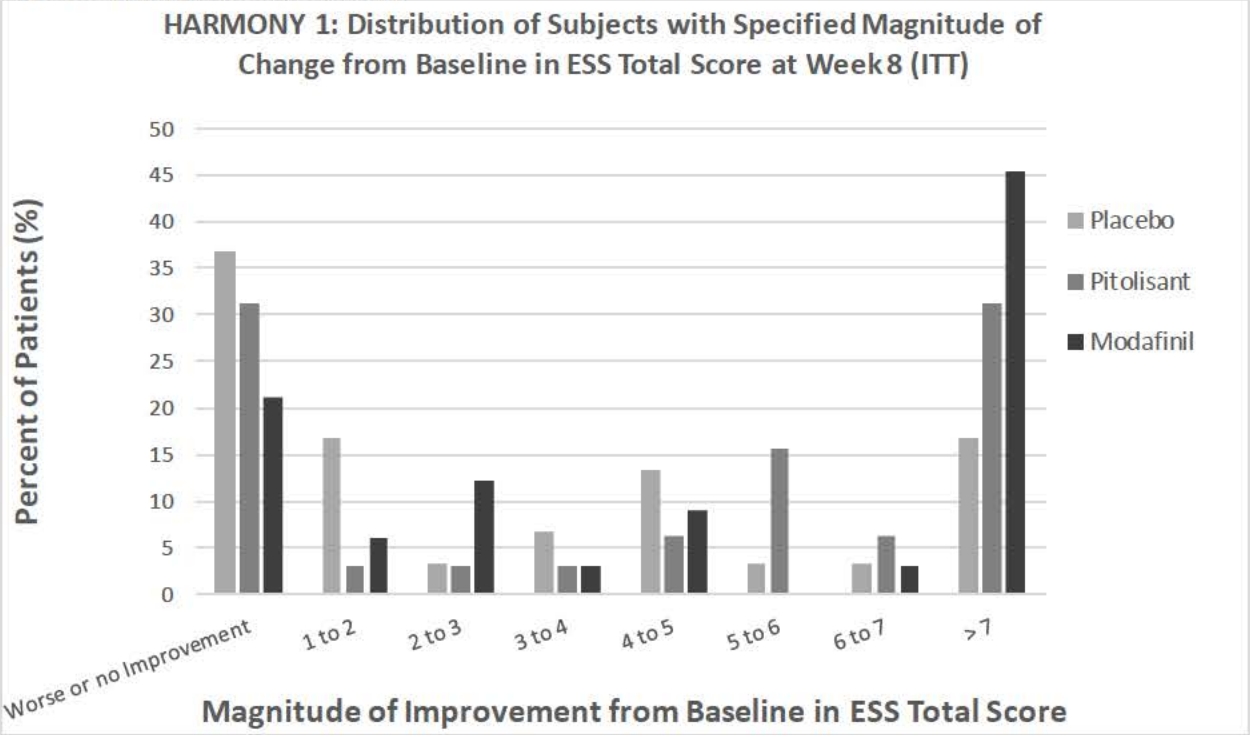
Additional analysis was conducted using endpoint: change from baseline to *average of the last two visits*. Estimated treatment effect for pitolisant-placebo (-3.11 (1.05); 95% CI: [-5.19, -1.04]; p = 0.003) and pitolisant-modafinil (0.72 (1.05); 95% CI: [-1.35, 2.79]; p = 0.49) yielded similar conclusions to applicant's analysis based on ANCOVA.

Sponsor's analyses based on the per-protocol dataset were similar to the primary efficacy analyses. Supportive analyses yielded similar results: using ANCOVA (without center effect), with or without adjustment for ESS baseline score.

Reviewer's Note: This reviewer has included a figure to visualize the distribution of change in ESS total score (Figure 9) for HARMONY 1. Distribution of improved subjects is categorized in a 2-unit bin; subjects who didn't show improvement are located in the left corner bins.

Figure 9 shows distribution of change from baseline in ESS total score at week 8. A large proportion of subjects in the placebo group had a '1-2' magnitudes of improvement; considerable proportion of subjects in the pitolisant showed improvement of '5-6' magnitude. Caution should be exercised when interpreting the distributional plot presented here. The trial is considered small in sample size and only very few subjects contribute data in each bin.

Figure 9: Percent of Patients with Specified Magnitude of ESS Total Score Improvement at Week 8 (ITT; HARMONY 1)



Source: Reviewer's Result

Secondary Endpoints
MWT and SART

Table 15: Summary of Efficacy Analysis Results for MWT and SART-HARMONY 1 (ITT)

	IT (N=94)					
	Comparison	**Control**	**BF**	**Est.**	**95% CI**	**P**
MWT	BF/PL	7.6	9.7	1.47	[1.01 ; 2.14]	0.044
	BF/MD	15.1	9.7	0.77	[0.52 ; 1.13]	0.173
SART-GO	BF/PL	2.7	2.2	0.80	[0.57 ; 1.13]	0.202
	BF/MD	2.5	2.2	0.81	[0.56 ; 1.15]	0.233
SART-NOGO	BF/PL	8.1	7.5	0.82	[0.67 ; 0.99]	0.042
	BF/MD	7.1	7.5	1.03	[0.83 ; 1.28]	0.780
SART-TOTAL	BF/PL	10.3	8.9	0.79	[0.64 ; 0.99]	0.041
	BF/MD	9.1	8.9	0.90	[0.70 ; 1.14]	0.363

Source: Table 16 of Sponsor's Clinical Study Report (Page 64) (Ref: Tables 14.2.3.1.13; 14.2.3.1.14; 14.2.3.1.17; 14.2.3.1.19; 14.2.3.1.21)
The geometric means between treatment groups (ratio of mean of Pitolisant/Placebo) were compared

based on t-test (pooled).

The rate of geometric mean in MWT (wakefulness) improved in the pitolisant group compared with placebo (p = 0.044). Also, pitolisant improved the rate of geometric mean in SART-NOGO error scores (p=0.042).

Reviewer's Comment 1: In their clarification note to the FDA on 27 March 2019, a response to FDA information request on 27 March 2019, the Applicant conducted additional analyses on secondary endpoints (MWT and/or SART) using non-parametric method Mann-Whitney test, with and without imputation of last observed value.

(a) The Mann-Whitney test on MWT in HARMONY 1 (P07-03) was consistent with the specified Student's t-test.
(b) The Mann-Whitney and Student's t-test results on MWT in HARMONY 1BIS (P09-15) were not statistically significant and not consistent with the results of the specified linear fixed effect model.
(c) The Mann-Whitney test on MWT in HARMONY CTP (P11-05) was consistent with the specified Student's t-test.

ESS Responder Rate: ESS ≤ 10

Responders were classified based on cutoff, ESSF≤10. Calculated responder rates by treatment groups were: 13.3% in the placebo group, 45.2% in the pitolisant group and 45.5% in the modafinil group (Table 15). The odds of response in the pitolisant group were significantly greater than placebo [OR=7.86; 95% CI: (1.59, 38.86); p = 0.013].

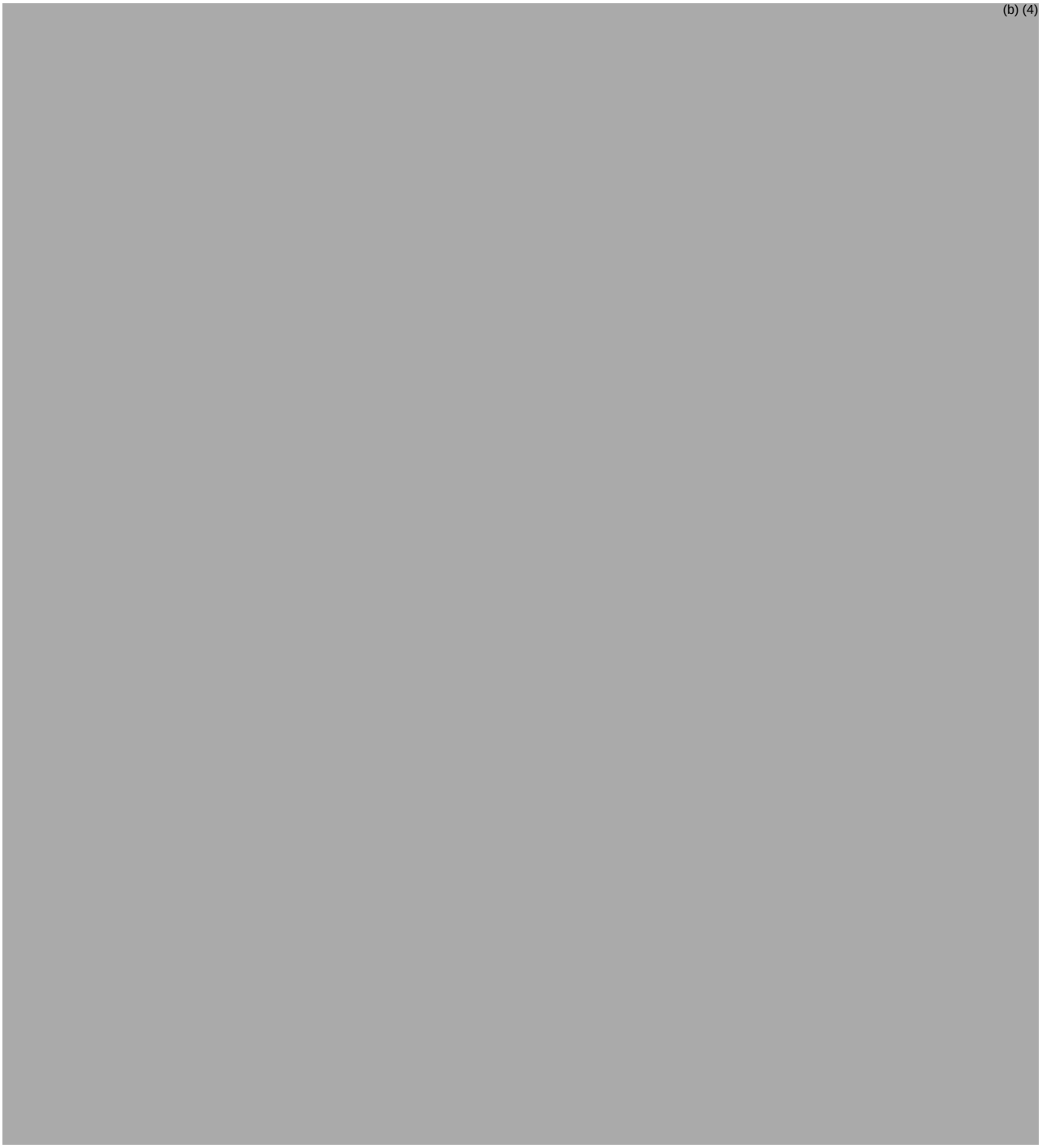
Table 16: Summary of Analysis of Responder Rate-HARMONY 1 [OR Pitolisant vs. Placebo and Pitolisant vs. Modafinil] - Logistic Regression Model (ITT)

Odds Ratio	ITT (N=94)					
	Comparison	**Control**	**BF**	**Est.**	**95% CI**	**p**
ESS ≤ 10	Pit/PB	13.3 (4)	45.2 (14)	7.86	[1.59; 38.86]	0.013
	Pit/MD	45.5 (15)	45.2 (14)	1.09	[0.31; 3.81]	0.892

Source: Table 14 of Sponsor's Clinical Study Report (Page 63)
OR = Odds Ratio of treatment responders adjusted on ESS Baseline (Logistic Regression Model)

(b) (4)

8 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page



3.2.4.3 HARMONY 1BIS

Primary Endpoint

Pitolisant was statistically significantly superior to placebo in the mean change in ESS total score at week 8, with a least square mean treatment difference from placebo of -2.19 (p-value = 0.03).

Patients treated with pitolisant have decreased chance of falling asleep compared to patients in the placebo group. The reviewer confirmed sponsor's efficacy findings (Table 26).

The primary analysis was based on covariance ANCOVA where the model for the final ESS was adjusted for baseline ESS, fixed factor treatment and random effect center. The conclusion was similar across the per-protocol† population.

†Per-Protocol Population: all patients in the ITT population who completed the study until at least V6 (i.e., having one value at V6 or V7), and without any major protocol deviation related to primary endpoint.

Table 27: Summary of ESS Scores [Mean +/- SD] by Visit and Treatment Group (ITT Population)-HARMONY 1BIS

ITT (N=163)						
	PLACEBO (N=32)		PITOLISANT (N=66)		MODAFINIL (N=65)	
Visit	n	MN ± SD	n	MN ± SD	n	MN ± SD
Visit 1	26	16.4 ± 4.8	48	16.6 ±3.8	48	16.1 ± 5.6
Visit 2	20	18.1 ± 2.4	58	18.1 ±2.4	54	18.0 ± 3.1
Visit 3	31	18.1 ± 2.6	66	18.5 ±2.7	64	18.2 ± 3.0
Visit 4	31	15.3 ± 4.4	65	14.7 ±5.1	64	12.7 ± 5.4
Visit 5	31	14.4 ± 5.3	63	13.9 ±5.5	64	10.9 ± 6.2
Visit 6	30	14.3 ± 6.1	60	13.3 ±5.6	62	10.5 ± 6.2
Visit 7	29	14.3 ± 6.1	61	13.6 ±5.5	62	10.4 ± 6.2
Visit 8	29	14.7 ± 6.2	60	14.1 ±5.7	59	11.7 ± 5.9
Baseline (BL)*	32	18.2 ± 2.3	66	18.3 ±2.4	65	18.1 ± 2.8
Final (F)**	31	14.5 ± 5.9	66	13.7 ±5.4	64	10.4 ± 6.0
Final (F) °	32	14.6 ± 5.8	66	13.7 ±5.4	65	10.3 ± 6.1
F°-BL	32	-3.6 ± 5.6	66	-4.6 ± 4.6	65	-7.8 ± 5.9
F**-BL	31	-3.6 ± 5.6	66	-4.6 ± 4.6	64	-7.8 ± 5.8
(F°-BL)/BL	32	-20.0%	66	-25.8%	65	-43.3%
(F**-BL)/BL	31	-20.3%	66	-25.7%	64	-43.3%
Mean‡	32	14.8 ± 5.1	66	14.0 ±5.0	65	11.2 ± 5.4

Source: Table 15 of Sponsor's Clinical Study Report (Page 78)
NOTE: Patients (b) (6) (placebo) and (b) (6) modafinil) had missing data for all visits (questionnaires); ESSBL and ESSF composite es were provided by the investigator in the CRFs.
* ESSBL = (ESSV2 + ESSV3)/2; or (ESSV1 + ESSV3)/2 if ESSV2 is missing; or (ESSV1 + ESSV2)/2 if ESSV3 is missing; ** Final (F)= ESS (sum of the last 2 available values post baseline)/2;
°Final (F)= ESS (last available value post baseline); or Last Observation Carried Forward (LOCF) if ESSV7 is missing; ‡ MEAN = Arithmetic mean across all visits between ESSBL and ESSF.

Table 28: Adjusted ESS Final Total Score at Week 8 (ITT; LME)-HARMONY 1BIS

Visit	Placebo N=32	Pitolisant N=66
Baseline (BL)*		
N	32	66
Mean ± SD	18.2 ±2.3	18.3 ±2.4
Final (F)** at Week 8		
N	32	66
LS Mean† ± SE	15.49±1.32	13.30 ±1.19
p-value		0.03
LS mean differences ± SE		-2.19 ±0.99
95% CI for differences		(-4.17, -0.22)

Source: Table 16 of Sponsor's Clinical Study Report (Page 80)
(BL)* = ESS (V2+V3)/2; Final (F)** = ESS (sum of the last two available values post-baseline)/2; CI = confidence interval; LS = least-squares; LME = mixed model repeated measures; SE = standard error; ITT = Intention to Treat; SD= Standard Deviation; †= The primary analysis was conducted using a linear mixed effects model (LME), featuring analysis of covariance ANCOVA on final ESSf adjusted on ESSb, with treatment considered as a fixed factor and re-allocated center as a random effect (thus hypothesis of center variability of the model intercept)
Note: Increase in ESST total score indicates increased chance of dozing.

Non-inferiority was not achieved for pitolisant (Table 27).

Table 29: Adjusted ESS Final Total Score at Week 8 (ITT; LME)-HARMONY 1BIS

Visit	Modafinil N=65	Pitolisant N=66
Baseline (BL)*		
N	65	66
Mean ± SD	18.1 ±2.8	18.3 ±2.4
Final (F)** at Week 8		
N	65	66
LS Mean† ± SE	10.59 ±1.08	13.34 ±1.08
p-value		0.002
LS mean differences ± SE		-2.75 ±0.87
95% CI for differences		(-4.48, -1.02)

Source: Table 16 of Sponsor's Clinical Study Report (Page 80)
(BL)* = ESS (V2+V3)/2; Final (F)** = ESS (sum of the last two available values post-baseline)/2; CI = confidence interval; LS = least-squares; LME = mixed model repeated measures; SE = standard error; ITT = Intention to Treat; SD= Standard Deviation; †= The primary analysis was conducted using a linear mixed effects model (LME), featuring analysis of covariance ANCOVA on final ESSf adjusted on ESSb, with treatment considered as a fixed factor and re-allocated center as a random effect (thus hypothesis of center variability of the model intercept)
Note: Increase in ESST total score indicates increased chance of dozing.

The per-protocol based sensitivity analyses and supportive analyses (Section 3.2.2.3) were comparable to the primary efficacy analysis.

<u>ESS Responder Rate</u>: ESS ≤ 10

The difference in responder rates between pitolisant and placebo groups were evaluated using Poisson regression analysis adjusting for baseline ESS value and center as random effect. The

response proportion for pitolisant group (65.2%) was statistically greater than the placebo group (34.4%) where estimated relative risk was 2.14 [95% CI (1.35, 3.39); p = 0.001]. Analysis result based on logistic regression was consistent.

There was a statistically significant difference in the ratio of the mean change in MWT (Final/Baseline) between pitolisant and placebo (Student's t-test) [1.46; 95% CI: (1.06, 2.01); p = 0.022].

Reviewer's Note: Both endpoints, MWT and SART, were analyzed using a linear fixed effect model on log (F/BL) with treatment as fixed effect and re-allocated center as random effect (CSR, page 82). The Mann-Whitney and Student's t-test results on MWT were not statistically significant and not consistent with the results of the specified linear fixed effect model.

Table 30: Summary of Analysis Results for Secondary Endpoints (ITT)-HARMONY 1BIS

ITT (N=163)								
Endpoint		PLACEBO (N=32)		PITOLISANT (N=66)		MODAFINIL (N=65)		
		BL	FINAL	BL	FINAL	BL	FINAL	
ESS[1] Responder	% (n)	34.4 (11)		65.2 (43)		76.9 (50)		
	RR	2.14 [1.35; 3.39] p = 0.001				0.87 [0.74; 1.02] p = 0.086		
MWT[2]	Value	8.31	8.28	7.34	9.10	7.01	10.90	
	F/BL	0.99		1.24		1.55		
	Treat	1.46 [1.06; 2.01] p = 0.022				0.85 [0.66; 1.09] p = 0.205		
SART-NOGO[2]	Value	7.53	7.76	8.21	6.73	8.88	6.50	
	F/BL	1.03		0.82		0.73		
	Treat	0.77 [0.65; 0.91] p = 0.002				1.08 [0.93; 1.26] p = 0.294		
SART-GO[2]	Value	3.05	2.60	3.23	2.71	2.94	2.33	
	F/BL	0.85		0.84		0.79		
	Treat	0.99 [0.77; 1.27] p = 0.910				1.06 [0.82; 1.37] p = 0.641		
SART - TOTAL[2]	Value	10.54	9.94	11.08	8.90	11.71	8.44	
	F/BL	0.94		0.82		0.74		
	Treat	0.83 [0.69; 0.99] p = 0.043				1.08 [0.90; 1.30] p = 0.407		

Source: Table 17 of Sponsor's Clinical Study Report (Page 84)

(1) Responder rate according to ESS (ESSf≤ 10 or ESS (F – BL) ≥ 3) was documented by the responder proportion (%) and treatment group sample size (n). Analysis was conducted using a Poisson regression model on final ESSf adjusted on ESSb, with treatment considered as a fixed factor and center as a random effect. Original SAR displayed placebo vs BF and BF vs modafinil, this analysis displays Pitolisant vs Placebo and Pitolisant vs modafinil.

(2) Mean Wakefulness Time (MWT), SART-nogo, SART-go, and SART total values are documented by **value** (geometric mean at baseline and final time), **F/B** (ratio of Final on Baseline values in each group, **treat** (the ratio F/B between BF and the compared treatment), and **treat** (tested treatment effect using linear fixed effect model with 95%CI and p value).

Reviewer's Note: According to EMA Public Assessment Report analysis of the primary efficacy data by "artificially clustering" small clinical study centers, the mean ESS decrease with pitolisant showed statistically significant improvement compared to placebo (-2.19; 95% CI (-4.17, -0.22); p = 0.03). The EMA report stated pooling of centers was not pre-planned. In contrast, the SAP which was issued a month (February 13, 2013) before the database lock (March 13, 2013) included an Appendix (see below) to display the random re-allocation of small centers into clusters. Analysis conducted without re-allocation of small study centers showed that pitolisant didn't demonstrate statistically significant separation from placebo (-1.94; 95% CI (-4.05, 0.07); p = 0.065). In clarifying FDA request, the applicant made clear (April 25, 2019) that the SAP for the study was amended prior to unbinding of study.

APPENDIX A. CLUSTERING OF CENTERS

Source: Applicant's SAP (Page 11)

3.3 Evaluation of Safety

Safety evaluation was not conducted in this review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

No special subgroups were investigated.

4.1 Gender, Race, Age, and Geographic Region

The majority of participants were white (94.7%), age group <=65 (98%) in HARMONY 1. Similarly, most participants were also whites (86.7%), age group <=65 (90.3%). Below subgroup exploration by sex was conducted for HARMONY 1 and HARMONY CTP.

The efficacy conclusion in the general population is consistent with the female subgroup in HARMONY 1. Estimated treatment effect of subgroups by sex weren't demonstrably inconsistent in HARMONY CTP.

Table 31: Subgroup Analysis by Sex (HARMONY 1; ITT; LME)

Male			
Visit	Placebo N=30	Pitolisant N=31	Pitolisant-Placebo 95% CI for Differences
Final (F)** at Week 8			
N	13	21	
LS Mean ± SE	13.40±1.61	12.31 ±1.40	-1.09; (-5.19, 3.01)

Female			
Visit	Placebo N=30	Pitolisant N=31	Pitolisant-Placebo 95% CI for Differences
Final (F)** at Week 8			
N	17	11	
LS Mean ± SE	17.63±1.33	11.90 ±1.52	-5.73; (-9.85, -1.62)

Source: Reviewer
Final (F)** = ESS (sum of the last two available values post-baseline)/2; CI = confidence interval; LS = least-squares; LME = linear mixed effect model; SE = standard error

Table 32: Subgroup Analysis by Sex (HARMONY CTP)

Male (N=61)					**Ratio of geometric mean**		
ITT- LOCF method with the average of the last 2 available values							
Analysis	**Estimate**	**SE***	**95% LCL**	**95% UCL**	**Exp† Estimate**	**Exp* LCL**	**Exp* UCL**
Poisson	-0.84	0.12	-1.09	-0.59	**0.43**	**0.34**	**0.56**

Female (N=56)					**Ratio of geometric mean**		
ITT- LOCF method with the average of the last 2 available values							
Analysis	**Estimate**	**SE***	**95% LCL**	**95% UCL**	**Exp† Estimate**	**Exp* LCL**	**Exp* UCL**
Poisson	-0.55	0.12	-0.80	-0.29	**0.58**	**0.45**	**0.75**

Source: Reviewer

4.2 Other Special/Subgroup Populations: U.S. versus Non-US

All the studies were conducted outside of the U.S.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Due to lack of thorough prior interactions or agreements with the applicant, we had to request clarifications on a range of issues such as endpoints, efficacy analysis methods for the primary or secondary endpoints.

In HARMONY 1, additional analysis was explored on a secondary endpoint: a subgroup of patients with a history of cataplexy. There was no prospectively planned correction for multiplicity to control the overall type I error rate for these secondary endpoints in this study. Moreover, in this subgroup of patients, the reduction in mean daily rate of cataplexy (p=0.034 without multiplicity adjustment) was based on a specific imputation method for subjects with zero or missing cataplectic events. The confirmatory findings depended on how the missing data were handled.

5.2 Collective Evidence

A total of three (3) efficacy studies were submitted – 2 studies (HARMONY 1, HARMONY 1BIS) to support for the treatment of excessive daytime sleepiness (EDS) in adult patients with narcolepsy; 1 study (HARMONY CTP) for the treatment of cataplexy in adult patients with narcolepsy.

The primary endpoint, ESS final score at the end of treatment period, in HARMONY 1 and HARMONY 1BIS, pitolisant demonstrated statistically significant separation from placebo when adjusted for baseline scores. Significance of the primary endpoint in HARMONY 1BIS was achieved after a random grouping of the small study centers within larger centers. The estimated treatment difference was at least 3 units in HARMONY 1 and 2 units in HARMONY 1BIS. For study HARMONY 1BIS, pitolisant showed a separation from placebo on the ESS endpoint (p-value = 0.03). The result was obtained by "artificially clustering" small clinical study centers into 5 clusters which was specified in the SAP before data unblinding, having learned the potential effect of sparse of data in clinical centers from HARMONY 1.

(b) (4)

5.3 Conclusions and Recommendations

European Medicines Agency (EMA) recommended a maximum daily oral dose of 36 mg of Wakix for the treatment of narcolepsy with or without cataplexy in the European Union (EU). The Applicant is seeking to get an approval on similar dose (35.6 mg) in the US for two indications, 1) the treatment of excessive daytime sleepiness (EDS) in adults with narcolepsy (supported by HARMONY 1, HARMONY 1BIS); 2) the treatment of cataplexy in adults with narcolepsy (supported by HARMONY CTP).

Efficacy results from HARMONY 1 and HARMONY 1BIS showed improved daytime sleepiness which supports the indication of EDS. (b) (4) [redacted]

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SEMHAR B OGBAGABER
07/13/2019 06:34:18 PM

JINGLIN ZHONG
07/15/2019 08:28:53 AM

HSIEN MING J HUNG
07/15/2019 03:26:55 PM

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

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	211150/0003
Supplement Number:	NA
Drug Name:	Wakix (pitolisant)
Indication(s):	(b) (4)
Applicant:	Bioprojet Pharma
Date(s):	Date of Document: 12/14/2018 Consult received date: 4/26/2019 Completion date: 6/25/2019
Review Priority:	60 days
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Wei Liu, Ph.D., DBVI/OB
Concurring Reviewers:	Qianyu Dang, Ph.D., Team Leader, DBVI/OB Yi Tsong, Ph.D., Division Director, DBVI/OB/OTS
Medical Division:	Controlled Substance Staff
The CSS Team:	Katherine R Bonson, Ph.D., Pharmacologist, OD/CSS Silvia Calderon, Senior Pharmacologist, OD/CSS
Project Manager:	Sandra Saltz, OD/CSS
Keywords: NDA review, clinical studies, Crossover design; Self-reported endpoint; Multiple endpoints; human drug abuse study	

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

The applicant, Bioprojet Pharma, submitted NDA 211150 for Wakix (pitolisant), a histamine 3 receptor antagonist/inverse agonist for the treatment of excessive daytime sleepiness in adult patients with narcolepsy. CSS requested a statistical consult review regarding the completed human abuse potential study P16-02 of NDA 211150.

Study #P16-02 was "A Randomized, Double-Blind, Active- and Placebo-Controlled, Single-Dummy, 4-Way Crossover Study to Determine the Abuse Potential of Pitolisant Compared to Phentermine and Placebo, in Healthy, Non-Dependent Recreational Stimulant Users." A total of 43 subjects were randomized into the treatment phase and 38 subjects completed the study.

The primary endpoint of Study P16-02 was the maximum (peak) effect (Emax) for Drug Liking ("at this moment"), assessed on bipolar (0–100 point) visual analog scales (VAS). The key secondary endpoints included the VAS Emax of Overall Drug Liking, High, Good Drug Effects, Bad Drug Effects, Any Drug Effects, and Take Drug Again.

This reviewer concluded that

(1) The study validation was confirmed based on a significant validation test.

(2) Subjects in the Treatment phase liked the active control drug phentermine HCl 60 mg more than pitolisant HCl at either 40 mg or 240 mg. The conclusion is based on that tests of the mean differences between phentermine HCl 60 mg and pitolisant HCl (40 mg and 240 mg) in the primary and most key secondary endpoints were statistically significant at one-sided level of 0.05 using a test margin of zero.

(3) For comparing Drug Liking VAS Emax between pitolisant and placebo, we used test margin of 11. The tests of pitolisant HCl at both doses (40 mg and 240 mg) vs placebo were statistically significant at level 0.05 one-sided. It indicates no abuse potential for pitolisant HCl. However, for the secondary endpoints of High VAS, Good Drug Effects VAS, and Any Drug Effects, pitolisant HCl 240 mg has significantly larger mean values than those of placebo. Therefore, pitolisant HCl at high dose (240 mg) may still have some abuse potential for recreational stimulant users.

The analysis findings of the primary and key secondary endpoints are summarized in Table 1 below.

Table 1 Summary of Treatment Effects of Pitolisant HCl (40 mg and 240 mg) Compared to Phentermine HCl 60 mg and Placebo (Completers, n=38).

endpoint	Pairwise Comparison	Mean Diff	SE	p-value	95% CI	
					LCL	UCL
Drug Liking VAS Emax	Validation, H_0: $\mu_C - \mu_p \leq 15$					
	Phentermine HCl 60 mg - P	22.7	2.9	0.0055	17.8	Infinity
	Positive controls vs. test drug, H_0: $\mu_C - \mu_T \leq 0$					
	Phentermine HCl 60 mg - Pitolisant HCl 40 mg	21.4	3.2	<.0001	16.0	Infinity
	Phentermine HCl 60 mg - Pitolisant HCl 240 mg	19.7	3.5	<.0001	13.7	Infinity
	Pitolisant HCl vs. Placebo, H_0: $\mu_T - \mu_P \geq 11$					
	Pitolisant HCl 40 mg - P	1.3	2.9	0.001	-Infinity	6.2
	Pitolisant HCl 240 mg - P	3.0	3.1	0.0073	-Infinity	8.3
Overall Drug Liking Emax	Phentermine HCl 60 mg - Pitolisant HCl 40 mg[a]	24.7	4.0	<.0001	17.9	Infinity
	Phentermine HCl 60 mg - Pitolisant HCl 240 mg[a]	28.2	5.7	<.0001	18.6	Infinity
	Pitolisant HCl 40 mg – P[b]	-1.7	2.7	0.265	-Infinity	2.8
	Pitolisant HCl 240 mg – P[b]	-5.2	4.6	0.1322	-Infinity	2.6
High VAS Emax	Phentermine HCl 60 mg - Pitolisant HCl 40 mg[a]	43.1	5.2	<.0001	34.3	Infinity
	Phentermine HCl 60 mg - Pitolisant HCl 240 mg[a]	23.4	5.4	<.0001	14.3	Infinity
	Pitolisant HCl 40 mg – P[b]	3.4	5.4	0.7358	-Infinity	12.5
	Pitolisant HCl 240 mg – P[b]	23.0	5.8	0.9999	-Infinity	32.7
Good Drug Effects VAS Emax	Phentermine HCl 60 mg - Pitolisant HCl 40 mg[a]	47.2	5.8	<.0001	37.5	Infinity
	Phentermine HCl 60 mg - Pitolisant HCl 240 mg[a]	36.6	5.9	<.0001	26.5	Infinity
	Pitolisant HCl 40 mg – P[b]	0.4	5.2	0.5302	-Infinity	9.1
	Pitolisant HCl 240 mg – P[b]	11.1	6.5	0.9517	-Infinity	22.0
Bad Drug Effects VAS Emax	Phentermine HCl 60 mg - Pitolisant HCl 40 mg[a]	8.0	4.5	0.0421	0.4	Infinity
	Phentermine HCl 60 mg - Pitolisant HCl 240 mg[a]	-13.5	5.9	0.9864	-23.5	Infinity
	Pitolisant HCl 40 mg – P[b]	-0.7	4.3	0.4395	-Infinity	6.6
	Pitolisant HCl 240 mg – P[b]	20.9	5.7	0.9996	-Infinity	30.5
Any Drug Effects VAS Emax	Phentermine HCl 60 mg - Pitolisant HCl 40 mg[a]	44.4	5.6	<.0001	34.9	Infinity
	Phentermine HCl 60 mg - Pitolisant HCl 240 mg[a]	22.1	5.6	0.0002	12.7	Infinity
	Pitolisant HCl 40 mg – P[b]	2.1	6.3	0.6274	-Infinity	12.8
	Pitolisant HCl 240 mg – P[b]	24.4	6.1	0.9998	-Infinity	34.7

Note: Analyses were carried out using a paired t-test in the Completers population. p-value: hypothesis tests at alpha=0.05, one-sided. LCL: lower confidence limit, UCL: upper confidence limit.

a. Phentermine vs. Placebo, H_0: $\mu_C - \mu_p \leq 0$; Phentermine vs. Pitolisant HCl, H_0: $\mu_C - \mu_T \leq 0$

b. Pitolisant HCl vs. Placebo, H_0: $\mu_T - \mu_P \geq 0$

Recommendations:
Recommendations for the proposed label are included in part 4.3.

2. INTRODUCTION

2.1 Overview

Pitolisant is a histamine 3 receptor antagonist/inverse agonist, which enhances the activity of brain histaminergic neurons (a major arousal system with widespread projections to the whole brain) via its blockade of histamine auto-receptors. Pitolisant also modulates various neurotransmitter systems, increasing acetylcholine, noradrenaline and dopamine release in the brain. Wakix (pitolisant) was investigated by the sponsor for therapeutic use for the debilitating symptoms of EDS and cataplexy in adult patients with narcolepsy, a serious, chronic, debilitating, rare neurologic disease of excessive daytime sleepiness.

2.2 Specific Studies Reviewed

Table 2.1: List of all studies included in analysis

Study ID (location)	Type and route	Phase and Design	Treatment	# of Subjects Randomized / completed
P16-02 (Canada)	HAP Oral	Phase 2/3 R, DB, AC, PC, MD, 4-way crossover study	A: Placebo B: Phentermine HCl, 60 mg C: Pitolisant HCl, 40 mg D: Pitolisant HCl, 240 mg	43/38

Abbreviations: R-randomized, DB = double blind; PC = placebo-controlled; AC = active-controlled; R = randomized; SD-single dose, MD=multi-dose

2.3 Data Source

Application:	NDA211150
Company	Bioprojet Pharma
Drug	Wakix (pitolisant)
CDER EDR link	\\CDSESUB1\evsprod\NDA211150\0003\m5\datasets\p16-02\tabulations\sdtm
Letter date	12/14/2018

This reviewer uncovered that no pharmacodynamic datasets of NDA211150 Study P16-02 were submitted for evaluating statistically the drug abuse potential of Wakix (pitolisant). This reviewer, via DPP project manager, sent the following two Information Requests, respectively, to the sponsor.

On 5/3/2019:

> "We are not able to locate the pharmacodynamic dataset of NDA211150 Study P16-02 for the analysis of the primary and secondary endpoints (such as Emax, Emin, TEmax, and TA_AUE). If the data were

not submitted, please submit the dataset containing all variables in the models pre-specified in your study protocol (treatment, period, treatment sequence and first-order carryover effect) with the treatments labelled as “Placebo”, “Phentermine HCl 60 mg”, “Pitolisant HCl 40 mg” and “Pitolisant HCl 240mg”, respectively. Please also submit the define.pdf document regarding this dataset.”

On 5/6/2019:

> “We are not able to locate the pharmacodynamic dataset of NDA211150 Study P16-02 for plotting the time courses of the primary and secondary endpoints (such as Drug Liking, Overall Drug Liking, High, Take Drug Again, Good Drug Effects, Bad Drug Effects, Any Drug Effects, etc.). We do find a dataset QS which, however, do not have the treatment variable (“Placebo”, “Phentermine HCl 60 mg”, “Pitolisant HCl 40 mg” and “Pitolisant HCl 240mg”) although it contains the VAS scores at different timepoints for the primary and secondary endpoint. If the data were not submitted, please submit the dataset, along with the define.pdf document regarding this dataset.”

The sponsor submitted the required datasets and documents on 5/8/2019 to \\CDSESUB1\evsprod\NDA211150\0005\m5\datasets\p16-02\tabulations\sdtm

3 STATISTICAL EVALUATION

3.1 REVIEW REPORT on STUDY (b) (4)

3.1.1 Study Design and Endpoints

The Study P16-02 was entitled “A Randomized, Double-Blind, Active- and Placebo-Controlled, Single-Dummy, 4-Way Crossover Study to Determine the Abuse Potential of Pitolisant Compared to Phentermine and Placebo, in Healthy, Non-Dependent Recreational Stimulant Users.”

STUDY OBJECTIVES

Primary Objective

- To assess the abuse potential of single doses of pitolisant relative to phentermine HCl and placebo, when administered to healthy, non-dependent, recreational stimulant users.

Secondary Objectives

- To evaluate the PK profile of a single dose of pitolisant when administered in healthy, non-dependent, recreational stimulant users
- To assess the safety and tolerability of a single dose of pitolisant when administered in healthy, non-dependent, recreational stimulant users

STUDY DESIGN

This study was a single-dose, randomized, double-blind, active- and placebo-controlled, single-dummy, 4-sequence, 4-way crossover study to determine the abuse potential of pitolisant relative to phentermine HCl and placebo, in healthy, non-dependent, recreational stimulant users. This study consisted of 4 phases: a Screening, Qualification, Treatment, and Follow-up Phase.

Each subject participated in a medical Screening Visit, a 4-day (3-night) Qualification Visit, four 3-day (2-night) Treatment Periods, and a Follow-up Visit.

Qualification Phase

Following a screening period, eligible subjects participated in a qualification phase to ensure that subjects were able to discriminate the drug effects of the active comparator (phentermine HCl).

During the qualification phase, subjects received single oral doses of each of the following treatments in a randomized, double-blind, single-dummy, crossover manner:

- Treatment Y: Placebo administered orally as a single dose
- Treatment Z: Phentermine HCl 60 mg;

Subjects were to be discharged approximately 24 hours after the second dosing, at the discretion of the investigator or designee to ensure subject safety.

Subjects must meet the following qualification criteria to be eligible to enter the treatment phase of this study:

1. Peak score in response to 60 mg phentermine HCl greater than that of placebo on Drug Liking (difference of at least 15 points) and score of at least 65 points for 60 mg phentermine HCl and acceptable overall responses on other VAS, as judged by the investigator or designee.
2. Acceptable placebo response based on Drug Liking (score between 40 and 60 points, inclusive).
3. Able to tolerate 60 mg phentermine HCl, as assessed by available safety data (eg, no emesis within 4 hours following dosing), and as otherwise judged by the investigator or designee.
4. General behavior suggests that the subject could successfully complete the study, as judged by the research site staff.

Subjects who completed the Qualification Phase and were eligible to continue in the study then entered the Treatment Phase. The last study drug administration in the Qualification Phase and the first study drug administration in the Treatment Phase were separated by a washout interval of at least 7 days.

Treatment Phase

In the Treatment Phase, subjects received single oral doses of each of the following treatments in a randomized, double-blind, single-dummy, crossover manner:

- Treatment A: Placebo administered orally as a single dose
- Treatment B: Phentermine HCl 60 mg;
- Treatment C: Wakix® (pitolisant HCl) 40 mg;
- Treatment D: Wakix® (pitolisant HCl) 240mg;

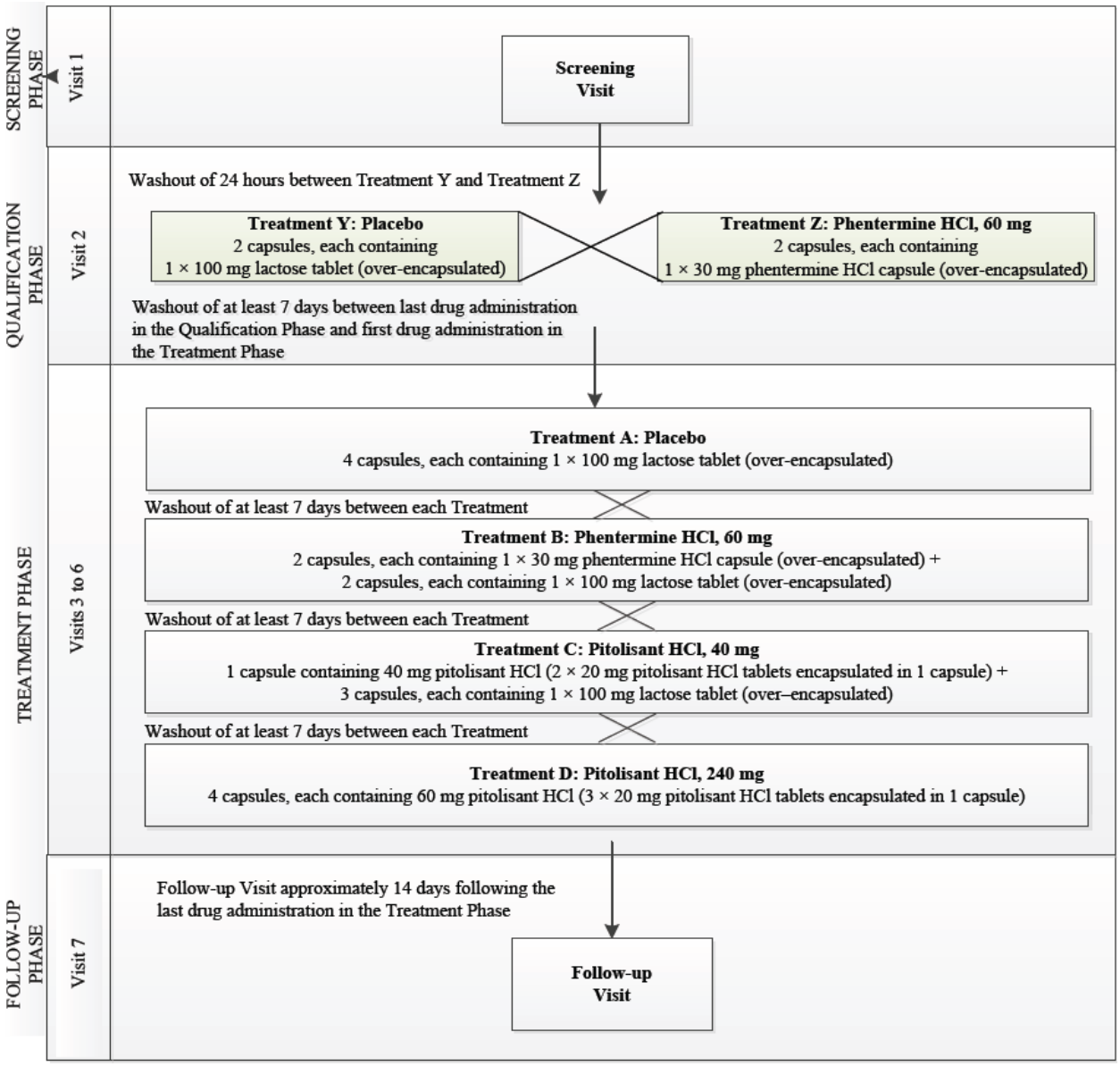
Subjects were to be discharged after study assessments were completed, approximately 24 hours after dosing. Study drug administration in each Treatment Period was separated by a minimum washout interval of 7 days between dosing.

A total of 43 subjects were randomized to the treatment phase and 38 subjects completed the study.

Subjects returned for an end-of-study safety Follow-up Visit approximately 14 days following the last study drug administration in the Treatment Phase, or at the time of early discontinuation.

An overview of the study design is presented in Figure 3.1.1.

Figure 3.1.1: Overview of Study Design



PHARMACODYNAMIC ENDPOINTS

Primary endpoint

The maximum effect (Emax) for drug liking VAS at the moment

Secondary endpoints

- Balance of effects:
  - Drug liking VAS (At the Moment; minimum effect [E_{min}], TEmax or time to minimum effect (TEmin), area under the effect curve (TA_AUE)
- Global effects:
  - Overall drug liking VAS (Emax and Emin)
  - Take Drug Again VAS (Emax and Emin)
- Positive/euphoric subjective effects:
  - High VAS (Emax, TEmax, TA_AUE)
  - Good Effects VAS (Emax, TEmax, TA_AUE)
- Negative subjective effects:
  - Bad Effects VAS (Emax, TEmax, TA_AUE)
  - Addiction Research Center Inventory (ARCI) Lysergic Acid Diethylamide (LSD) scale (Emax, TEmax, TA_AUE)
- Euphoria effects:
  - ARCI Morphine Benzedrine Group (MBG) scale (Emax, TEmax, and TA_AUE)

In this study, the key secondary endpoints were Drug Liking VAS (Emin and TA_AUE), ODL VAS (Emax and Emin), TDA VAS (Emax and Emin), High VAS (Emax and TA_AUE), and Good Drug Effects VAS (Emax and TA_AUE).

Sample Size Determination

The sample size calculation was conducted based on the sponsor's unpublished Drug Liking VAS Emax (bipolar scale) data collected at the investigational site, which included 45 and 90 mg phentermine HCl as the investigational positive controls. Based on these data, the mean paired difference results (phentermine HCl - placebo) were 18.0 and 29.8 for the phentermine 45 and 90 mg doses, respectively. The mean difference was therefore conservatively estimated to be 18.0. Within-group SDs were 17.4889 for phentermine HCl 45 mg and 10.1767 for placebo. As determined by a published algorithm, 22 adjusting for 4 periods and 4 sequences, with a 1-sided significance level of 0.05 and $\delta 1=5$, a sample size of 36 subjects would have at least 90% power to detect a difference in Drug Liking VAS Emax (bipolar scale). Assuming an approximate 20% dropout rate, 44 subjects (11 subjects per sequence) needed to be randomized into the Treatment Phase, with the intention to complete approximately 36 subjects (9 subjects per sequence)

Disposition of Subjects

Forty-three eligible subjects were randomized to treatment in the Treatment Phase. Of these, 38 subjects (88.4%) completed the study and 5 subjects (11.6%) discontinued during the Treatment Phase. Subjects did not complete the study for the following reasons: withdrawal of consent (3 subjects), extended vacation (1 subject), and moving out of town (1 subject).

3.1.2 Statistical Methodologies of the Sponsor

Analysis population:

- Randomized Population: All subjects who are assigned a randomization number in the Treatment Phase.
- Safety Population: All randomized subjects who receive any study treatment in the Treatment Phase.

- Pharmacodynamic (PD) Population: All subjects in the Safety population who receive any study treatments in the Treatment Phase and who have no protocol deviations or other circumstances that would exclude them from PD analysis.
- Completers Population: All subjects in the Safety population who receive all study treatments and complete all treatment periods in the Treatment Phase regardless whether they have protocol deviations.

Statistical methodologies:

Pharmacodynamic data will be analyzed for the Completers Population. In addition, the PD Population will be used for all analysis on the primary endpoint, Drug Liking VAS Emax.

Pharmacodynamic endpoints will be analyzed using a mixed-effect model for a crossover study. The model will include treatment, period, treatment sequence and first-order carryover effect as fixed effects, and subject nested within treatment sequence as a random effect. If the carryover effect is found to be non-significant at the alpha=0.25 level of significance, then the term will be dropped from the analysis model.

The residuals from the mixed-effect model will be investigated for normality using the Shapiro-Wilk W-test. Parameters will be analyzed as having a normal distribution if the probability value of the test is ≥0.05 and paired t-tests will be used for comparisons. A 2.5% Type-I error with a *P* value less than 0.025 will be considered as statistically significant for all individual hypothesis tests. All statistical tests will be performed using one-tailed significance criteria. Multiple comparison adjustments will not be made.

The assumptions for these *t*- tests are listed in Table 11.

Table 11 Assumptions of Various t-Type Tests

Test	Assumptions
Student's *t*	D is normally distributed or sample size is large and standard deviation is finite.
Johnson's t_1	The sample size is small and D is asymmetrical as exponential distribution (for upper-tailed test only).
Chen's test t_2	The sample size is small and D is positively skewed with large skewness (for upper-tailed test only).

If D is positively skewed, for a lower-tailed test, the Student's *t* test is still robust. If D is quite skewed, the normal approximation for the sign test will be used to test the median difference (assuming n≥12). When the sign test is used, overall treatment effect will be assessed using Friedman's test. Median, Q1 and Q3 of the differences and the *P* value will be presented for the pairwise differences.

The following treatment comparisons were made for the primary and secondary PD endpoints, except Drug Similarity VAS.

Abuse Potential Contrast	Phentermine HCl 60 mg vs. Pitolisant HCl 40 mg
	Phentermine HCl 60 mg vs. Pitolisant HCl 240 mg
Abuse liability contrasts	Pitolisant HCl 40 mg vs. Placebo
	Pitolisant HCl 240 mg vs. Placebo

Hypothesis testing:

For study validity purposes, the null hypothesis is that the mean in Emax Drug Liking for phentermine HCl is less than or equal to the mean in Emax Drug Liking for placebo:

H_0: $\mu_C - \mu_p \leq \delta 1$ vs H_A: $\mu_C - \mu_p > \delta 1$, where $\delta 1 = 5$

where μ_C is the mean for the positive control phentermine HCl, μ_P is the mean for placebo, and μ_T is the mean for the test drug, pitolisant.

The hypothesis for comparison between the test drug and the positive control will be:

Ho: $\mu_C - \mu_T \leq \delta 2$ versus Ha: $\mu_C - \mu_T > \delta 2$, where $\delta 2 = 0$

and will be applied to the following contrasts:

- Treatment C: Pitolisant HCl, 40 mg vs Treatment B: Phentermine HCl, 60 mg
- Treatment D: Pitolisant HCl, 240 mg vs Treatment B: Phentermine HCl, 60 mg

The hypothesis for comparison between the test drug and placebo will be:

H_0: $\mu_T - \mu_P \geq 11$ vs H_A: $\mu_T - \mu_P < 11$

For PD derived endpoints that were not primary or key secondary endpoints, the following hypotheses were used:

1. Ho: $\mu_C - \mu_P = 0$ versus Ha: $\mu_C - \mu_P \neq 0$
2. Ho: $\mu_C - \mu_T = 0$ versus Ha: $\mu_C - \mu_T \neq 0$
3. Ho: $\mu_T - \mu_P = 0$ versus Ha: $\mu_T - \mu_P \neq 0$

The significance level of 0.05 was used for 1-sided tests (primary and key secondary endpoints) and the significance level of 0.05 was used for 2-sided tests (other secondary endpoints).

Multiple Comparisons/Multiplicity:

No adjustments were made for multiple comparisons.

Handling of Dropouts or Missing Data: completers analysis

For PD analyses, missing data for subjects who were administered all scheduled study treatments for all the treatment periods were considered as random non-informative missing for analysis purposes.

Changes in the Conduct of the Study

The protocol (version date 16NOV2017) was amended once. The original protocol was not submitted to the IRB. The protocol was amended based on recommendations made by the FDA (Type A meeting, 06FEB2018), including modification of the tablet manipulation method and addition of OxyContin as an active control. The first protocol amendment (version date 02MAY2018) was approved by the IRB on 11MAY2018.

3.1.3 Sponsor's Summary and Conclusions

The mean difference in Drug Liking VAS Emax was statistically significant for phentermine HCl vs pitolisant HCl 40 mg and 240 mg, demonstrating that pitolisant HCl (40 mg and 240 mg) was less liked than phentermine HCl by the recreational stimulant users. The mean difference in Drug Liking Emax was statistically significant ($P < 0.0001$ for each comparison) and the alternative hypothesis was accepted for phentermine HCl vs pitolisant HCl 40 mg and 240 mg.

The comparisons of Drug Liking VAS Emax between pitolisant HCl 40 mg vs placebo and pitolisant 240 mg vs placebo were statistically significant, and therefore supported the hypothesis that pitolisant HCl drug liking was similar to placebo. The null hypothesis was specified as the difference in Drug Liking Emax ≥ 11 and the alternative hypothesis was specified as the difference < 11. The comparisons of Drug Liking Emax for pitolisant HCl 40 mg vs placebo and pitolisant 240 mg vs placebo were significant ($P \leq 0.003$) and the alternative hypothesis was accepted.

Overall, the study results indicate that pitolisant HCl was not associated with a profile suggestive of a potential for recreational drug use or abuse.

3.1.4 Reviewer's Assessment

Descriptive Analysis

This reviewer verified the sponsor's descriptive analysis. The VAS score time course of Drug Liking, Overall Drug Liking, Take Drug Again, High, Good Drug Effects, Bad Drug Effects, and Any Drug Effects, respectively, are shown in Figures 3.1.2 to 3.1.4.

In both Figures 3.1.2 for Drug Liking VAS and 3.1.3 for Overall Drug Liking VAS and Take Drug Again VAS, the peak levels of the positive control Phentermine HCl 60 mg were much higher than that of other treatments while that of Pitolisant HCl 240 mg were lower than Pitolisant HCl 40 mg or even lower than Placebo. For other secondary endpoints as seen in Figure 3.1.4, the peak VAS levels of Pitolisant HCl 240 mg were between those of Phentermine HCl 60 mg and Pitolisant HCl 40 mg, and obviously higher than that of Placebo for High, Good Drug Effects, and Any Drug Effects. However, the peak level of Pitolisant HCl 240 mg was remarkably higher than that of all other treatments including the active control Phentermine HCl 60 mg.

Figure 3.1.2: Mean VAS Time course of Drug Liking VAS (n=38).

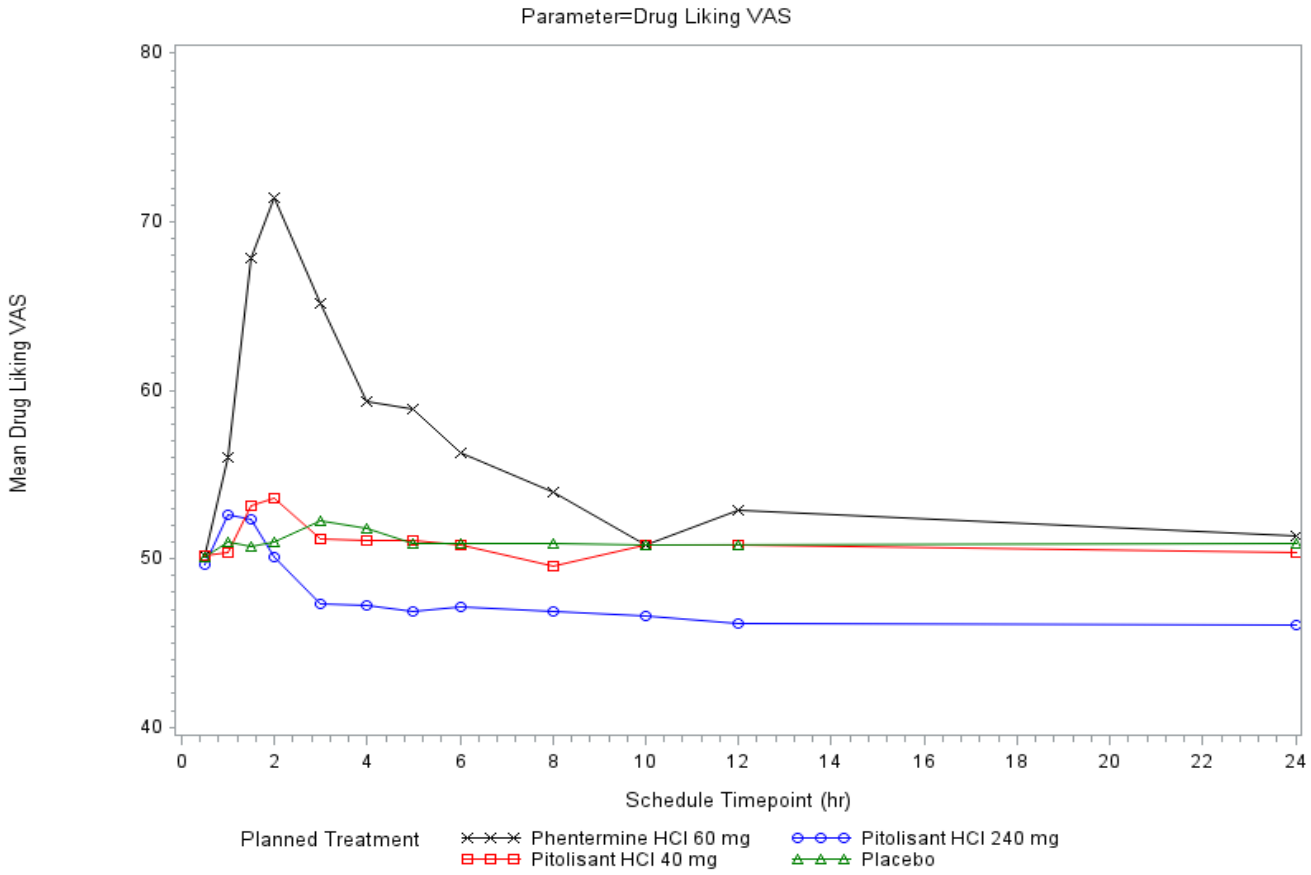
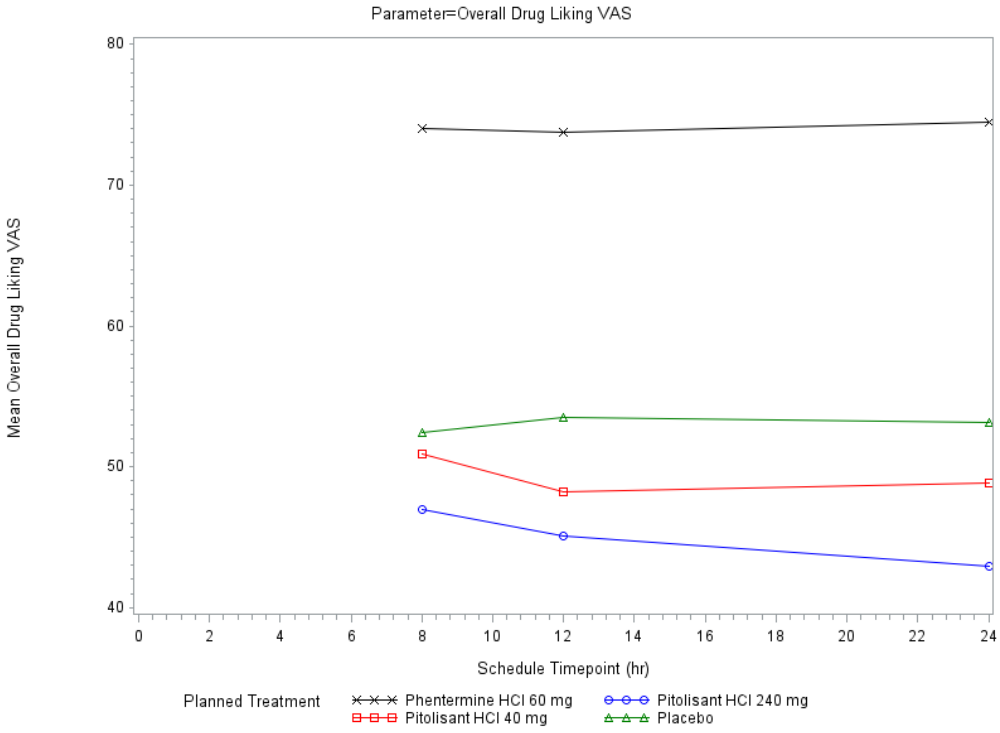


Figure 3.1.3: Mean VAS Time course of (A) Overall Drug Liking and (B) Take Drug Again (n=38).

A.



B.

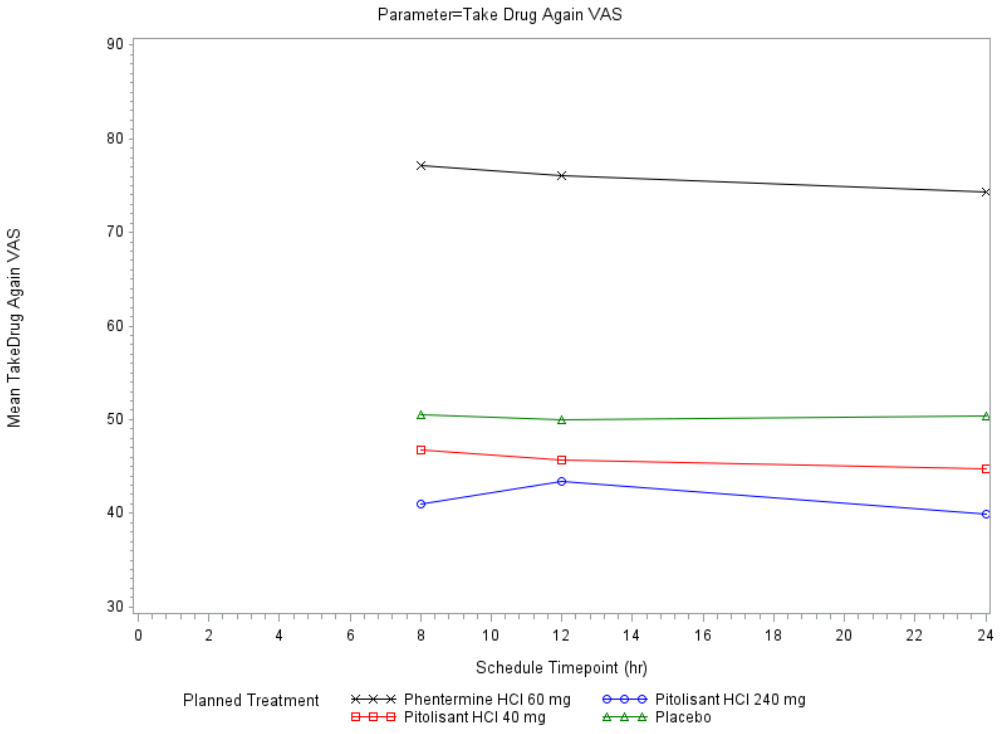
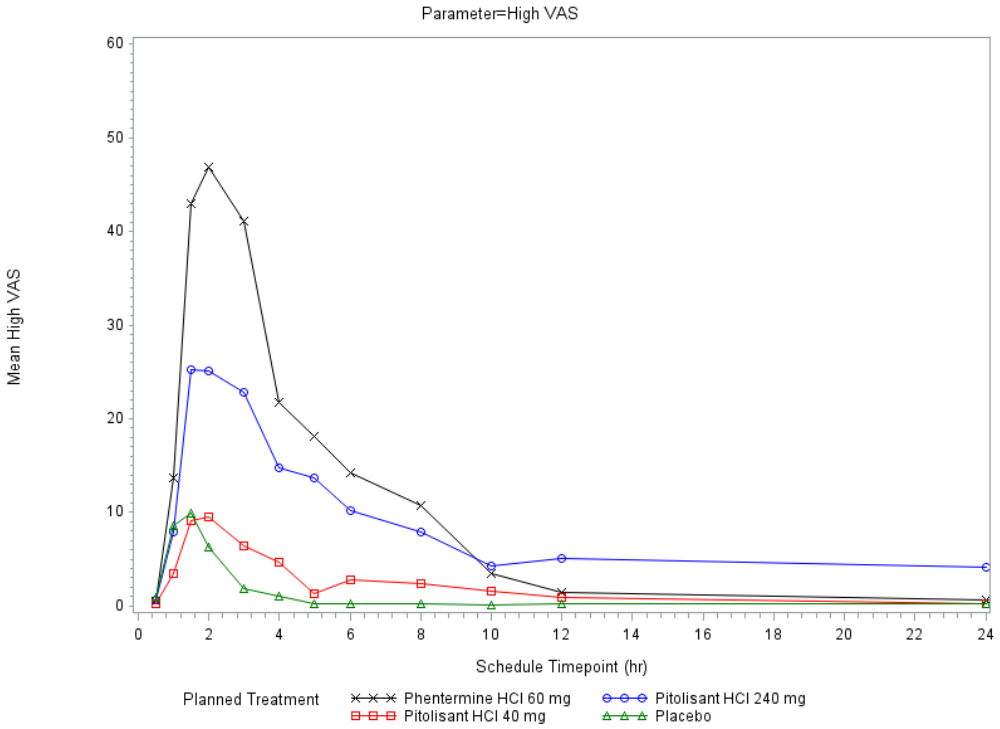


Figure 3.1.4: Mean VAS Time course of (A) High, (B) Good Drug Effects, (C) Bad Drug Effects, and (D) Any Drug Effects (n=38).

A.



B.

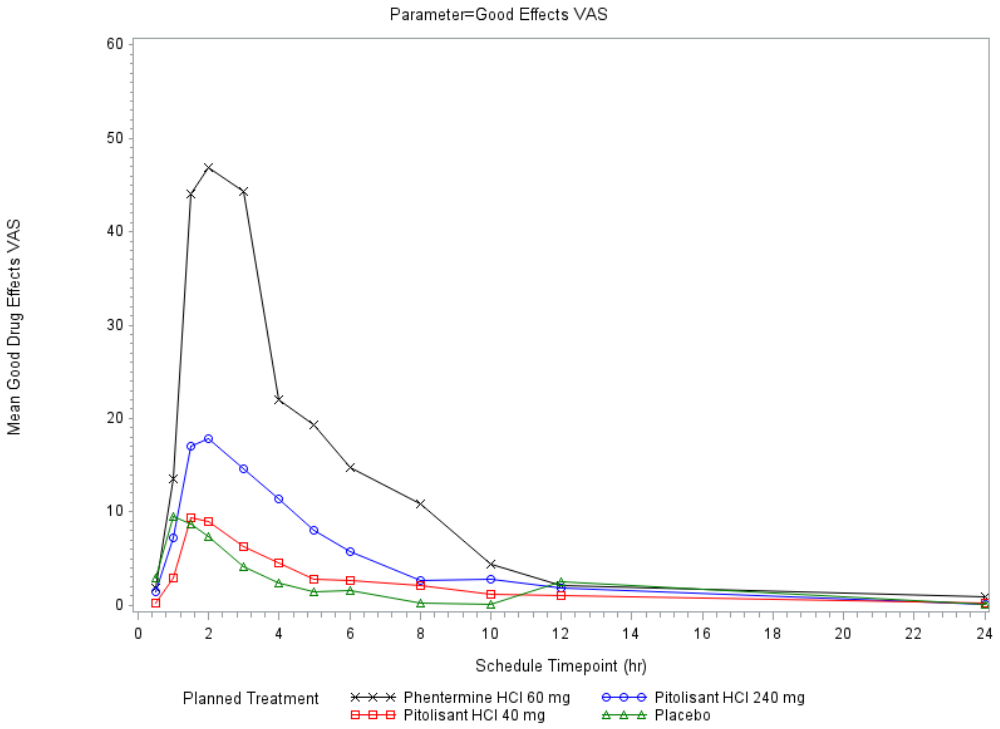
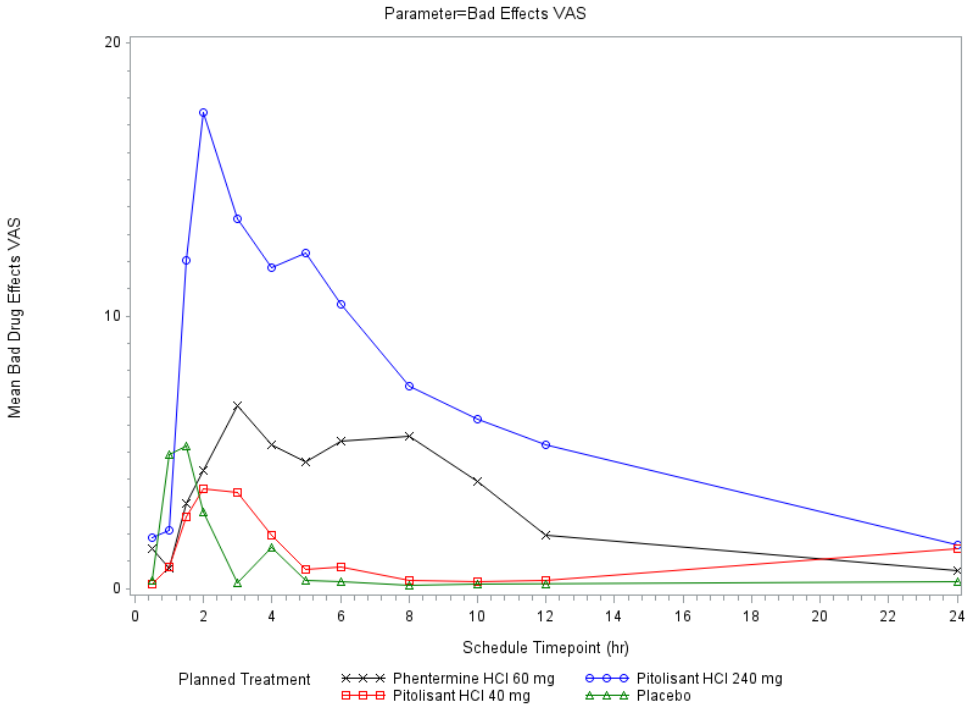
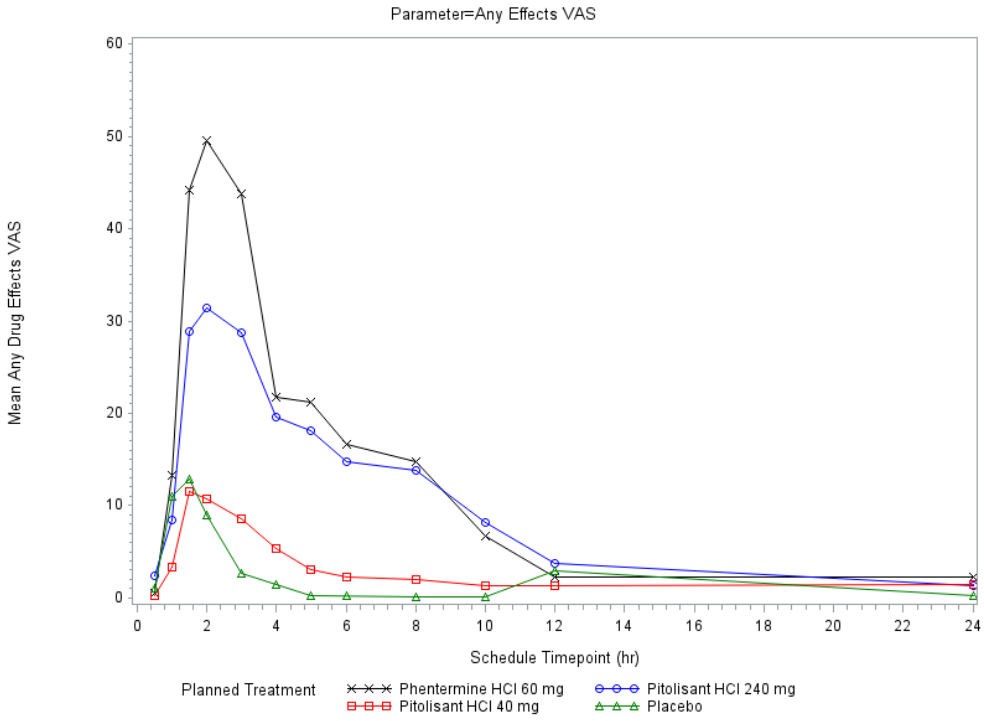


Figure 3.1.4: Continous. Mean VAS Time courses of (A) High, (B) Good Drug Effects, (C) Bad Drug Effects, and (D) Any Drug Effects (n=38).

C.



D.



The descriptive statistics of the primary and key secondary endpoints using the raw data are summarized in Table 3.1.1.

Table 3.1.1. Descriptive Analysis of the Primary and Key Secondary Endpoints (Raw data, Completers, n=38)

Endpoint	Treatment	Mean	SD	Min	Q1	Med	Q3	Max
Drug liking Emax	Placebo	56.1	13.1	50	51	51	51	100
	Phentermine HCl 60 mg	78.7	17.5	50	65	80	100	100
	Pitolisant HCl 40 mg	57.3	12.9	50	51	51	58	100
	Pitolisant HCl 240 mg	59.0	13.2	50	51	51	66	100
Overall Drug Liking Emax	Placebo	54.4	13.9	13	50	51	51	100
	Phentermine HCl 60 mg	77.4	23.2	11	64	82	100	100
	Pitolisant HCl 40 mg	52.7	12.8	17	50	50	51	100
	Pitolisant HCl 240 mg	49.2	26.7	0	42	50	59	100
Take Drug Again Emax	Placebo	51.0	17.7	0	50	50	51	100
	Phentermine HCl 60 mg	78.7	26.3	10	62	91	100	100
	Pitolisant HCl 40 mg	49.4	20.7	0	50	51	51	100
	Pitolisant HCl 240 mg	44.5	30.0	0	19	50	57	100
High Emax	Placebo	12.1	24.2	-1	0	0	11	100
	Phentermine HCl 60 mg	58.5	30.9	0	43	63	81	100
	Pitolisant HCl 40 mg	15.5	25.3	-1	0	1	22	97
	Pitolisant HCl 240 mg	35.1	34.7	0	0	28.5	57	100
Good Drug Effects Emax	Placebo	15.3	26.8	0	0	1	22	100
	Phentermine HCl 60 mg	62.9	31.8	0	42	70	88	100
	Pitolisant HCl 40 mg	15.7	24.9	0	0	1	25	92
	Pitolisant HCl 240 mg	26.3	29.6	0	1	12.5	50	100
Bad Drug Effects Emax	Placebo	7.4	19.7	0	0	1	1	92
	Phentermine HCl 60 mg	14.7	21.6	0	0	2	20	71
	Pitolisant HCl 40 mg	6.7	18.0	0	0	1	3	99
	Pitolisant HCl 240 mg	28.2	35.1	0	0	8	53	100
Any Drug Effects Emax	Placebo	17.2	30.4	0	0	1	21	100
	Phentermine HCl 60 mg	63.6	30.9	0	37	70.5	89	100
	Pitolisant HCl 40 mg	19.3	27.5	0	0	4.5	32	94
	Pitolisant HCl 240 mg	41.6	37.8	0	1	42	72	100

2.3.1.2 Statistical Testing

This reviewer carried out the following comparisons on the primary and key secondary endpoints:

- Validation: Phentermine HCl 60 mg vs. Placebo
- Phentermine HCl 60 mg vs. Pitolisant HCl 40 mg (for
- Phentermine HCl 60 mg vs. Pitolisant HCl 240 mg
- Pitolisant HCl 40 mg vs. Placebo
- Pitolisant HCl 240 mg vs. Placebo

Since the normality tests of the residuals from the mixed-effect model did not support normal distributions for above comparisons based on the Shapiro-Wilk W-test, this reviewer carried out pairwise t-tests for comparisons at a level of 0.025 (one-sided). A pairwise t-test is considered appropriate if the distribution is not too skewed. The results of above comparisons are shown in Table 3.1.2 the pair-wised comparison.

This reviewer confirmed that the validation test for comparing Drug Liking VAS Emax between Phentermine HCl 60 mg and Placebo. The test margin proposed by the sponsor for the validation test was unacceptable because the margin should be 15 for validation test. The lower 95% confidence limit (one-sided) was 16.9, larger than 15 thus validated the study. The mean difference between phentermine HCl 60 mg and both doses of pitolisant HCl in Drug Liking VAS Emax was statistically significant larger than zero, supporting that pitolisant HCl (40 mg and 240 mg) was less liked than phentermine HCl 60 mg by the recreational stimulant users. Supportive results were obtained in the analyses of most key secondary endpoints.

For comparing Drug Liking VAS Emax between pitolisant and placebo using a test margin of 11, the test of pitolisant HCl at both doses (40 mg and 240 mg) vs placebo was statistically significant at level 0.05 one-sided, suggesting no abuse potential for pitolisant HCl. However, for the secondary endpoints High VAS, Good Drug Effects VAS, and Any Drug Effects VAS, the mean values of pitolisant HCl 240 mg were significantly larger than those of placebo by large margin. Therefore, pitolisant HCl at high dose (240 mg) may still have some abuse potential for recreational stimulant users.

Table 3.1.2: Summary of Drug Abuse Potential Analysis of the Primary and key Secondary endpoints (Completers, N=38)

Pairwise Comparison	Mean Diff	StdErr	p-value	one-sided 95% CI	
				LCL	UCL
Drug Liking VAS Emax					
Validation, H_0: $\mu_C - \mu_P \leq 15$					
Phentermine HCl 60 mg - Pcb	22.7	2.9	0.0055	17.8	Infinity
Positive controls vs. test drug, H_0: $\mu_C - \mu_T \leq 0$					
Phentermine HCl 60 mg - Pitolisant HCl 40 mg	21.4	3.2	<.0001	16.0	Infinity
Phentermine HCl 60 mg - Pitolisant HCl 240 mg	19.7	3.5	<.0001	13.7	Infinity
Pitolisant HCl vs. Placebo, H_0: $\mu_T - \mu_P \geq 11$					
Pitolisant HCl 40 mg – Pcb	1.3	2.9	0.001	-Infinity	6.2
Pitolisant HCl 240 mg – Pcb	3.0	3.1	0.0073	-Infinity	8.3
Overall Drug Liking Emax					
Phentermine HCl 60 mg -Pcb[a]	23.0	4.0	<.0001	16.2	Infinity
Phentermine HCl 60 mg - Pitolisant HCl 40 mg[a]	24.7	4.0	<.0001	17.9	Infinity
Phentermine HCl 60 mg - Pitolisant HCl 240 mg[a]	28.2	5.7	<.0001	18.6	Infinity
Pitolisant HCl 40 mg – Pcb[b]	-1.7	2.7	0.265	-Infinity	2.8
Pitolisant HCl 240 mg – Pcb[b]	-5.2	4.6	0.1322	-Infinity	2.6
Take Drug Again VAS Emax					
Phentermine HCl 60 mg -Pcb[a]	27.7	5.0	<.0001	19.3	Infinity
Phentermine HCl 60 mg - Pitolisant HCl 40 mg[a]	29.3	5.8	<.0001	19.6	Infinity
Phentermine HCl 60 mg - Pitolisant HCl 240 mg[a]	34.2	6.8	<.0001	22.8	Infinity
Pitolisant HCl 40 mg – Pcb[b]	-1.6	4.2	0.3508	-Infinity	5.4
Pitolisant HCl 240 mg – Pcb[b]	-6.5	5.5	0.1232	-Infinity	2.8

Note: Analyses were carried out using a paired t-test in the Completers population. p-value: hypothesis tests at alpha=0.05, one-sided. LCL: lower confidence limit, UCL: upper confidence limit.

a. Phentermine 60 mg vs. Placebo, H_0: $\mu_C - \mu_P \leq 0$; phentermine 60 mg vs. pitolisant HCl, H_0: $\mu_C - \mu_T \leq 0$

b. Pitolisant HCl vs. Placebo, H_0: $\mu_T - \mu_P \geq 0$

Table 3.1.2: Continued --- Summary of Drug Abuse Potential Analysis of the Primary and key Secondary endpoints (Completers, N=38)

Pairwise Comparison	Mean Diff	StdErr	p-value	one-sided 95% CI	
				LCL	UCL
High VAS Emax					
Phentermine HCl 60 mg - Pcb[a]	46.5	5.1	<.0001	37.9	Infinity
Phentermine HCl 60 mg - Pitolisant HCl 40 mg[a]	43.1	5.2	<.0001	34.3	Infinity
Phentermine HCl 60 mg - Pitolisant HCl 240 mg[a]	23.4	5.4	<.0001	14.3	Infinity
Pitolisant HCl 40 mg – Pcb[b]	3.4	5.4	0.7358	-Infinity	12.5
Pitolisant HCl 240 mg – Pcb[b]	23.0	5.8	0.9999	-Infinity	32.7
Good Drug Effects VAS Emax					
Phentermine HCl 60 mg - Pcb[a]	47.6	5.9	<.0001	37.7	Infinity
Phentermine HCl 60 mg - Pitolisant HCl 40 mg[a]	47.2	5.8	<.0001	37.5	Infinity
Phentermine HCl 60 mg - Pitolisant HCl 240 mg[a]	36.6	5.9	<.0001	26.5	Infinity
Pitolisant HCl 40 mg – P[b]	0.4	5.2	0.5302	-Infinity	9.1
Pitolisant HCl 240 mg – P[b]	11.1	6.5	0.9517	-Infinity	22.0
Bad Drug Effects VAS Emax					
Phentermine HCl 60 mg - Pcb[a]	7.3	4.2	0.0453	0.2	Infinity
Phentermine HCl 60 mg - Pitolisant HCl 40 mg[a]	8.0	4.5	0.0421	0.4	Infinity
Phentermine HCl 60 mg - Pitolisant HCl 240 mg[a]	-13.5	5.9	0.9864	-23.5	Infinity
Pitolisant HCl 40 mg – Pcb[b]	-0.7	4.3	0.4395	-Infinity	6.6
Pitolisant HCl 240 mg – Pcb[b]	20.9	5.7	0.9996	-Infinity	30.5
Any Drug Effects VAS Emax					
Phentermine HCl 60 mg - Pcb[a]	46.4	6.2	<.0001	36.0	Infinity
Phentermine HCl 60 mg - Pitolisant HCl 40 mg[a]	44.4	5.6	<.0001	34.9	Infinity
Phentermine HCl 60 mg - Pitolisant HCl 240 mg[a]	22.1	5.6	0.0002	12.7	Infinity
Pitolisant HCl 40 mg – Pcb[b]	2.1	6.3	0.6274	-Infinity	12.8
Pitolisant HCl 240 mg – Pcb[b]	24.4	6.1	0.9998	-Infinity	34.7

Note: Analyses were carried out using a paired t-test in the Completers population. p-value: hypothesis tests at alpha=0.05, one-sided. LCL: lower confidence limit, UCL: upper confidence limit.

a. Active controls vs. Placebo, H0: $\mu C - \mu p \leq 0$; Active controls vs. Test drug, H0: $\mu C - \mu T \leq 0$

b. Pitolisant HCl vs. Placebo, H0: $\mu T - \mu P \geq 0$

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues

For study validation, the selection of hypothesis test margin of 5 is not logic: if the sponsor believed that the test drug Pitolisant is less abusable than the positive control Phentermine HCl 60 mg, then the margin for testing (Phentermine HCl 60 mg – Placebo) should be at least no smaller than the margin for testing (Pitolisant – Placebo) which was predefined by the sponsor being 11.

4.2 Conclusions and Recommendations

This reviewer confirmed the following findings:

(1) The study validation was confirmed based on a significant validation test.

(2) Subjects in the Treatment phase liked the active control drug phentermine HCl 60 mg more than they liked pitolisant HCl at either 40 mg or 240 mg. The conclusion is based on that tests of the mean differences between phentermine HCl 60 mg and pitolisant HCl (40 mg and 240 mg) in the primary and most key secondary endpoints were statistically significant at one-sided level of 0.05 using a test margin of zero.

(3) For comparing Drug Liking VAS Emax between pitolisant and placebo, we used test margin of 11. The tests of pitolisant HCl at both doses (40 mg and 240 mg) vs placebo were statistically significant at level 0.05 one-sided. It indicates no abuse potential for pitolisant HCl. However, for the secondary endpoints of High VAS, Good Drug Effects VAS, and Any Drug Effects, pitolisant HCl 240 mg has significantly larger mean values than those of placebo. Therefore, pitolisant HCl at high dose (240 mg) may still have some abuse potential for recreational stimulant users.

4.3 Labeling Recommendations (optional)

The finding that pitolisant HCl 240 mg may have some abuse potential for recreational stimulant users may be considered to be included in Section 9.

5. Appendix:

A. My exploratory analysis of the following key secondary endpoints supports the finding that pitolisant 240 mg has drug abuse potential as summarized in Table A bellow. The margins of 27 and 20 for these secondary endpoints are determined by converting the margins of 15 and 11 that are used for the analysis of Drug Liking VAS Emax, respectively. The convertor is based on my internal research on the correlation between Drug Liking VAS Emax and each of the key secondary endpoints (VAS Emax) based on historical NDA data. As seen in Table A, the validation tests on the secondary endpoints using a margin of 27 are all significant at level of 0.05 (one-sided), supporting their ability to discriminate the active control drug phentermine 60 mg from placebo. Moreover, comparing pitolisan HCl to placebo with the margin of 20, the tests for the lower dose pitolisan (40 mg) were significant with the upper confidence limit less than the margin of 20, but that for the higher pitolisan dose (240 mg) were not. Note further, the upper confidence limits for testing pitolisan 240 mg to placebo were not just merely greater than 20, but remarkably larger than the margin. Therefore, the boundary evidence of the drug abuse potential pitolisant 240 mg as revealed by the primary analysis on Drug Liking VAS Emax were confirmed by the analysis of the key secondary endpoints, VAS Emax of High, Good Drug Effects, and Any Drug Effects.

Table A Summary of Treatment Effects of Pitolisant HCl (40 mg and 240 mg) Compared to Phentermine HCl 60 mg and Placebo (Completers, n=38). NDA211150

endpoint	Pairwise Comparison	Mean Diff	SE	p-value	One-sided 95% CI	
					LCL	UCL
High VAS Emax	Validation, H_0: $\mu_C - \mu_p \leq 27$					
	Phentermine HCl 60 mg - P	46.5	5.1	0.0002	37.9	Infinity
	Pitolisant HCl vs. Placebo, H_0: $\mu_T - \mu_P \geq 20$					
	Pitolisant HCl 40 mg – P	3.4	5.4	0.0019	-Infinity	12.5
	Pitolisant HCl 240 mg – P	23.0	5.8	0.6989	-Infinity	32.7
Good Drug Effects VAS Emax	Validation, H_0: $\mu_C - \mu_p \leq 27$					
	Phentermine HCl 60 mg - P	47.6	5.9	0.0006	37.7	Infinity
	Pitolisant HCl vs. Placebo, H_0: $\mu_T - \mu_P \geq 20$					
	Pitolisant HCl 40 mg – P	0.4	5.2	0.0003	-Infinity	9.1
	Pitolisant HCl 240 mg – P	11.1	6.5	0.0879	-Infinity	22.0
Any Drug Effects VAS Emax	Validation, H_0: $\mu_C - \mu_p \leq 27$					
	Phentermine HCl 60 mg - P	46.4	6.2	0.0017	36.0	Infinity
	Pitolisant HCl vs. Placebo, H_0: $\mu_T - \mu_P \geq 20$					
	Pitolisant HCl 40 mg – P	2.1	6.3	0.0038	-Infinity	12.8
	Pitolisant HCl 240 mg – P	24.4	6.1	0.7591	-Infinity	34.7

Note: Analyses were carried out using a paired t-test in the Completers population. p-value: hypothesis tests at alpha=0.05, one-sided. LCL: lower confidence limit, UCL: upper confidence limit.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WEI LIU
07/01/2019 03:41:30 PM

QIANYU DANG
07/01/2019 03:44:13 PM

YI TSONG
07/02/2019 08:09:53 AM