CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number:	NDA 212839
Drug Name:	Cenobamate (YKP3089)
Indication(s):	Treatment of Partial-Onset Seizures in Adult Patients.
Studies	One Two Year Oral Gavage Carcinogenicity Study in Rats and One Six-Month Oral Gavage Carcinogenicity Study in rasH2 Transgenic Mice.
Applicant:	Sponsor: Sk Life Science Inc 22-10 Route 208 South Fair Lawn, NJ 07410, United States Test facility for rat study: (b) (4) Test facility for mouse study (b) (4)
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1. Background

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in transgenic mice. These studies were intended to assess the carcinogenic potential of Cenobamate (YKP3089) in rats and mice when administered orally by gavage at appropriate drug levels for about 104 weeks in rats and 26 weeks in mice. Results of this review have been discussed with the reviewing pharmacologist Dr. Fisher.

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

2. Rat Study

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups and one vehicle control group. Two hundred and sixty Sprague-Dawley rats of each sex were assigned to three treated groups and one vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 65 animals, as indicated in Table 1. The dose levels for the three treated groups were 4, 8, and 20 mg/kg/day for both male and female rats, for up to 104 weeks. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The vehicle control group received the vehicle only (0.5% (w/v) methylcellulose prepared in reverse osmosis water), administered orally by gavage for about 104 weeks in the same manner as the treated groups. Due to early termination threshold of 20 survivor's rats in the male vehicle control groups, early final scheduled necropsies were carried out during Week 87 for males and Week 90 for females (based on FDA recommendations).

Table 1: Experimental Design in Rat Study

Group Name	Group N0.	Dose Level (mg/kg/day)		Number of Animal	
		Male	Female	Males	Females
Vehicle Control	1	0	0	65	65
Low	2	4	4	65	65
Medium	3	8	8	65	65
High	4	20	20	65	65

early final scheduled necropsies were conducted during Week 87 for males and Week 90 for females

During the study period all animals were observed for general health/mortality and moribundity twice daily (a.m. and p.m.), abnormal findings were recorded throughout the study. Cage side observations were conducted for each carcinogenicity animal once daily during the dosing phase, except on days when detailed observations were conducted. Detailed observations were conducted for each animal at least once prior to dosing on Day 1, and weekly thereafter throughout the dosing phase. Detailed examinations for palpable masses were done weekly, the time of onset, location, size, appearance, and progression of each grossly visible or palpable mass, observed in carcinogenicity rats, were recorded weekly, particular attention being paid to the animals during and for the four hours after dosing. Any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively was euthanized. Observations will include, but will not be limited to, evaluation for reaction to treatment. Histopathological examinations were performed on all animals found dead or killed moribund or sacrificed at the end of the experiment. Body weights were recorded once during the predose phase, before dosing on Day 1 of the dosing phase, weekly thereafter to Week 14, once every 4 weeks thereafter during the dosing phase, and for each animal of that sex/group during the week of sacrifice.

2.1. Sponsor's analyses

2.1.1. Survival analysis

In the sponsor's analysis, the tests for survival comparisons were performed with a two-sided risk for increasing and decreasing mortality with dose. Tests were performed for dose response (vehicle control and dosed groups only), and for each dosed group against vehicle control group using Kaplan-Meier product-limit estimates, along with log-rank and Wilcoxon tests. These tests were performed using the LIFETEST procedure in SAS. The time to death or sacrifice (in weeks) was the dependent variable.

Any animal with accidental injury that causes its death, or its unscheduled sacrifice was censored in the estimation. In addition, all animals with a death or sacrifice status recorded as a scheduled sacrifice (interim or terminal) or accidental death were censored in the analysis. Results of all pair-wise comparisons are reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests.

Sponsor's findings:

Sponsor's analysis showed the numbers of rats surviving to their terminal necropsy were 20 (30.8%), 27 (41.5%), 28 (43.1%), and 25 (38.5%), in the vehicle control group, low, medium, and high dose groups, in male rats, respectively, and 19 (29.2%), 29 (44.6%), 19 (29.2%), and 22 (33.8%) in vehicle control, low, medium, and high dose groups, in female rats, respectively. The sponsor's report concluded that, there was no statistically significant dose response relationship in the mortality in either male or female rats. The pairwise comparisons showed statistically significant decrease in mortality in the low dose group when compared the vehicle control group in both male and female rats (p=0.0247 and p=0.0422, respectively, for the Log-Rank test and p=0.0084 and p=0.0330, respectively, for Wilcoxon tests)

Also, the pairwise comparisons showed statistically significant decrease in mortality in the medium dose group when compared the vehicle control group in male rats (p=0.0372 for the Wilcoxon test.).

2.1.2. Tumor data analysis

In the sponsor's analysis, tests to compare tumor incidence were performed, with a one-sided risk for increasing incidence with dose. Tests were performed for dose response (vehicle control and dosed groups only) and for each dosed group against the vehicle control group. Occult or non-palpable tumors were analyzed by the IARC asymptotic fixed interval-based test (Peto et al., 1980). The cut-off points for the interval-based test were Weeks 0 to 52, 53 to 78, 79 to before terminal sacrifice, and the terminal sacrifice. Actual dose levels were used as the scores. Fatal and non-fatal tumors were analyzed together, with separate stratum for each using the death-rate method and the prevalence methods, respectively. Tumors of uncertain context were included in the analysis as non-fatal. The test was implemented using PROC MULTTEST in the SAS system (SAS, 2008). In the case of sparse tables (<10 total tumor bearing animals in the groups analyzed for the trend or pairwise test), the exact form of the test was used. Otherwise, the asymptotic version of the test was used. Observable or palpable (superficial as in mammary or skin) tumors were analyzed using the onset methods using the time to death or time of detection of the tumor (in weeks) as a surrogate for the tumor onset time. For each given tumor type, statistical analysis was performed if the incidence in at least one dosed group was increased by at least two occurrences over the vehicle control group.

Site or tumor combinations were statistically analyzed if the incidence in at least one dosed group was increased by at least two occurrences over the vehicle control group. Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded in the data and were not assigned based on the day/week of necropsy.

Adjustment for the multiplicity:

The data was analyzed in accordance with current FDA guidelines (FDA Draft Guidance for Industry, 2001). The incidence rate for defining whether a tumor type is rare or common was based on site-specific background historical data. The study pathologist determined whether a tumor type was rare or common.

Sponsor's findings:

The dose response test in female rats presented in the sponsor's report showed a p-value lower than 0.05 in mammary adenoma (p-value = 0.0130 for the Log-Rank test). However, following the multiple testing adjustment method described above, this test was not statistically significant since this tumor type was considered as common tumors. The pairwise comparison test presented in the sponsor's report showed a p-value lower than 0.05, in mammary adenoma in the high dose group in female rats, when compared to the vehicle control group (p=0.0391 and p=0.0397 for the Log-Rank and Wilcoxon tests respectively). Also, in the sponsor's report in female rats, the pairwise comparisons test showed p-value lower than 0.05, in mammary fibroadenoma and in mammary adenoma and fibroadenoma combined in the low dose group, when compared to the vehicle control group, (p= p=0.0232 and p= 0.0232 for the Log-Rank test, respectively).

Since these tumor types were considered as common tumors, then following the multiple testing adjustment method described above, these comparisons were not statistically significant.

No significant findings were noted in males

2.2 Reviewer's analyses

To verify sponsor's analysis and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed the survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically on November 21, 2018 via SN 0001.

2.2.1 Survival analysis

In the reviewer's analysis, intercurrent mortality data were analyzed using the Kaplan-Meier product limit method. The Kaplan-Meier's curves were presented graphically for male and female rats separately. The dose response relationship and homogeneity of survival distributions were tested for the treatment groups using the Likelihood Ratio test and the Log-Rank test. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female rats, respectively.

Reviewer's findings:

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 20

(30.8%), 27 (41.5%), 28 (43.1%), and 25 (38.5%), in the vehicle control group, low, medium, and high dose groups, in male rats, respectively, and 19 (29.2%), 29 (44.6%), 19 (29.2%), and 22 (33.8%) in vehicle control, low, medium, and high dose groups, in female rats, respectively. This reviewer's analysis showed no statistically significant dose response relationship in the mortality of both male and female rats. The pairwise comparisons showed statistically significant decrease in mortality in the low dose group when compared the vehicle control group in both male and female rats (p=0.0270 and p=0.0458, respectively)

2.2.2. Tumor data analysis

In the reviewer's analysis, the tumor data were analyzed for dose response relationship across vehicle control group and the treated groups, as well as the pairwise comparisons of vehicle control group with each of the treated groups using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method, an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice with development of the tumor type being tested gets a score of s_h =1. An animal that dies at Week w_h without development of the given tumor type before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}} \right)^k$ <1. The adjusted group size is defined as Σs_h . As an interpretation, an animal with score s_h =1 can be considered as a whole animal, while an animal with score s_h <1 can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal develops the given tumor being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise comparison) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104-week standard rat and mouse studies, a value of k=3 is suggested in the literature [Gebregziabher and Hoel (2009), Moon et al. (2003), Portier, et al. (1986)]. Hence, this reviewer used k=3 for the analysis of the data. Based on the intent to treat (ITT) principle Wmax was considered as 105 for both male and female rats.

For the calculation of p-values, if there were less than 10 tumor bearing animals across all treatment groups for a given tumor type, the exact tests based on the discrete permutation distribution were used, with dose levels (0, 4, 8, and 20 for both male and female rats) as scores, and asymptotic tests were used for tumor types with higher incidences. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male rats and female rats, respectively.

Multiple testing adjustments:

Following the FDA more recently revised draft guidance for the carcinogenicity study design and data analysis 2015, for the two-year rat study this reviewer used significance levels of 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

A tumor is defined as a rare tumor if the published spontaneous rate or the spontaneous rate of the vehicle control of the tumor is less than 1%, and a common tumor is defined as one with tumor rate greater than or equal to 1%.

Reviewer's findings:

The tumor types with p-values less than 0.05 for dose response relationship and/or pairwise comparisons of vehicle control and treated groups are reported in Table 2.

Table 2: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons
Treated Groups and Control Group in Rats

sex	Organ Name	Tumor Name	0 mg Cont (N=65) P - Trend	4 mg Low (N=65) P - C vs. L	8 mg Med (N=65) P - C vs. M	20 mg High (N=65) P - C vs. H
Female	Mammary Gland, Female	B-Adenoma	0/65 (27)	0/65 (31)	2/65 (29)	3/65 (30)
			0.0249*	NC	0.2636	0.1388
		B-Fibroadenoma	18/65 (37)	33/65 (47)	19/65 (37)	25/65 (41)
			0.3576	0.0372@	0.5000	0.1936
		B-Adenoma/ B-Fibroadenoma	18/65 (37)	33/65 (47)	20/65 (38)	27/65 (42)
			0.2359	0.0372@	0.4547	0.1204

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.
*: Statistically significant at 0.025 for rare tumor in dose response relationship,
@: not Statistically significant at 0.01 for common tumor in pairwise comparison.

Following the multiple testing adjustment method described above, this reviewer's analysis showed a statistically significant dose response relationship in tumor incidences with increased YKP3089 dose across the vehicle control and the treated groups of female rats for the incidence of benign adenoma in the mammary gland (p-value = 0.0249), since this tumor type is considered as rare tumor. The pairwise comparisons showed no tumor types with a statistically significant increase in tumor incidences in YKP3089 treated groups, when compare to the vehicle control group in either male or female rats.

3. Mouse Study

Two separate experiments were conducted, one in male mice and one in female mice. In each of these two experiments there were three treated groups, one vehicle control group, and one positive control group. One hundred and ten Tg rasH2 transgenic mice of each sex were assigned randomly to one of the five groups by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 25 animals except the positive control group which had 10 animals. The dose levels for the three treated groups were 5, 15, and 35 mg/kg/day for both male and female mice, for up to 26 weeks, as indicated in Table 3. In this review, these dose groups would be referred to as the low, medium, and high dose group, respectively. The positive control group was administered with three intra-peritoneal injections of 1000 mg/kg/day of urethane in saline once on Days 1, 3 and 5. This group was included to verify sensitivity of the test system to detect carcinogenicity effect. The vehicle control group received daily oral vehicle control article only [0.5% w/v methylcellulose (1500 cps) in de-ionized (DI) water], were administered in the same manner as the treated groups. The positive control mice were sacrificed on Day 72 (females) or Day 74 (males).

Table 3: Experimental Design in Mouse Study

Group Name	Group N0.	Dose Level (mg/kg/day)		Number of Animal	
		Male	Female	Males	Females
Vehicle Control	1	0	0	25	25
Low	2	5	5	25	25
Medium	3	15	15	25	25
High	4	35	35	25	25
Positive control	5	1000(urethane)	1000(urethane)	10	10

The positive control was administered with 3 intraperitoneal (i.p.) injections of urethane in saline on Days 1, 3 and 5.

During the study period, all animals were observed for general health/mortality and moribundity twice daily (at least 6 hours apart), abnormal findings were recorded throughout the study. For cage side only, positive control animals were observed on Days 1, 3, and 5. Also for the Main Cohort, detailed hands-on examination was performed on Day 1 and weekly thereafter for the duration of the study. Observations included, but not limited to, evaluation for reaction to treatment. The time of onset, location, size, appearance, and progression of each grossly visible or palpable mass, observed in carcinogenicity mice, were recorded at the same intervals as detailed observations, particular attention being paid to the animals during and for the first hour after dosing. Any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively was euthanized. Histopathological examinations were performed on all animals found dead, killed moribund, or sacrificed at the end of the experiment. Body weights of individual animals were recorded pre-dose on Day 1, weekly through Week 13, and biweekly thereafter.

3.1. Sponsor's analyses

3.1.1 Survival analysis

The Kaplan-Meier's curves were presented graphically for male and female mice separately. The generalized Wilcoxon test for survival was used to compare the homogeneity of survival rates across the groups at the 0.05 significance level. If the survival rates were significantly different, the generalized Wilcoxon test was used to make pairwise comparisons of each treated group with the vehicle control group. Additionally, the positive control group was compared to the vehicle control group using the generalized Wilcoxon test.

Survival times in which the status of the animal's death was classified as an accidental death, planned interim sacrifice or terminal sacrifice were considered censored values for the purpose of the Kaplan-Meier estimates and survival rate analyses.

Sponsor's findings:

Sponsor's analysis showed the numbers of mice surviving to their terminal necropsy were 23 (92%), 23 (92%), 24 (96%), and 23 (92%), in vehicle control, low, medium, and high dose groups in male mice, respectively, and 25 (100%), 24 (96%), 23 (92%), and 25 (100%), in female mice, respectively. The sponsor's report concluded that there were no statistically significant findings in survival rate in either sex of mice.

3.1.2 Tumor data analysis

Tumor incidence data were analyzed within each sex, via Peto's mortality-prevalence methods, without continuity correction, incorporating the context (incidental or fatal, or mortality-independent) in which tumors were observed. The incidence of each tumor type was analyzed with a one-sided trend test using the positive dose response relationship in tumor occurrence across vehicle control and treated groups. In addition, one-sided pairwise comparisons of vehicle control and individual treated groups were conducted. The analysis of tumors was based on the following fixed time intervals Days 1 through 99 and Days 100 through and including terminal sacrifice, for male and female mice. The actual dose levels were used as the scores. Tumors classified as mortality-independent such as, but not limited to, those of the mammary gland and skin, were analyzed with Peto's mortality-independent method (onset rate method) incorporating the day of detection. All animals that died or were sacrificed after the first animal of that sex was terminally sacrificed were included in the scheduled terminal sacrifice interval for the incidental finding analyses. All tumors in the scheduled terminal sacrifice interval were considered incidental for the purpose of statistical analysis.

For the calculation of p-values, if there were less than 10 tumor bearing animals across all treatment groups for a given tumor type, the exact tests based on the discrete permutation distribution were used and asymptotic tests were used for tumor types with higher incidences.

Each diagnosed tumor type was analyzed separately. All metastases and invasive tumors will be considered secondary and not statistically analyzed. In addition, tumors were combined for analysis purposes at the discretion of the Study Director.

Tumor incidence in the positive control group will be compared to the vehicle control group with a 1-sided Fisher's exact test at both the 0.01 and 0.05 significance levels. Only the following tumors were statistically analyzed: alveolar-bronchiolar adenoma, alveolar-bronchiolar carcinoma, and hemangiosarcoma in the spleen.

Multiple testing adjustment:

For multiplicity adjustment testing, no detailed information was provided in the sponsor's report.

Sponsor's findings:

For both males and females, there were no statistically significant tumor findings.

3.2 Reviewer's analyses

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

3.2.1 Survival analysis

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

Reviewer's findings:

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy were 23 (92%), 23 (92%), 24 (96%), and 23 (92%), in vehicle control, low, medium, and high dose groups in male mice, respectively, and 25 (100%), 24 (96%), 23 (92%), and 25 (100%), in female mice, respectively. This reviewer's analysis showed no statistically significant increase dose response relationship in the mortality of either male or female mice. The pairwise comparisons also showed no statistically significant increase or decrease in mortality between the treated groups, and the vehicle control group in either sex of mice.

3.2.2 Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and the pairwise comparisons of vehicle control and treated groups are given in Table 6A and 6B in the appendix for male and female mice, respectively.

Multiple testing adjustment:

Also following the same FDA more recently revised draft guidance for the carcinogenicity study design and data analysis 2015, for mouse study the significance levels were 0.05 for all dose response relationship tests and pairwise comparisons, regardless of common or rare tumors.

Reviewer's findings:

The tumor types with p-values less than 0.05 for dose response relationship and/or pairwise comparisons of vehicle control and treated groups are reported in Table 4.

Table 4: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons
Treated Groups and Control Group in Mice

sex	Organ Name	Tumor Name	0 mg Cont (N=65) P - Trend	5 mg Low (N=65) P - C vs. L	15 mg Med (N=65) P - C vs. M	35 mg High (N=65) P - C vs. H
Male	WHOLE_BODY	hemangiosarcoma	2/25 (24) 0.0474*	1/25 (24) 0.8830	1/25 (25) 0.8901	5/25 (25) 0.2258

& 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 for common or rare tumor in dose response relationship.

Following the multiple testing adjustment method described above, this reviewer's analyses showed a statistically significant dose response relationships across the vehicle control and the treated groups of male mice for the incidence of hemangiosarcoma, in the whole body (p-value = 0.0474). The pairwise comparisons showed no tumor types with a statistically significant increase in tumor incidences in YKP3089 treated groups, when compare to the vehicle control group in either male or female mice.

The pairwise comparisons showed statistically significant increases in the positive control group for the incidences of adenoma alveolar-bronchiolar, the combined adenoma alveolar-bronchiolar and carcinoma alveolar-bronchiolar in lungs with bronchi, hemangiosarcoma in the spleen and in the whole body, when compared to the vehicle control group in both male and female mice (p-values <0.001, <0.001, <0.001,

<0.001, and <0.001, <0.001, <0.001, <0.001, respectively).

4. Summary

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in transgenic mice. These studies were intended to assess the carcinogenic potential of Cenobamate (YKP3089) in rats and mice when administered orally by gavage at appropriate drug levels for about 104 weeks in rats and 26 weeks in mice.

Rat Study:

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups and one vehicle control group. Two hundred and sixty Sprague-Dawley rats of each sex were assigned to three treated groups and one vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 65 animals. The dose levels for the three treated groups were 4, 8, and 20 mg/kg/day for both male and female rats, for up to 104 weeks. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The vehicle control group received the vehicle only (0.5% (w/v) methylcellulose prepared in reverse osmosis water), administered orally by gavage for about 104 weeks in the same manner as the treated groups. Due to early termination threshold of 20 survivor's rats in the male vehicle control groups, early final scheduled necropsies were carried out during Week 87 for males and Week 90 for females (based on FDA recommendations).

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 20 (30.8%), 27 (42.8%), 28 (43.8%), and 25 (39.1%) in the vehicle control group, low, medium, and high dose groups, in male rats, respectively, and 19 (29.2%), 29 (44.6%), 19 (29.2%), and 22 (33.8%) in vehicle control, low, medium, and high dose groups, in female rats, respectively. This reviewer's analysis showed no statistically significant dose response relationship in the mortality of both male and female rats. The pairwise comparisons showed statistically significant decrease in mortality in the low dose group when compared the vehicle control group in both male and female rats (p=0.0270 and p=0.0458, respectively)

For tumor data, this reviewer's analysis showed a statistically significant dose response relationship in tumor incidences with increased YKP3089 dose across the control and the treated groups of female rats for the incidence of benign adenoma in the mammary gland (p-value = 0.0249), since this tumor type is considered as rare tumor. The pairwise comparisons showed no tumor types with a statistically significant increase in tumor incidences in YKP3089 treated groups, when compare to the vehicle control group in either male or female rats.

Mouse Study:

Two separate experiments were conducted, one in male mice and one in female mice. In each of these two experiments there were three treated groups, one vehicle control group, and one positive control group. One hundred and ten Tg rasH2 transgenic mice of each sex were assigned randomly to one of the five groups by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 25 animals except the positive control group which had 10 animals. The dose levels for the three treated groups were 5, 15, and 35 mg/kg/day for both male and female mice, for up to 26 weeks. In this review, these dose groups would be referred to as the low, medium, and high dose group, respectively. The positive control group was administered with three intra-peritoneal injections of 1000 mg/kg/day of urethane in saline once on Days 1, 3 and 5. This group was included to verify sensitivity of the test system to detect carcinogenicity

effect. The vehicle control group received daily oral vehicle control article only [0.5% w/v methylcellulose (1500 cps) in de-ionized (DI) water], were administered in the same manner as the treated groups. The positive control mice were sacrificed on Day 72 (females) or Day 74 (males).

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy were 23 (92%), 23 (92%), 24 (96%), and 23 (92%), in vehicle control, low, medium, and high dose groups in male mice, respectively, and 25 (100%), 24 (96%), 23 (92%), and 25 (100%), in female mice, respectively. This reviewer's analysis showed no statistically significant increase dose response relationship in the mortality of either male or female mice. The pairwise comparisons also showed no statistically significant increase or decrease in mortality between the treated groups, and the vehicle control group in either sex of mice.

For tumor data, following the multiple testing adjustment method described above, this reviewer's analyses showed a statistically significant dose response relationships across the vehicle control and the treated groups of male mice for the incidence of hemangiosarcoma, in the whole body (p-value = 0.0474). The pairwise comparisons showed no tumor types with a statistically significant increase in tumor incidences in YKP3089 treated groups, when compare to the vehicle control group in either male or female mice.

The pairwise comparisons showed statistically significant increases in the positive control group for the incidences of adenoma alveolar-bronchiolar, the combined adenoma alveolar-bronchiolar and carcinoma alveolar-bronchiolar in lungs with bronchi and hemangiosarcoma in the spleen, when compared to the vehicle control group in both male and female mice (p-values <0.001, <0.001, <0.001, and <0.001, <0.001, <0.001, respectively).

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

Table1A: Intercurrent Mortality Rate
Male Rats

	0mg|kg|day Vehicle Control		4mg|kg|day Low		8mg|kg|day Med		20mg|kg|day High	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	10	15.38	5	7.69	7	10.77	6	9.23
53 - 78	31	63.08	19	36.92	17	36.92	22	43.08
79 - 86	4	69.23	12	55.38	12	55.38	11	60.00
ADD	.	.	2	3.08	1	1.54	1	1.54
Ter. Sac.	20	30.77	27	41.54	28	43.08	25	38.46
Total	65	100.00	65	100.00	65	100.00	65	100.00

early final scheduled necropsies were conducted during Week 87
Animals were assigned to the terminal sacrifice strata based on the sacrifice status recorded
ADD: accidental death

Table1B: Intercurrent Mortality Rate
Female Rats

	0mg|kg|day Vehicle Control		4mg|kg|day Low		8mg|kg|day Med		20mg|kg|day High	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**Week**	**No. of Death**	**Cum. %**	**No. of Death**
0 - 52	7	10.77	1	1.54	1	1.54	4	6.15
53 - 78	27	52.31	20	32.31	30	47.69	22	40.00
79 - 89	12	70.77	15	55.38	15	70.77	17	66.15
Ter. Sac.	19	29.23	29	44.62	19	29.23	22	33.85
Total	65	100.00	65	100.00	65	100.00	65	100.00

early final scheduled necropsies were conducted during Week 90
Animals were assigned to the terminal sacrifice strata based on the sacrifice status recorded

Table 2A: Intercurrent Mortality Comparison for
Male Rats

Test Statistics	**P-value for Vehicle Cont. Low, Med, high**	**P-value for Vehicle Cont. vs Low**	**P-value for Vehicle Cont. vs Med**	**P-value for Vehicle Cont. vs High**
Dose-Response (Likelihood Ratio)	0.4394	0.0270*	0.0555	0.1771
Homogeneity (Log-Rank)	0.1006	0.0247*	0.0525	0.1712

* = statistically significant at the 0.05 significance level.

Table 2B: Intercurrent Mortality Comparison for
Female Rats

Test Statistics	**P-value for Vehicle Cont. Low, Med, high**	**P-value for Vehicle Cont. vs Low**	**P-value for Vehicle Cont. vs Med**	**P-value for Vehicle Cont. vs High**
Dose-Response (Likelihood Ratio)	0.8841	0.0458*	0.9361	0.4249
Homogeneity (Log-Rank)	0.1500	0.0422*	0.9351	0.4176

* = statistically significant at the 0.05 significance level

Table3A: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Male Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=65) P - Trend	4 mg Low (N=65) P - C vs. L	8 mg Med (N=65) P - C vs. M	20 mg High (N=65) P - C vs. H
Adrenal, Cortex	B-Adenoma	2/65 (23) 0.9514	0/65 (28) 1.0000	1/65 (27) 0.9096	0/65 (26) 1.0000
	M-Carcinoma	1/65 (23) 1.0000	0/65 (28) 1.0000	0/65 (27) 1.0000	0/65 (26) 1.0000
	Adenoma/Carcinoma	3/65 (24) 0.9859	0/65 (28) 1.0000	1/65 (27) 0.9575	0/65 (26) 1.0000
Adrenal, Medulla	B-Pheochromocytoma	5/65 (25) 0.3482	6/65 (31) 0.6566	8/65 (31) 0.4261	7/65 (29) 0.4874
	M-Malignant Pheochromocytoma	0/65 (22) 0.3341	1/65 (28) 0.5600	0/65 (27) NC	1/65 (26) 0.5417
	B-Pheochromocytoma/ M-Malignant Pheochromocytoma	5/65 (25) 0.2595	6/65 (31) 0.6566	8/65 (31) 0.4261	8/65 (30) 0.3995
Brain	B-Granular Cell Tumor	0/65 (22) 0.7864	1/65 (28) 0.5600	0/65 (27) NC	0/65 (26) NC
	B-Oligodendroglioma	1/65 (23) 1.0000	0/65 (28) 1.0000	0/65 (27) 1.0000	0/65 (26) 1.0000
	M-Glioma, Malignant	0/65 (22) 0.8142	3/65 (29) 0.1755	2/65 (28) 0.3086	0/65 (26) NC
	B-Oligodendroglioma/ M-Glioma, Malignant	1/65 (23) 0.9034	3/65 (29) 0.3982	2/65 (28) 0.5748	0/65 (26) 1.0000
Cecum	M-Malignant Mesothelioma	0/63 (22) 0.5243	0/64 (27) NC	1/64 (28) 0.5600	0/64 (26) NC
Duodenum	M-Malignant Mesothelioma	0/65 (22) 0.5098	0/65 (28) NC	1/63 (27) 0.5510	0/64 (25) NC
Epididymis	M-Malignant Mesothelioma	1/65 (23) 0.8357	0/65 (28) 1.0000	1/65 (28) 0.8016	0/65 (26) 1.0000
Heart	M-Endocardial Schwannoma	2/65 (23) 0.6523	0/65 (28) 1.0000	0/65 (27) 1.0000	1/65 (26) 0.9039
Hemolympho-Reticular System	M-Histiocytic Sarcoma	0/65 (22) 0.6510	1/65 (29) 0.5686	1/65 (27) 0.5510	0/65 (26) NC
	M-Leukemia, Granulocytic	1/65 (23) 1.0000	0/65 (28) 1.0000	0/65 (27) 1.0000	0/65 (26) 1.0000
	M-Malignant Lymphoma	0/65 (22) 0.1955	0/65 (28) NC	1/65 (27) 0.5510	1/65 (26) 0.5417
Ileum	M-Malignant Mesothelioma	0/64 (22) 0.5149	0/62 (27) NC	1/63 (27) 0.5510	0/62 (25) NC
Kidney	B-Adenoma, Tubule Cell	0/65 (22) 0.2524	0/65 (28) NC	0/65 (27) NC	1/65 (26) 0.5417
	B-Lipoma	1/65 (23) 1.0000	0/65 (28) 1.0000	0/65 (27) 1.0000	0/65 (26) 1.0000
	M-Schwannoma	0/65 (22) 0.5146	0/65 (28) NC	1/65 (27) 0.5510	0/65 (26) NC
Liver	B-Adenoma, Hepatocellular	0/65 (22) 0.2524	0/65 (28) NC	0/65 (27) NC	1/65 (26) 0.5417
	M-Carcinoma, Hepatocellular	1/65 (23) 0.8969	2/65 (29) 0.5879	1/65 (27) 0.7935	0/65 (26) 1.0000
	B-Adenoma /M-Carcinoma, Hepatocellular	1/65 (23) 0.6400	2/65 (29) 0.5879	1/65 (27) 0.7935	1/65 (26) 0.7849

Male Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=65) P - Trend	4 mg Low (N=65) P - C vs. L	8 mg Med (N=65) P - C vs. M	20 mg High (N=65) P - C vs. H
	M-Cholangiocarcinoma	0/65 (22) 0.5146	0/65 (28) NC	1/65 (27) 0.5510	0/65 (26) NC
Lung	M-Hemangiosarcoma	0/65 (22) 0.5146	0/65 (28) NC	1/65 (27) 0.5510	0/65 (26) NC
	M-Malignant Mesothelioma	0/65 (22) 0.2524	0/65 (28) NC	0/65 (27) NC	1/65 (26) 0.5417
Lymph Node, Mesenteric	B-Hemangioma	0/61 (21) 0.7283	2/65 (29) 0.3314	3/64 (29) 0.1864	0/62 (24) NC
	M-Hemangiosarcoma	0/61 (21) 0.2475	0/65 (28) NC	0/64 (27) NC	1/62 (25) 0.5435
	B-Hemangioma/ M-Hemangiosarcoma	0/65 (22) 0.4796	2/65 (29) 0.3184	3/65 (29) 0.1755	1/65 (27) 0.5510
Mammary Gland, Male	B-Fibroadenoma	1/65 (23) 0.8325	0/65 (28) 1.0000	1/65 (27) 0.7935	0/65 (26) 1.0000
	M-Carcinoma	0/65 (22) 0.3341	1/65 (28) 0.5600	0/65 (27) NC	1/65 (26) 0.5417
	M-Carcinosarcoma	0/65 (22) 0.5192	0/65 (28) NC	1/65 (28) 0.5600	0/65 (26) NC
Muscle, Skeletal, Other	M-Schwannoma	0/65 (22) 0.7885	1/65 (29) 0.5686	0/65 (27) NC	0/65 (26) NC
Pancreas	B-Adenoma, Acinar Cell	0/65 (22) 0.2524	0/65 (28) NC	0/65 (27) NC	1/65 (26) 0.5417
	B-Adenoma, Islet Cell	1/65 (23) 0.4779	3/65 (29) 0.3982	1/65 (27) 0.7935	2/65 (27) 0.5611
	M-Carcinoma, Islet Cell	0/65 (22) 0.5099	0/65 (28) NC	2/65 (28) 0.3086	0/65 (26) NC
	B-Adenoma, Islet Cell/ M-Carcinoma, Islet Cell	1/65 (23) 0.4865	3/65 (29) 0.3982	3/65 (28) 0.3834	2/65 (27) 0.5611
	M-Malignant Mesothelioma	0/65 (22) 0.5192	0/65 (28) NC	1/65 (28) 0.5600	0/65 (26) NC
Pituitary	B-Adenoma	34/64 (43) 0.1155	35/65 (47) 0.7773	35/63 (47) 0.7773	44/65 (51) 0.2572
	M-Carcinoma	0/64 (22) 0.7843	1/65 (28) 0.5600	0/63 (26) NC	0/65 (26) NC
	B-Adenoma /M-Carcinoma	34/65 (43) 0.1197	36/65 (48) 0.7602	35/65 (47) 0.7773	44/65 (51) 0.2572
Prostate	M-Carcinoma	0/65 (22) 0.5192	0/65 (28) NC	1/64 (28) 0.5600	0/65 (26) NC
Skin/Subcutis	B-Adenoma, Sebaceous	1/65 (23) 1.0000	0/65 (28) 1.0000	0/65 (27) 1.0000	0/65 (26) 1.0000
	B-Fibroma	4/65 (24) 0.6135	2/65 (29) 0.9404	4/65 (29) 0.7510	3/65 (27) 0.8368
	B-Keratoacanthoma	0/65 (22) 0.3341	1/65 (28) 0.5600	0/65 (27) NC	1/65 (26) 0.5417
	B-Pilomatricoma	1/65 (23) 1.0000	0/65 (28) 1.0000	0/65 (27) 1.0000	0/65 (26) 1.0000
	M-Carcinoma, Squamous Cell	2/65 (24) 0.9495	0/65 (28) 1.0000	1/65 (28) 0.9084	0/65 (26) 1.0000

Male Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=65) P - Trend	4 mg Low (N=65) P - C vs. L	8 mg Med (N=65) P - C vs. M	20 mg High (N=65) P - C vs. H
	M-Fibrosarcoma	3/65 (25) 0.9585	0/65 (28) 1.0000	2/65 (28) 0.8581	0/65 (26) 1.0000
	M-Hemangiosarcoma	0/65 (22) 0.2596	0/65 (28) NC	0/65 (27) NC	1/65 (27) 0.5510
	M-Malignant Basal Cell Tumor	0/65 (22) 0.1966	0/65 (28) NC	1/65 (28) 0.5600	1/65 (26) 0.5417
	M-Malignant Melanoma	0/65 (22) 0.2524	0/65 (28) NC	0/65 (27) NC	1/65 (26) 0.5417
Spleen	M-Hemangiosarcoma	1/65 (23) 1.0000	0/65 (28) 1.0000	0/65 (27) 1.0000	0/65 (26) 1.0000
	M-Liposarcoma	0/65 (22) 0.2524	0/65 (28) NC	0/65 (27) NC	1/65 (26) 0.5417
	M-Malignant Mesothelioma	0/65 (22) 0.5192	0/65 (28) NC	1/65 (28) 0.5600	0/65 (26) NC
Stomach, Glandular	M-Malignant Mesothelioma	0/65 (22) 0.5192	0/65 (28) NC	1/65 (28) 0.5600	0/65 (26) NC
Stomach, Nonglandular	M-Carcinoma, Squamous Cell	0/64 (22) 0.1955	0/65 (28) NC	1/64 (27) 0.5510	1/65 (26) 0.5417
Testis	B-Interstitial Cell Tumor	1/65 (23) 0.8969	2/65 (29) 0.5879	1/65 (27) 0.7935	0/65 (26) 1.0000
	M-Malignant Mesothelioma	1/65 (23) 1.0000	0/65 (28) 1.0000	0/65 (27) 1.0000	0/65 (26) 1.0000
Thymus	B-Thymoma	1/65 (23) 1.0000	0/62 (26) 1.0000	0/61 (25) 1.0000	0/61 (23) 1.0000
	M-Malignant Mesothelioma	0/65 (22) 0.2474	0/62 (26) NC	0/61 (25) NC	1/61 (24) 0.5217
	M-Malignant Thymoma	0/65 (22) 0.5052	0/62 (26) NC	1/61 (26) 0.5417	0/61 (23) NC
	B-Thymoma/ M-Malignant Thymoma	1/65 (23) 0.8357	0/65 (28) 1.0000	1/65 (28) 0.8016	0/65 (26) 1.0000
Thyroid	B-Adenoma, C-Cell	4/65 (24) 0.3104	7/65 (31) 0.4231	5/65 (29) 0.6244	7/65 (29) 0.3746
	B-Adenoma, Follicular Cell	2/65 (23) 0.7449	1/65 (28) 0.9150	0/65 (27) 1.0000	1/65 (26) 0.9039
	M-Carcinoma, C-Cell	0/65 (22) 0.6537	1/65 (28) 0.5600	1/65 (27) 0.5510	0/65 (26) NC
	M-Carcinoma, Follicular Cell	1/65 (23) 0.8661	1/65 (28) 0.8016	1/65 (27) 0.7935	0/65 (26) 1.0000
	B-Adenoma/ M-Carcinoma, C-Cell	4/65 (24) 0.3539	8/65 (32) 0.3397	6/65 (30) 0.5189	7/65 (29) 0.3746
Urinary Bladder	B-Adenoma/ Follicular Cell	3/65 (24) 0.8813	2/65 (29) 0.8778	1/65 (27) 0.9575	1/65 (26) 0.9539
	M-Carcinoma, Squamous Cell	1/65 (23) 1.0000	0/64 (27) 1.0000	0/63 (27) 1.0000	0/65 (26) 1.0000
Whole Body	M-Malignant Mesothelioma	1/65 (23) 0.4537	0/65 (28) 1.0000	1/65 (28) 0.8016	1/65 (26) 0.7849
Zymbal Gland	M-Carcinoma	0/54 (18) 0.7955	1/54 (24) 0.5714	0/53 (22) NC	0/59 (24) NC

Table3B: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Female Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=65) P - Trend	4 mg Low (N=65) P - C vs. L	8 mg Med (N=65) P - C vs. M	20 mg High (N=65) P - C vs. H
Adipose, Other	M-Malignant Mesothelioma	0/65 (27) 0.7652	1/65 (32) 0.5424	0/65 (27) NC	0/65 (29) NC
Adrenal, Cortex	B-Adenoma	3/65 (28) 0.3993	1/65 (32) 0.9580	1/65 (28) 0.9443	3/65 (31) 0.7127
	M-Carcinoma	0/65 (27) 0.0664	0/65 (31) NC	0/65 (27) NC	2/65 (30) 0.2726
	Adenoma/Carcinoma	3/65 (28) 0.1124	1/65 (32) 0.9580	1/65 (28) 0.9443	5/65 (31) 0.4133
Adrenal, Medulla	B-Pheochromocytoma	2/65 (28) 0.9420	1/65 (32) 0.9043	1/64 (27) 0.8751	0/64 (28) 1.0000
Brain	B-Granular Cell Tumor	1/65 (27) 1.0000	0/65 (31) 1.0000	0/65 (27) 1.0000	0/65 (29) 1.0000
	M-Glioma, Malignant	0/65 (27) 0.7652	1/65 (32) 0.5424	0/65 (27) NC	0/65 (29) NC
Cervix	B-Leiomyoma	0/65 (27) 0.4957	0/65 (31) NC	1/65 (28) 0.5091	0/65 (29) NC
	M-Schwannoma	0/65 (27) 0.4957	0/65 (31) NC	1/65 (28) 0.5091	0/65 (29) NC
Duodenum	M-Malignant Mesothelioma	0/65 (27) 0.7652	1/65 (32) 0.5424	0/65 (27) NC	0/65 (29) NC
Eye	M-Melanoma	0/65 (27) 0.3242	1/64 (31) 0.5345	0/65 (27) NC	1/65 (29) 0.5179
Harderian Gland	B-Adenoma	0/65 (27) 0.2544	0/64 (31) NC	0/65 (27) NC	1/65 (29) 0.5179
	M-Malignant Schwannoma	0/65 (27) 0.7652	1/64 (32) 0.5424	0/65 (27) NC	0/65 (29) NC
Hemolympho-Reticular System	M-Histiocytic Sarcoma	0/65 (27) 0.7652	1/65 (32) 0.5424	0/65 (27) NC	0/65 (29) NC
	M-Large Granular Cell Leuke*	1/65 (27) 1.0000	0/65 (31) 1.0000	0/65 (27) 1.0000	0/65 (29) 1.0000
	M-Leukemia, Granulocytic	0/65 (27) 0.2544	0/65 (31) NC	0/65 (27) NC	1/65 (29) 0.5179
	M-Malignant Lymphoma	0/65 (27) 0.7652	1/65 (32) 0.5424	0/65 (27) NC	0/65 (29) NC
Kidney	B-Lipoma	1/65 (27) 1.0000	0/65 (31) 1.0000	0/65 (27) 1.0000	0/65 (29) 1.0000
	M-Carcinoma, Tubule Cell, A*	0/65 (27) 0.1912	0/65 (31) NC	1/65 (28) 0.5091	1/65 (30) 0.5263
Liver	B-Adenoma, Hepatocellular	0/65 (27) 0.1912	0/65 (31) NC	1/65 (28) 0.5091	1/65 (30) 0.5263
Mammary Gland, Female	B-Adenoma	0/65 (27) 0.0249*	0/65 (31) NC	2/65 (29) 0.2636	3/65 (30) 0.1388
	B-Fibroadenoma	18/65 (37) 0.3576	33/65 (47) 0.0372	19/65 (37) 0.5000	25/65 (41) 0.1936
	B-Adenoma/Fibroadenoma	18/65 (37) 0.2359	33/65 (47) 0.0372@	20/65 (38) 0.4547	27/65 (42) 0.1204
	M-Carcinoma	25/65 (42) 0.9472	25/65 (46) 0.7594	21/65 (40) 0.8059	16/65 (38) 0.9628

Female Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=65) P - Trend	4 mg Low (N=65) P - C vs. L	8 mg Med (N=65) P - C vs. M	20 mg High (N=65) P - C vs. H
	B-Adenoma/ M-Carcinoma	25/65 (42) 0.8620	25/65 (46) 0.7594	23/65 (41) 0.7047	19/65 (40) 0.9055
Mesentery	M-Mesothelioma	0/65 (27) 0.7652	1/65 (32) 0.5424	0/65 (27) NC	0/65 (29) NC
Ovary	M-Cystadenocarcinoma	0/65 (27) 0.2544	0/65 (31) NC	0/65 (27) NC	1/65 (29) 0.5179
	M-Malignant Granulosa/Theca*	1/65 (27) 1.0000	0/65 (31) 1.0000	0/65 (27) 1.0000	0/65 (29) 1.0000
	M-Malignant Mesothelioma	0/65 (27) 0.7652	1/65 (32) 0.5424	0/65 (27) NC	0/65 (29) NC
Pancreas	B-Adenoma, Acinar Cell	0/65 (27) 0.2544	0/65 (31) NC	0/65 (27) NC	1/65 (29) 0.5179
	B-Adenoma, Islet Cell	2/65 (28) 0.7236	1/65 (32) 0.9043	1/65 (28) 0.8818	1/65 (30) 0.8938
	M-Carcinoma, Acinar Cell	0/65 (27) 0.4957	0/65 (31) NC	1/65 (28) 0.5091	0/65 (29) NC
	M-Carcinoma, Islet Cell	0/65 (27) 0.4957	0/65 (31) NC	1/65 (28) 0.5091	0/65 (29) NC
	B-Adenoma/ M-Carcinoma, Islet Cell	2/65 (28) 0.7016	1/65 (32) 0.9043	2/65 (28) 0.6945	1/65 (30) 0.8938
	M-Malignant Mesothelioma	0/65 (27) 0.7652	1/65 (32) 0.5424	0/65 (27) NC	0/65 (29) NC
Parathyroid	B-Adenoma	1/62 (26) 0.8453	1/57 (28) 0.7729	1/56 (23) 0.7236	0/63 (28) 1.0000
Pituitary	B-Adenoma	57/65 (59) 0.8209	47/65 (56) 0.9968	46/65 (55) 0.9971	51/65 (58) 0.9850
	B-Adenoma, Pars Nervosa	0/65 (27) 0.7652	1/65 (32) 0.5424	0/65 (27) NC	0/65 (29) NC
	M-Carcinoma	0/65 (27) 0.4957	0/65 (31) NC	1/65 (28) 0.5091	0/65 (29) NC
	Adenoma/Carcinoma	57/65 (59) 0.8247	47/65 (56) 0.9968	47/65 (55) 0.9941	51/65 (58) 0.9850
Rectum	B-Leiomyoma	0/65 (27) 0.7652	1/65 (32) 0.5424	0/65 (27) NC	0/65 (29) NC
Skin/Subcutis	B-Lipoma	1/65 (27) 0.7403	0/65 (31) 1.0000	2/65 (28) 0.5139	0/65 (29) 1.0000
	B-Papilloma, Squamous Cell	0/65 (27) 0.7652	1/65 (32) 0.5424	0/65 (27) NC	0/65 (29) NC
	M-Fibrosarcoma	0/65 (27) 0.8077	3/65 (33) 0.1594	1/65 (28) 0.5091	0/65 (29) NC
	M-Malignant Melanoma	1/65 (27) 1.0000	0/65 (31) 1.0000	0/65 (27) 1.0000	0/65 (29) 1.0000
	M-Myxosarcoma	0/65 (27) 0.2544	0/65 (31) NC	0/65 (27) NC	1/65 (29) 0.5179
Stomach, Glandular	M-Malignant Mesothelioma	0/65 (27) 0.7652	1/65 (32) 0.5424	0/65 (27) NC	0/65 (29) NC
Stomach, Nonglandular	M-Malignant Mesothelioma	0/65 (27) 0.7652	1/65 (32) 0.5424	0/65 (27) NC	0/65 (29) NC
Thymus	M-Malignant Thymoma	0/62 (26) 0.2569	0/61 (29) NC	0/61 (26) NC	1/63 (28) 0.5185

Female Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=65) P - Trend	4 mg Low (N=65) P - C vs. L	8 mg Med (N=65) P - C vs. M	20 mg High (N=65) P - C vs. H
Thyroid	B-Adenoma, C-Cell	4/65 (29) 0.3421	10/63 (35) 0.1310	6/65 (30) 0.3878	8/65 (34) 0.2567
	B-Adenoma, Follicular Cell	0/65 (27) 0.7632	1/63 (31) 0.5345	0/65 (27) NC	0/65 (29) NC
	M-Carcinoma, C-Cell	1/65 (28) 0.1636	0/63 (31) 1.0000	0/65 (27) 1.0000	2/65 (30) 0.5263
	M-Carcinoma, Follicular Cell	1/65 (27) 0.4457	0/63 (31) 1.0000	0/65 (27) 1.0000	1/65 (29) 0.7721
	B-Adenoma /M-Carcinoma, C-Cell	5/65 (29) 0.2277	10/65 (36) 0.2415	6/65 (30) 0.5252	10/65 (35) 0.2221
	B-Adenoma/ M-Carcinoma, Follicular Cell	1/65 (27) 0.5561	1/65 (32) 0.7949	0/65 (27) 1.0000	1/65 (29) 0.7721
Tongue	B-Papilloma, Squamous Cell	0/65 (27) 0.2609	0/64 (31) NC	0/65 (27) NC	1/65 (30) 0.5263
Uterus	B-Polyp, Endometrial Stromal	1/65 (28) 0.9433	1/65 (32) 0.7864	0/65 (27) 1.0000	0/65 (29) 1.0000
Vagina	B-Granular Cell Tumor	1/65 (28) 0.8105	5/65 (34) 0.1486	0/65 (27) 1.0000	1/65 (29) 0.7632
	M-Schwannoma	0/65 (27) 0.1912	0/65 (31) NC	1/65 (28) 0.5091	1/65 (30) 0.5263
Whole Body	M-Malignant Mesothelioma	0/65 (27) 0.7652	1/65 (32) 0.5424	0/65 (27) NC	0/65 (29) NC
Zymbal Gland	M-Carcinoma	1/57 (25) 0.9451	1/53 (27) 0.7738	0/60 (26) 1.0000	0/61 (27) 1.0000

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
*: Statistically significant at 0.025 for rare tumor in dose response relationship

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

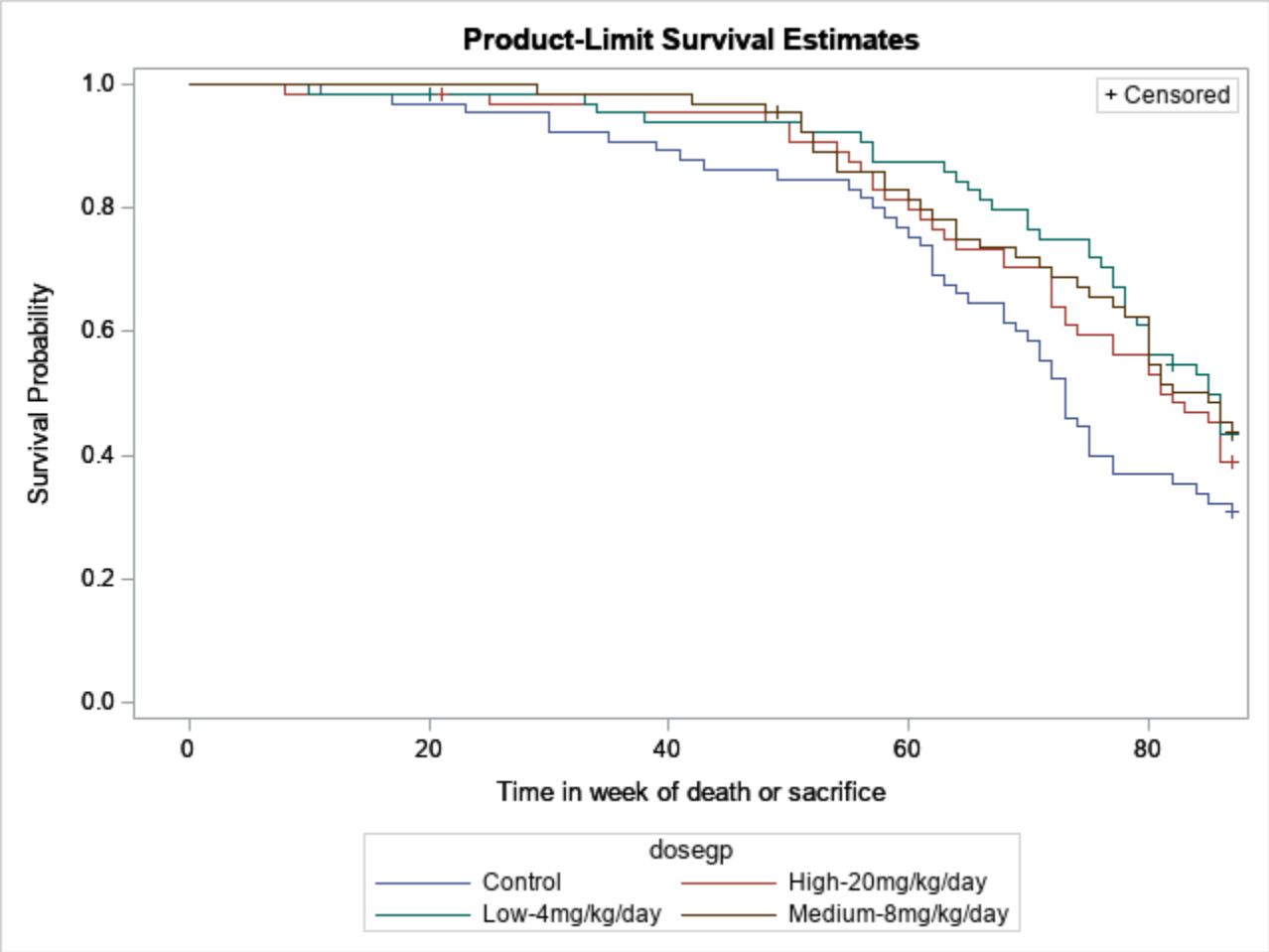


Figure 1B: Kaplan-Meier Survival Curves **for Female Rats**

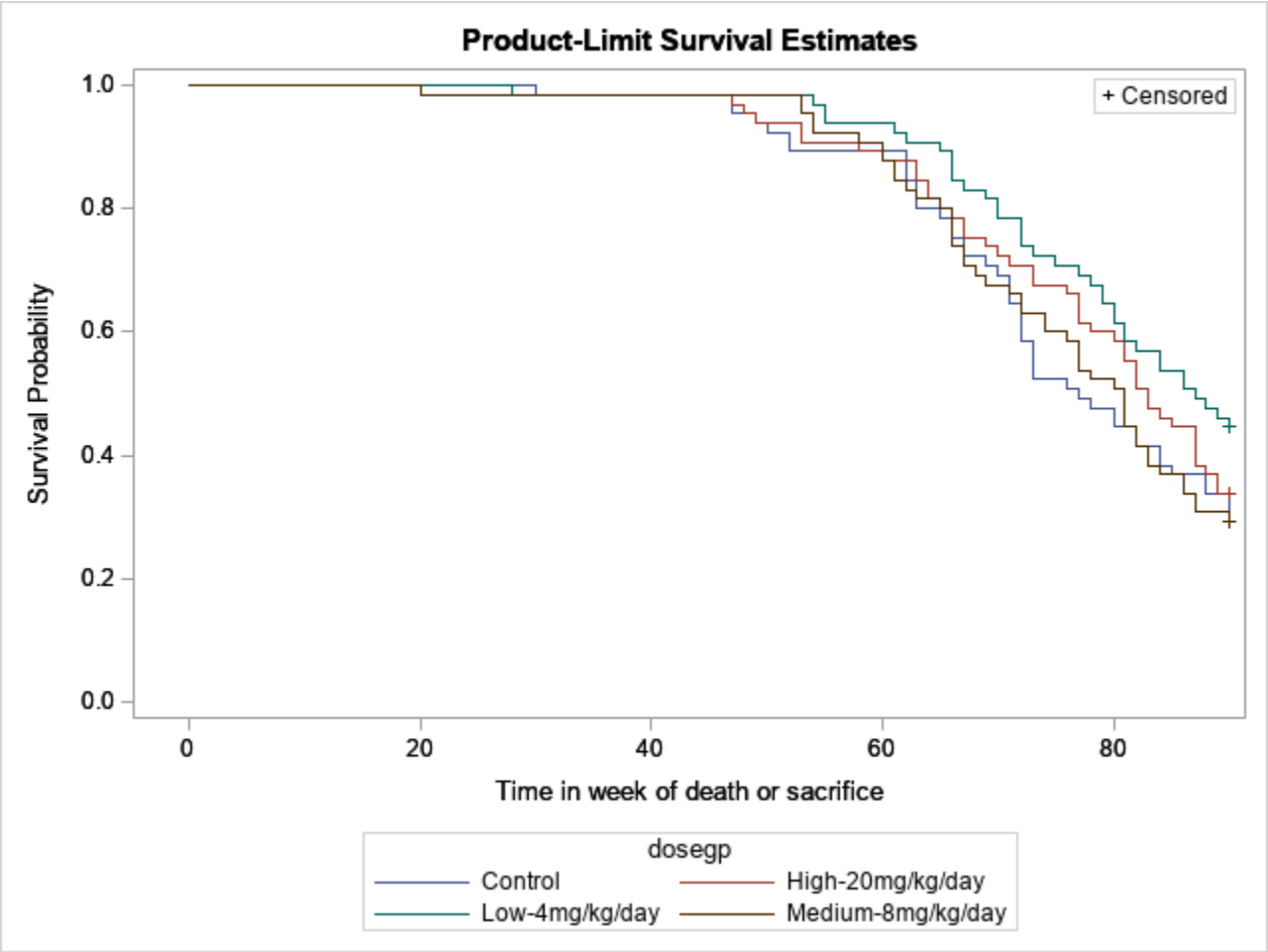


Table4A: Intercurrent Mortality Rate
Male Mice

	0mg|kg|day Vehicle Cont.		5mg|kg|day Low		15mg|kg|day Med		35mg|kg|day High		1000 mg|kg|day Positive Cont.	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
IS	.	.	.	.	.	.	.	.	10	100.00
0 - 13	1	4.00	.	.	.	.	.	.	.	.
14 - 26	1	8.00	2	8.00	1	4.00	2	8.00	.	.
Ter. Sac.	23	92.00	23	92.00	24	96.00	23	92.00	.	.
Total	25	100.00	25	100.00	25	100.00	25	100.00	10	100.00

Animals were assigned to the terminal sacrifice strata based on the sacrifice status recorded
IS: Interim sacrifice on Day 74

Table4B: Intercurrent Mortality Rate
Female Mice

	0mg|kg|day Vehicle Cont.		5mg|kg|day Low		15mg|kg|day Med		35mg|kg|day High		1000 mg|kg|day Positive Cont.	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
IS	.	.	.	.	.	.	.	.	10	100.00
0 - 13	.	.	.	.	.	.	.	.	.	.
14 - 26	.	.	1	4.00	2	8.00	.	.	.	.
Ter. Sac.	25	100.00	24	96.00	23	92.00	25	100.00	.	.
Total	25	100.00	25	100.00	25	100.00	25	100.00	10	100.00

Animals were assigned to the terminal sacrifice strata based on the sacrifice status recorded
IS: Interim sacrifice on Day 72

Table 5A: Intercurrent Mortality Comparison for
Male Mice

Test Statistics	P-value for Vehicle Cont. Low, Med, high	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs High	P-value for Vehicle Cont. vs Positive Cont.
Dose-Response (Likelihood Ratio)	0.9666	0.9997	0.5521	0.9997	0.4120
Homogeneity (Log-Rank)	0.9316	0.9997	0.5557	0.9997	0.5271

Table 5B: Intercurrent Mortality Comparison for
Female Mice

Test Statistics	P-value for Vehicle Cont. Low, Med, high	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs High	P-value for Vehicle Cont. vs Positive Cont.
Dose-Response (Likelihood Ratio)	0.9141	0.2390	0.0935	NC	NC
Homogeneity (Log-Rank)	0.2882	0.3173	0.1531	NC	NC

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and the pairwise Comparisons

Male Mice Using Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=25) P - Trend	5 mg Low (N=25) P - C vs. L	15 mg Med (N=25) P - C vs. M	35 mg High (N=25) P - C vs. H	1000 mg Posi (N=10) P - VC vs. PC
Cavity, Nasal	Adenocarcinoma	0/25 (24) 0.2500	0/25 (24) NC	0/25 (24) NC	1/25 (24) 0.5000	NC
	Hemangioma	0/25 (24) 0.1868	0/25 (24) NC	1/25 (24) 0.5000	1/25 (24) 0.5000	NC
	Hemangiosarcoma	0/25 (24) 0.3132	1/25 (24) 0.5000	0/25 (24) NC	1/25 (24) 0.5000	NC
Harderian Glands	Adenoma	0/25 (24) 0.3222	1/25 (24) 0.5000	0/25 (24) NC	1/25 (25) 0.5102	NC
	Carcinoma	1/25 (24) 0.9395	1/25 (24) 0.7553	0/25 (24) 1.0000	0/25 (24) 1.0000	NC
Liver	Hepatocellular Adenoma	0/25 (24) 0.7500	1/25 (24) 0.5000	0/25 (24) NC	0/25 (24) NC	NC
Lungs With Bronchi	Alveolar-Bronchiolar Adenoma	3/25 (24) 0.4767	0/25 (24) 1.0000	3/25 (24) 0.6669	2/25 (25) 0.8384	10/10 (10) <0.0001*
	Alveolar-Bronchiolar Carcinoma	1/25 (24) 1.0000	0/25 (24) 1.0000	0/25 (24) 1.0000	0/25 (24) 1.0000	0/10 (1) 1.0000
	Alveolar-Bronchiolar Adenoma/Carcinoma	4/25 (24) 0.6194	0/25 (24) 1.0000	3/25 (24) 0.7921	2/25 (25) 0.9144	10/10 (10) <0.0001*
	Hemangiosarcoma	1/25 (24) 0.4395	0/25 (24) 1.0000	0/25 (24) 1.0000	1/25 (24) 0.7553	0/10 (1) 1.0000
Multicentric	Hemangiosarcoma	0/25 (24) 0.2577	0/25 (24) NC	0/25 (24) NC	1/25 (25) 0.5102	0/10 (1) NC
	Histiocytic Sarcoma	0/25 (24) 0.7500	1/25 (24) 0.5000	0/25 (24) NC	0/25 (24) NC	0/10 (1) NC
Spleen	Hemangiosarcoma	0/25 (24) 0.2500	0/25 (24) NC	0/25 (24) NC	1/25 (24) 0.5000	6/10 (6) <0.0001*
	Histiocytic Sarcoma	0/25 (24) 0.7500	1/25 (24) 0.5000	0/25 (24) NC	0/25 (24) NC	0/10 (1) NC
Stomach	Squamous Cell Carcinoma	1/25 (25) 1.0000	0/25 (24) 1.0000	0/25 (24) 1.0000	0/25 (24) 1.0000	NC
Urinary Bladder	Hemangiosarcoma	1/25 (24) 1.0000	0/25 (24) 1.0000	0/25 (24) 1.0000	0/25 (24) 1.0000	NC
Whole Body	Hemangiosarcoma	2/25 (24) 0.0474	1/25 (24) 0.8830	1/25 (25) 0.8901	5/25 (25) 0.2258	6/10 (6) <0.0001 *

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

NC = Not calculable

*: Statistically significant at 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and The pairwise comparisons
Female Mice Using Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=25) P - Trend	5 mg Low (N=25) P - VC vs. L	15 mg Med (N=25) P - VC vs. M	35 mg High (N=25) P -VC vs. H	1000 mg Posi (N=10) P - VC vs. PC
Cavity, Nasal	Adenocarcinoma	1/25 (25) 0.3915	0/25 (25) 1.0000	1/25 (24) 0.7449	1/25 (25) 0.7551	NC
	Hemangiosarcoma	0/25 (25) 0.4949	0/25 (25) NC	1/25 (24) 0.4898	0/25 (25) NC	NC
Harderian Glands	Adenoma	0/25 (25) 0.2036	2/25 (25) 0.2449	0/25 (24) NC	2/25 (25) 0.2449	NC
Lungs With Bronchi	Alveolar-Bronchiolar Adenoma	4/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000	10/10 (10) <0.0001*
	Alveolar-Bronchiolar Carcinoma	0/25 (25) 0.2525	0/25 (25) NC	0/25 (24) NC	1/25 (25) 0.5000	0/10 (1) NC
	Alveolar-Bronchiolar Adenoma/Carcinoma	4/25 (25) 0.8885	0/25 (25) 1.0000	0/25 (24) 1.0000	1/25 (25) 0.9749	10/10 (10) <0.0001*
Mammary Gland	Adenocarcinoma	1/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000	NC
Multicentric	Hemangiosarcoma	0/25 (25) 0.5000	0/25 (25) NC	1/25 (25) 0.5000	0/25 (25) NC	0/10 (1) NC
Spleen	Hemangiosarcoma	2/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000	10/10 (10) <0.0001*
Thymus	Thymoma	1/25 (25) 0.8763	2/25 (25) 0.5000	1/25 (24) 0.7449	0/25 (25) 1.0000	NC
Whole Body	Hemangiosarcoma	2/25 (25) 0.8608	1/25 (25) 0.8827	3/25 (25) 0.5000	0/25 (25) 1.0000	10/10 (10) <0.0001 *

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ= total number of animals observed;
NC = Not calculable;
*: Statistically significant at 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons

Figure 2A: Kaplan-Meier Survival Curves for

Male Mice

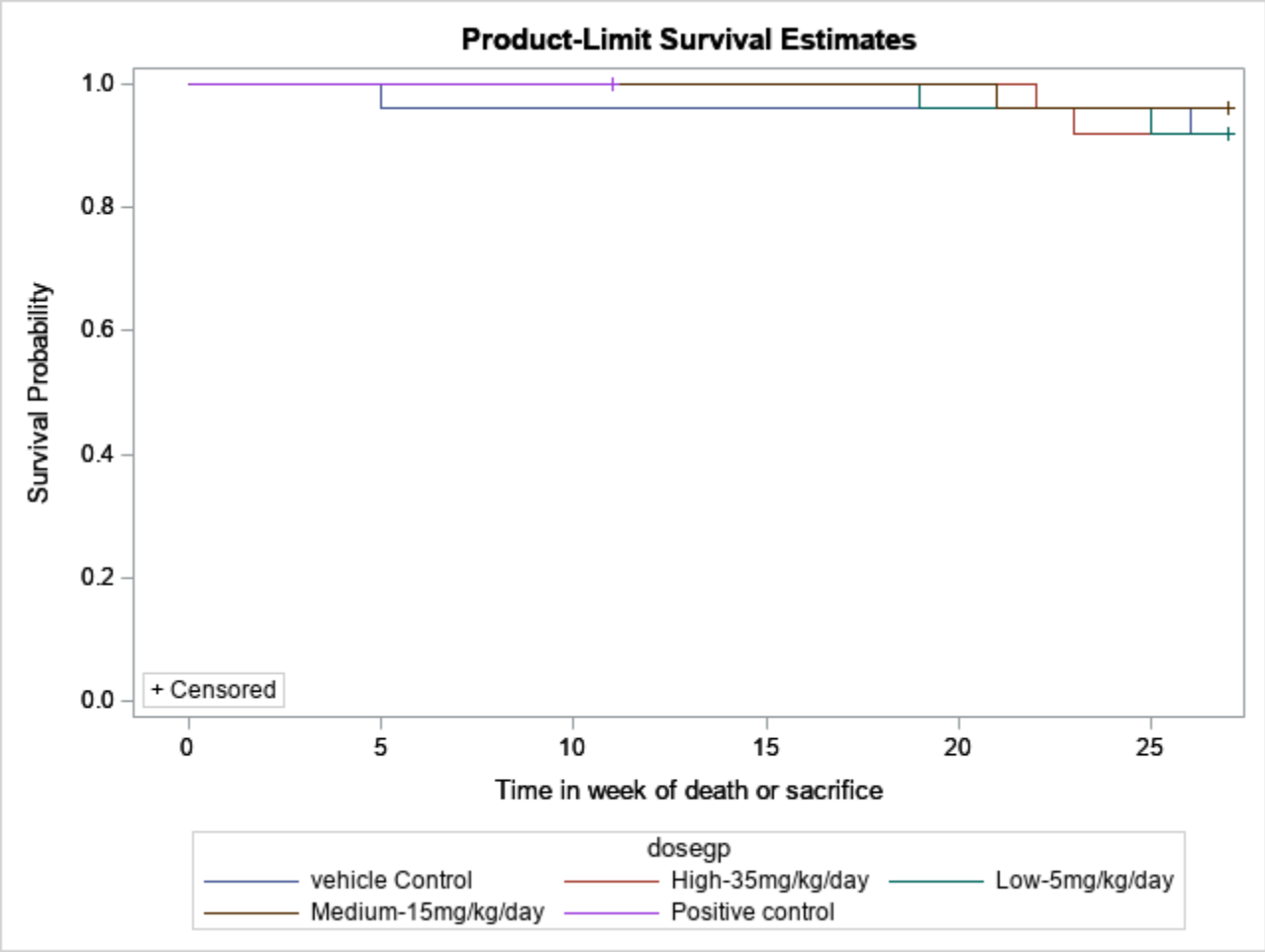
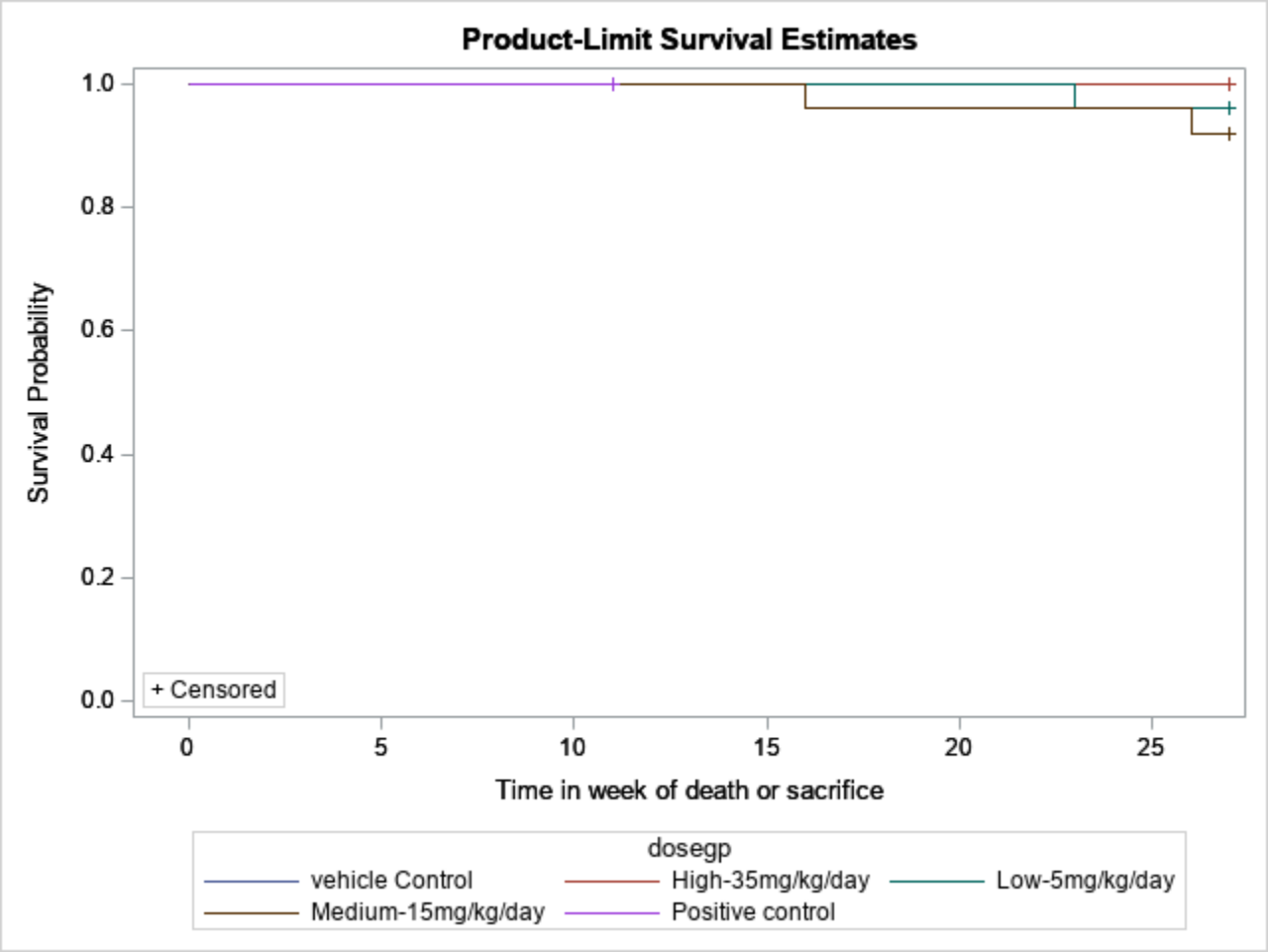


Figure 2B: Kaplan-Meier Survival Curves for
Female Mice



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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 Number:	212839
Drug Name:	Xcopri (cenobamate)
Indication:	Treatment of partial-onset seizures in adult patients
Applicant:	SK Life Science, Inc.
Dates:	Receipt date: November 21, 2018 PDUFA Goal Date: November 21, 2019
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Xiangmin Zhang, Ph.D.
Concurring Reviewers:	Kun Jin, Ph.D., Team Leader Hsien Ming Hung, Ph.D., Director
Medical Division:	Division of Neurology Products
Clinical Team:	Steven Dinsmore, D.O., Clinical Reviewer Philip Sheridan, M.D. Team Leader Nicholas Kozauer, M.D., Associate Director Eric Bastings, M.D., Deputy Director William Dunn, M.D., Director
Project Manager:	LaShawn Dianat, Pharm.D.

Keywords: clinical studies, NDA review

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1 EXECUTIVE SUMMARY

On November 21, 2018, SK Life Science, Inc. (the Applicant) submitted an original new drug application (NDA) for Xcopri (cenobamate; or YKP3089 under the Applicant's clinical development program). The application relies on two clinical studies – Study YKP3089C013 (Study 13) and Study YKP3089C017 (Study 17) – to support the proposed indication "treatment of partial-onset seizures in adult patients". Both studies were randomized, double-blind, placebo-controlled, parallel-group, clinical studies. Study 13 had two treatment groups (YKP3089 200 mg/day and placebo) while Study 17 had four treatment groups (YKP3089 400 mg/day, YKP3089 200 mg/day, YKP3089 100 mg/day, and placebo). Both studies used the percent change from baseline in seizure frequency per 28 days in the treatment period as the primary endpoint.

Study 13 showed that the observed medians of percent change from baseline in seizure frequency per 28 days were -55.6% (reduction from baseline) for the YKP3089 200 mg/day group and -21.5% for the placebo group and demonstrated statistical significance for YKP3089-placebo difference (p-value < 0.0001). Study 17 showed that the observed medians of percent change from baseline in seizure frequency per 28 days were -55.3%, -55.2%, -36.3%, and -24.3% for the YKP3089 400 mg/day group, YKP3089 200 mg/day group, YKP3089 100 mg/day group , and placebo group, respectively. Comparisons of the three YKP3089 dose groups and the placebo group were all statistically significant (p-values < 0.001, < 0.001, = 0.006 for the the YKP3089 400 mg/day group, YKP3089 200 mg/day group, and YKP3089 100 mg/day group, respectively).

2 INTRODUCTION

2.1 Overview

This original NDA for Xcopri for the treatment of partial onset seizures in adult patients relies on two randomized, double-blind, placebo-controlled clinical studies to support the proposed indication. The two clinical studies are summarized below and reviewed in Section 3.

Table 1. Clinical studies in this review

Study	Phase and Design	Study Duration	Study Arm (Number of randomized subjects per arm)	Study Population
YKP3089C013 (Study 13)	Phase 2, randomized, double-blind, placebo-controlled, parallel-group	8-week baseline period, 12-week treatment period (6-week titration and 6-week maintenance), and 1-week taper period	200 mg (113) Placebo (109)	Female and male patients aged 18-65 years diagnosed with treatment resitiant partial epilepsy
YKP3089C017 (Study 17)	Phase 2, randomized, double-blind, placebo-controlled, parallel-group	8-week baseline period, 18-week treatment peirod (6-week titration and 12-week maintenance), and 3-week taper period	400 mg (111) 200 mg (110) 100 mg (108) Placebo (108)	Female and male patients aged 18-70 years diagnosed with partial epilepsy

Source: statistical reviewer's summary

2.2 Data Sources

The electronic submission of the NDA is located at
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The study reports are located at
\\CDSESUB1\evsprod\NDA212839\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\seizures\5351-stud-rep-contr\ykp3089c013\
\\CDSESUB1\evsprod\NDA212839\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\seizures\5351-stud-rep-contr\ykp3089c017\

The datasets are located at
\\CDSESUB1\evsprod\NDA212839\0001\m5\datasets\
\\ CDSESUB1\evsprod\NDA212839\0019\m5\datasets\

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The statistical reviewer was able to perform independent review using the Applicant's submitted datasets and confirm the Applicant's analysis results.

There were some difficiencies with the data and analysis quality of Study 17. During the site inspections, the FDA's field investigator found that the eCRF system did not allow entries for daily seizure counts > 99. As a result, for example, a daily seizure count of 100 was recorded as 0 in the

dataset. After the FDA identified this issue, the Applicant was requested to update the dataset for subjects that had daily seizure counts > 99 and the efficacy analyses. This affected three seizure diary records for three subjects in Study 17. Another issue with the data and analysis quality of Study 17 is that the values of the primary endpoint were rounded to integers in the dataset, limiting the effective digits in the reporting of primary analysis results. For example, a -73.4% change from baseline in seizure frequency per 28 days was rounded to -73% and used for primary analysis. This issue has been addressed in the analysis results reported in this review.

3.2 Evaluation of Efficacy

3.2.1 Study 13

3.2.1.1 Design and Endpoints

Study 13 was a randomized, placebo-controlled, double-blind, parallel-group, 2-arm, multi-center, Phase 2 clinical study to evaluate the efficacy of YKP3089 at doseage up to 200 mg/day in treating subjects with partial onset seizures not fully controlled despite their treatment with one to three concomitant anti-epileptic drugs. The study also aimed to evaluate the long-term safety and tolerability of YKP3089. Approximately 200 subjects aged 18-65 years (inclusive) were planned to be enrolled and randomized in a 1:1 ratio to receive YKP3089 or placebo.

The study consisted of an 8-week baseline period, a 12-week treatment period (6-week titration and 6-week maintenance), a 1-week taper period, and a follow-up visit 21 days after discontinuation of the study medication. During the treatment period, subjects were planned to receive 50 mg YKP3089 (or placebo) once daily for the first two weeks. Subjects were planned to increase their daily dose of YKP3089 by 50 mg every two weeks if they showed tolerability until they reached 200 mg or remain on the same dose otherwise.

The primary endpoint was the percent change in seizure (simple partial seizures with motor component, complex partial seizures, and secondarily generalized tonic-clonic seizures) frequency per 28 days in the treatment period compared to the baseline. The seizure frequcny per 28 days was calculated by dividing the total number of seizures by the number of non-missing days then multiplying it by 28.

3.2.1.2 Statistical Methodologies

The efficacy analysis population was the intention-to-treat (ITT) population, defined as all randomized sujbects who have taken a single dose of YKP3089 or placebo and have at least one efficay evaluation.

The Statistical Analysis Plan (SAP) described several models for the primary endpoint:

Model 1. an analysis of covariance (ANCOVA) model that include the percent change from baseline in 28-day seizure frequency as the dependent variable and baseline 28-day seizure frequency, treatment, country, and treatment-by-country interaction.

Model 2. an ANCOVA model that use the change from baseline in logarithm transformed 28-day seizure frequency, i.e. log(28-day seizure frequency + 1/3), as the dependent variable.
Model 3. "a rank ANCOVA model fit to the observed data".
Model 4. "a rank ANCOVA model fit to the logarithmic transformed seizure rate (frequency) data".

The SAP planned to examine the robustness of the model relative to influential data points and normality assumption of Models 1, 2, 3, and 4 sequentially: if a model can pass the diagnostics, it is considered the primary analysis, otherwise the next model in the sequence is examined. All statistical models were planned to include the treatment-by-country interaction as an adjustment， which was also planned not to be interpreted statistically but to serve as a term for fitting the statistical model.

When the two rank models do not exhibit statistical significance on the baseline coefficient, a Wilcoxon rank-sum test was planned to be used to "to support the claim that the median seizure frequency at post baseline for the treatment groups are significantly different from the median seizure frequency for the placebo subjects".

Statistical reviewer's comments:

The SAP was not submitted to the FDA for review at the investigational new drug stage but only in this NDA. Neither the diagnositics criteria of the analysis models nor the model details of the rank models were clearly pre-specified in the SAP, leading to an ambicuous primary analysis model. According to the Applican's March 27, 2019 responses to information request, only diagnostics of Model 1, Model 2, and the following Model were originally explored:

> *"an ANCOVA model that use the log-transformed ranked percent change from baseline in 28-day seizure frequency as the dependent variable".*

The Applicant states that the Wilcoxon rank-sum test was selected based on the diagnostics of Model 1 and Model 2 and that it is the most appropriate method for the primary analysis.

The SAP planned an ublinded interim look of the clinical data for the design and planning of the Phase 2b study only; the SAP did not plan to change the conduct of Study 13 based on the interim analys results or adjust significance level for the hypothesis testing for the final statistical analysis. The SAP did not provide any pre-specification of the timing of the interim analysis or regarding who would have access to the interim analysis results.

Statistical reviewer's comments:

The Applicant should plan strong firewall to protect the blinding and intergrity of the study.

3.2.1.3 Subject Disposition, Demographic and Baseline Characteristics

Table 2. Study 13 subject disposition

	YKP3089 (N=113)	Placebo (N=109)	All Subjects (N=222)
	n (%)	n (%)	n (%)
Screened			285
Randomized (Enrolled) Subjects	113	109	222
Modified ITT Population	113 (100.0)	109 (100.0)	222 (100.0)
ITT Population	113 (100.0)	108 (99.1)	221 (99.5)
Per-Protocol Population	107 (94.7)	106 (97.2)	213 (95.9)
Safety Population	113 (100.0)	109 (100.0)	222 (100.0)
Completed Study Double-blind treatment period	102 (90.3)	99 (90.8)	201 (90.5)
Entered Open-Label Extension	76 (67.3)	73 (67.0)	149 (67.1)
Discontinued Double-blind treatment period	11 (9.7)	10 (9.2)	21 (9.5)
Reason for Terminating Double-blind treatment period			
Adverse Event	4 (3.5)	4 (3.7)	8 (3.6)
Lost to Follow-up	2 (1.8)	0	2 (0.9)
Other	0	1 (0.9)	1 (0.5)
Protocol Violation	0	1 (0.9)	1 (0.5)
Withdrawal by Subject	5 (4.4)	4 (3.7)	9 (4.1)

Note: Percentages are based on the number of randomized subjects in each group.

Source: Table 2 in the clinical study report body of Study YKP3089C013

Table 2 presents the subject disposition of Study 13. A total of 285 subjects were screened in 40 study centers in four countries (India, Korea, Poland, and United States); a total of 222 subjects were randomized in 38 study centers in four countries. Among the randomized subjects, 113 subjects (50.9%) were randomized to the YKP2089 group and 109 (49.1%) to the placebo group.

Table 3. Study 13 subject demographics, randomized population

		YKP3089 (N=113)	Placebo (N=109)	All Subjects (N=222)
Gender	n	113	109	222
Male	n (%)	55 (48.7)	58 (53.2)	113 (50.9)
Female	n (%)	58 (51.3)	51 (46.8)	109 (49.1)
Race	n	113	109	222
White	n (%)	57 (50.4)	58 (53.2)	115 (51.8)
Black or African American	n (%)	3 (2.7)	2 (1.8)	5 (2.3)
Asian	n (%)	49 (43.4)	45 (41.3)	94 (42.3)
Other	n (%)	1 (0.9)	2 (1.8)	3 (1.4)
Unknown	n (%)	3 (2.7)	2 (1.8)	5 (2.3)
Age (years)	n	113	109	222
	Mean (SD)	36.2 (11.27)	37.5 (11.38)	36.9 (11.31)
	Median	36.0	38.0	37.0
	Min, Max	18, 61	18, 59	18, 61

Source: selected from Table 3 in the clinical study report body of Study YKP3089C013, with a numerical error corrected by the statistical reviewer

Table 3 summarizes the demographics of subjects in the randomized population. The YKP3089 and placebo groups appeared similar in terms of sex, race, and age. The average age of the subjects was approximately 36.9 years (standard deviation (SD) = 11.3). The percentage of females or males was around 50%. Over 50% of the randomized population were white. The second largest race was Asian, with over 40% of randomized population.

3.2.1.4 Results and Conclusions

The unblinded interim analysis was performed on the first 88 randomized subjects, among which 87 were in the ITT population with 44 subjects in the YKP3089 group and 43 in the placebo group. A formal interim analysis report was not drafted at the time of the analysis. Instead, the NDA included a post-hoc interim report that summarized events surrounding the interim analysis and evaluated the potential impact of the interim analysis on the interpretation of the primary analysis. The post-hoc interim report clarified that "senior management at SKLSI and SK Holdings, the parent company in South Korea" received interim analysis results and that "none of the individuals involved in the conduct of the study were involved with or were aware of the results of the interim analysis." The post-hoc interim report also clarified that "there was no change to the primary efficacy analysis or the primary analysis population prospectively specified in the original protocol, and there was no change to the sample size."

Table 4. Study 13 analysis of the primary endpoint, ITT population

		YKP3089 (N=113)		Placebo (N=108)	
Visit		**Actual**	**Percent Change from Baseline**	**Actual**	**Percent Change from Baseline**
Baseline	n	113		108	
	Mean (SD)	16.2 (24.71)		15.4 (29.53)	
	Median	7.5		5.5	
	Min, Max	0.0, 186.8		2.0, 236.5	
Endpoint	n	113	113	108	108
	Mean (SD)	12.2 (27.20)	35.5 (74.48)	15.6 (31.79)	2.0 (91.57)
	Median	3.8	55.6	5.0	21.5
	Min, Max	0.0, 196.3	-417.3, 100.0	0.0, 206.3	-588.0, 100.0
p-value comparing YNP3089 vs. Placebo [1]			<0.0001		

Note: Baseline Seizure Frequency per 28 Days = Number of seizures over baseline period (56 days prior to Study Day 1) divided by the number of days in the interval multiplied by 28.

Note: Endpoint 28 Day Frequency = Number of seizures over entire treatment period divided by the number of days in the interval multiplied by 28.

Note Percent change from baseline = (baseline seizure frequency per 28Days – endpoint 28 Day frequency)/ baseline seizure frequency per 28 Days * 100.

[1] p-value is based on a Wilcoxon rank-sum test assessing if the median percent change in seizure frequency for the treatment group is significantly different from the median percent change in seizure frequency for the placebo subjects.

Source: Table 5 in the clinical study report body of Study YKP3089C013

Table 4 presents the descriptive statistics of the primary endpoint and the p-value from the Wilconxon rank-sum test that was performed on the primary endpoint. The "percent change from baseline" in the table was calculated by

$$\frac{baseline\ seizure\ frequency\ per\ 28\ days - endpoint\ seizure\ frequency\ per\ 28\ days}{baseline\ seizure\ frequency\ per\ 28\ days} \times 100\%$$

In other words, a postive percent change from baseline in the table represents a reduction of seizure frequency from baseline. The observed medians of percent reduction from baseline in seizure frequence per 28 days were 55.6% for the YKP3089 group and 21.5% for placebo group. The p-value for comparing the medians of the two treatment groups was nominally smaller than 0.05. Statistical results for comparing means or medians of the YKP3089 group and the placebo group under the four ANCOVA or rank ANCOVA models (see Models 1-4 in Section **3.2.1.2** of this review) were reported in the Applican's March 27, 2019 responses to information request; the p-values were all nominally smaller than 0.05.

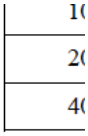
3.2.2 Study 17

3.2.2.1 Design and Endpoints

Study 17 was a randomized, placebo-controlled, double-blind, parallel-group, 4-arm, multi-center, Phase 2 clinical study to determine the effective dose range of YKP3089 as adjunctive therapy for the treatment of parital seizures. The study also aimed to evaluate the safety and tolerability of tolerability of YKP3089 in the partial epilepsy population. Approximately 400 subjects aged 18-70 years (inclusive) were planned to be enrolled and randomized in a 1:1:1:1 ratio to receive YKP3089 400 mg once daily, YKP3089 200 mg once daily, YKP3089 100 mg once daily, or placebo.

The study consisted of an 8-week baseline period, an 18-week treatment period (6-week titration and 12-week maintenance), a 3-week taper period, and a follow-up visit 2 weeks after the last dose of the study medication.

Table 5. Study 17 titration plan



Source: Table 3 in the protocol amendment of Study YKP3089C017

Table 5 depicts the titration plan. All subjects were planned to receive 50 mg YKP3089 (or placebo) once daily initially and increase their daily doses of YKP3089 by 50 mg per week if they showed tolerability until they reached 200 mg or, otherwise, remain on the same doses or reduce their doses. After that, daily dose of YKP3089 were planned to increase by 100 mg per week.

The primary endpoint was the percent change from baseline in seizure (simple partial seizures with motor component, complex partial seizures, and secondarily generalized tonic-clonic seizures) frequency per 28 days in the treatment period.

3.2.2.2 Statistical Methodologies

The efficacy analysis population was the modified intention-to-treat (mITT) population, defined as all subjects randomly assigned to study drug who have taken at least 1 dose of YKP3089 (or placebo) and have a post-dose evaluation will be considered modified intention-to-treat subjects.

The primary analysis was an ANCOVA model fit to the ranked values of the primary endpoint and include ranked baseline seizure frequency and treatment group.

The testing of the multiple dose groups was planned in the following hierarchy:

1. YKP3089 200 mg.day group vs placebo group
2. YKP3089 400 mg.day group vs placebo group
3. YKP3089 100 mg.day group vs placebo group

Each test was planned to be based on the two-sided significance level of 0.05.

3.2.2.3 Subject Disposition, Demographic and Baseline Characteristics

Table 6. Study 17 subject disposition

	Number (%) of Subjects				
	YKP3089 100 mg qd	YKP3089 200 mg qd	YKP3089 400 mg qd	Placebo qd	All Subjects
Enrolled					533
Screen failure[a]					83 (15.6)
Treatment not assigned					13 (2.9)
Randomized subjects	108	110	111	108	437
ITT population[b]	108 (100)	110 (100)	111 (100)	108 (100)	437 (97.1)
MITT population[b]	108 (100)	109 (99.1)	111 (100)	106 (98.1)	434 (96.4)
Discontinued double-blind treatment period[b]	13 (12.0)	20 (18.2)	30 (27.0)	14 (13.0)	77 (17.1)
Reason for terminating double-blind treatment period[b]					
Adverse event	12 (11.1)	15 (13.6)	23 (20.7)	5 (4.6)	55 (12.2)
Withdrawal by subject	0	4 (3.6)	3 (2.7)	5 (4.6)	12 (2.7)
Protocol violation	0	1 (0.9)	1 (0.9)	0	2 (0.4)
Lack of efficacy	1 (0.9)	0	1 (0.9)	0	2 (0.4)
Lost to follow-up	0	0	1 (0.9)	0	1 (0.2)
Death	0	0	0	0	0
Pregnancy	0	0	0	1 (0.9)	1 (0.2)
Other	0	0	1 (0.9)	3 (2.8)	4 (0.9)

Abbreviations: ITT = intention-to-treat; MITT = modified intention-to-treat; qd = once daily.
Notes: Treatment not assigned = subjects withdrawn from the trial before being assigned to a treatment who were not screen failures.
The ITT population includes all randomized subjects; MITT population includes all randomized subjects with at least 1 dose of YKP3089 or placebo and any postbaseline seizure data.
Completed study double-blind treatment period includes subjects who completed the titration phase and the maintenance phase.

[a] Percentages are based enrolled subjects.
[b] Percentages are based on the number of randomized subjects in each group.

Source: selected from Table 5-1 in the clinical study report body of Study YKP3089C017

Table 6 presents the subject disposition of Study 17. A total of 533 subjects were screened in 96 study centers in 16 countries (Australia, Bulgaria, Czech Republic, Germany, France, Hungary, Isreal, South Korea, Poland, Romania, Serbia, Spain, Thailand, Ukraine, United Kingdom, United States); a total of 437 subjects were randomized in 90 study centers in 16 countries. Among the randomized subjects, 111 subjects (25.4%) were randomized to the YKP3089 400 mg/day group, 110 (25.2%) to the YKP3089 200 mg/day group, 108 (24.7%) to the YKP3089 100 mg/day, and 108 (24.7%) to the placebo group.

Table 7. Study 17 subject demographics, randomized population

		YKP3089 100 mg qd (N=108)	YKP3089 200 mg qd (N=110)	YKP3089 400 mg qd (N=111)	Placebo qd (N=108)	All Subjects (N=437)
Gender	n	108	110	111	108	437
Male	n (%)	57 (52.8)	54 (49.1)	52 (46.8)	58 (53.7)	221 (50.6)
Female	n (%)	51 (47.2)	56 (50.9)	59 (53.2)	50 (46.3)	216 (49.4)
Race	n	108	110	111	108	437
White	n (%)	89 (82.4)	94 (85.5)	96 (86.5)	93 (86.1)	372 (85.1)
Black or African American	n (%)	4 (3.7)	3 (2.7)	1 (0.9)	4 (3.7)	12 (2.7)
Asian	n (%)	10 (9.3)	11 (10.0)	11 (9.9)	9 (8.3)	41 (9.4)
Other	n (%)	5 (4.6)	2 (1.8)	3 (2.7)	2 (1.9)	12 (2.7)
Age (years) at screening	n	108	110	111	108	437
	Mean (SD)	39.0 (12.06)	40.9 (12.4)	39.6 (10.3)	39.6 (12.38)	39.8 (11.79)
	Median	37.5	40.5	38.0	38.0	38.0
	Min, Max	19, 66	19, 69	21, 66	19, 70	19, 70

Source: selected from Table 5-3 in the clinical study report body of Study YKP3089C017

Table 7 summarizes the demographics of subjects in the randomized population. The YKP3089 and placebo groups appeared similar in terms of sex, race, and age. The average age of the subjects was approximately 39.8 years (SD = 11.8). The percentage of females or males was around 50%. The majority of the randomized population were white.

3.2.2.4 Results and Conclusions

Table 8. Study 17 primary analysis, mITT population

	YKP3089 100 mg qd (N=108)		YKP3089 200 mg qd (N=109)		YKP3089 400 mg qd (N=111)		Placebo qd (N=106)	
	Actual	Percent Change from Baseline	Actual	Percent Change from Baseline	Actual	Percent Change from Baseline	Actual	Percent Change from Baseline
Baseline (n)	108		109		111		106	
Mean (SD)	21.9 (33.75)		30.6 (60.87)		24.1 (63.08)		25.8 (76.81)	
Median	9.5		11.0		9.0		8.4	
Min, Max	3.5, 202		4, 418		4, 638		4, 759	
Endpoint (n)	108	108	109	109	111	111	106	106
Mean (SD)	12.3 (20.68)	–33.6 (45.68)	22.4 (59.58)	–41.7 (50.59)	13.6 (43.86)	–48.3 (46.65)	21.6 (65.43)	–17.0 (50.26)
Median	5.8	–36.3	5.8	–55.2	3.8	–55.3	6.8	–24.3
Min, Max	0, 164.6	–100.0, 205.6	0, 373.7	–100.0, 191.1	0, 424.9	–100.0, 166.7	0.7, 640.8	–90.6, 198.4
P value vs placebo[a]		0.006		<0.001		<0.001		

Abbreviations: Max = maximum; Min = minimum, MITT = modified intention-to-treat.

Notes: Endpoint seizure frequency per 28 days = (number of seizures over the entire double-blind treatment period/by the number of days in the interval) × 28.

Baseline seizure frequency per 28 days = (number of seizures over the baseline period [56 days prior to randomization]/by the number of days in the interval) × 28.

Percentage change from baseline = (endpoint seizure frequency per 28 days [baseline seizure frequency per 28 days]/baseline seizure frequency per 28 days) × 100.

Includes seizure types of all simple partial motor, complex partial, or secondarily generalized seizures.

[a] *P* value is based on an analysis of covariance model with terms for ranked baseline seizure rate and randomized treatment group.

Source: Table 6-1 in the July 16, 2019 responses to information request, with rounding errors corrected by the statistical reviewer

Table 8 presents the primary analysis of the percent change from baseline in seizure frequency per 28 days. All three YKP3089 dose groups were statistically significantly different from the placebo based on the rank ANCOVA model. The observed medians of percent change from baseline in seizure frequency per 28 days were -55.3%, -55.2%, -36.3%, and -24.3% for the YKP3089 400 mg/day group, YKP3089 200 mg/day group, YKP3089 100 mg/day group, and placebo group, respectively.

3.3 Evaluation of Safety

Please refer to Dr. Steven Dinsmore's clinical review for a detailed evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 9. Study 13 and 17 subgroup analyses by gender

	Study 13 ITT population[a]		Study 17 mITT population[a]			
Seizure frequency per 28 days	**YKP3089 200 mg (N = 113)**	**Placebo (N = 108)**	**YKP3089 400 mg (N = 111)**	**YKP3089 200 mg (N = 109)**	**YKP3089 100 mg (N = 108)**	**Placebo (N = 106)**
Female						
n	58	50	59	55	51	50
Median at baseline	8.2	8.1	8.0	16.0	10.0	9.3
Median of the treatment period	4.0	9.8	4.2	6.7	6.2	8.9
Median percent change from baseline	-58.3	-17.5	-53.3	-55.6	-44.4	-21.3
Male						
n	55	58	52	54	57	56
Median at baseline	6.5	5.3	9.8	9.3	8.0	7.8
Median of the treatment period	3.7	3.8	3.3	5.2	5.2	6.1
Median percent change from baseline	-44.7	-30.4	-58.9	-53.5	-32.2	-25.9

[a]The primary efficacy analysis population was called the ITT population in Study YKP3089C013 and the mITT population in Study YKP3089C017

Source: selected from Table 2.1.1 in the integrated summary of efficacy and Table 2.2.1ph in the July 16, 2019 responses to information request

Table 10. Study 13 and Study 17 subgroup analyses by race

	Study 13 ITT population[a]		Study 17 mITT population[a]			
Seizure frequency per 28 days	**YKP3089 200 mg (N = 113)**	**Placebo (N = 108)**	**YKP3089 400 mg (N = 111)**	**YKP3089 200 mg (N = 109)**	**YKP3089 100 mg (N = 108)**	**Placebo (N = 106)**
Non-White						
N	56	51	15	16	19	15
Median at baseline	6.5	5.0	8.5	10.0	7.0	8.7
Median of the treatment period	3.3	4.9	4.2	4.1	6.1	6.1
Median percent change from baseline	-58.3	-18.4	-56.0	-61.3	-18.1	-24.4
White						
n	57	57	96	93	89	91
Median at baseline	8.5	7.0	9.0	13.0	10.0	8.2
Median of the treatment period	4.0	5.3	3.7	5.8	5.8	7.1
Median percent change from baseline	-44.7	-23.5	-55.0	-52.5	-39.5	-23.4

[a]The primary efficacy analysis population was called the ITT population in Study YKP3089C013 and the mITT population in Study YKP3089C017

Source: selected from Table 2.1.3 in the integrated summary of efficacy and Table 2.2.3ph in the July 16, 2019 responses to information request

Table 11. Study 13 and Study 17 subgroup analyses by region

	Study 13 ITT population[a]		Study 17 mITT population[a]			
Seizure frequency per 28 days	**YKP3089 200 mg (N = 113)**	**Placebo (N = 108)**	**YKP3089 400 mg (N = 111)**	**YKP3089 200 mg (N = 109)**	**YKP3089 100 mg (N = 108)**	**Placebo (N = 106)**
US						
n	43	43	28	27	28	26
Median at baseline	9.3	10.5	10.8	26.5	12.5	14.3
Median of the treatment period	4.7	9.1	4.2	11.5	6.2	12.4
Median percent change from baseline	-34.0	-18.4	-53.4	-52.2	-38.5	-16.8
Non-US						
n	70	65	83	82	80	80
Median at baseline	6.5	4.5	8.5	9.5	8.3	7.8
Median of the treatment period	3.1	3.5	3.4	4.5	5.5	6.0
Median percent change from baseline	-57.9	-25.7	-56.5	-55.5	-33.0	-25.6

[a]The primary efficacy analysis population was called the ITT population in Study YKP3089C013 and the mITT population in Study YKP3089C017

Source: the statistical reviewer and selected from Table 2.1.4 in the integrated summary of efficacy and Table 2.2.4ph in the July 16, 2019 responses to information request

Table 9, **Table 10**, and **Table 11** present the analyses of the primary endpoints of Study 13 and Sutdy 17 by gender, race, and geographic region, respectively. None of the subjects was older than 65 years in Study 13; less than five subjects were older than 65 years in each treatment group in Study 17. Therefore, there is no subgroup analyses by age group in this review. There is no compelling evidence from the subgroup analyses that a specific gender, race, or geographic region benefits differently from YKP3089. One unusual observation is that for non-white subjects in Study 17, the YKP3089 100 mg/day group had a -18.1% median percent change from baseline, which was a smaller reduction from baseline in seizure frequency, compared to that of the placebo group (-24.4% median percent change from baseline). However, the numbers of non-white subjects in these groups were too small to draw conclusions.

4.2 Other Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Study 13 was orginially planned as a proof of concept study. The lack of pre-specifications of the unblinded interim anlysis, such as the timing, firewall, details of analyses to be conducted, jeopardized the credibility of Study 13. Although this statistical reviewer did not find changes of study conduct of Study 13 before and after the interim analysis, the impact of the unblinded interim analysis on efficacy remains difficult to evaluate. In additon, the ambiguity in the primary analysis adds complexity to the evaluation of the efficacy evidence in Study 13. In spite of these issues, Study 13 demonstrated similar treatment effects and supported the findings from Study 17. The statistical issues do not change the overall conclusions.

5.2 Collective Evidence

Collective evidence from Study 13 and Study 17 indicates that YKP3089 is effective for the treatment of partial onset seizures in adult patientce. Study 13 showed that the observed medians of percent change from baseline in seizure frequency per 28 days were -55.6% (reduction from baseline) for the YKP3089 200 mg/day group and -21.5% for the placebo group. Study 17 showed that the observed medians of percent change from baseline in seizure frequency per 28 days were -55.3%, -55.2%, -36.3%, and -24.3% for the YKP3089 400 mg/day group, YKP3089 200 mg/day group, YKP3089 100 mg/day group , and placebo group, respectively. The medians oberseved in both studies supported the effectiveness of YKP3089 compared to placebo. Comparisons of the YKP3089 and placebo groups, with repect to the change from baseline in seizure frequence per 28 days, for Study 13 and Study 17 were all statistically significant (p-value < 0.0001 for Study 13; p-values < 0.001, < 0.001, $= 0.006$ for the the YKP3089 400 mg/day group, YKP3089 200 mg/day group, and YKP3089 100 mg/day group, respectively for Study 17).

5.3 Conclusions and Recommendations

Study 13 and Study 17 provided statistical evidence that YKP3089 is effective for the treatment of partial onset seizures in adult patients.

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/s/

XIANGMIN ZHANG
07/29/2019 09:10:07 AM

KUN JIN
07/29/2019 09:30:07 AM
I concur with the review.

HSIEN MING J HUNG
07/29/2019 02:42:59 PM

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

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	212839/0001
Supplement Number:	
Drug Name:	Cenobamate (YKP 3089)
Indication(s):	Partial Onset Seizures
Applicant:	SK Life Science, Inc.
Date(s):	Date of Document: 11/21/2018 Consult received date: 1/15/2018 Completion date: 2/15/2018
Review Priority:	S
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Ran Bi, Ph.D., Visiting Associate, CSS supporting team/DBVI/OB
Concurring Reviewers:	Qianyu Dang, Ph.D., Team Leader, CSS supporting team/DBVI/OB Yi Tsong, Ph.D., Division Director, DBVI/OB/OTS
Medical Division:	Controlled Substance Staff
The CSS Team:	Edward Hawkins, Ph.D., Pharmacologist, OD/CSS
Project Manager:	Sandra Saltz, OD/CSS
Keywords: Crossover design; Human abuse potential study; Self-reported endpoints.	

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1. Executive Summary

The applicant, SK Life Science, Inc., submitted the results from the human abuse potential study YKP3089C024 for the assessment of abuse potential of Cenobamate (YKP3089).

Study YKP3089C024 was a randomized, double-blind, double-dummy, 5-way crossover study to evaluate the abuse potential of Cenobamate relative to Alprazolam and Placebo when administered orally in non-dependent, recreational drug users with sedative experience. The primary objective was to evaluate the abuse potential of single oral doses of Cenobamate relative to alprazolam and placebo when administered to recreational drug users with sedative drug use experience. The treatments in the Treatment Phase were placebo, Alprazolam 1.5 mg, Alprazolam 3.0 mg, Cenobamate 200 mg and Cenobamate 400 mg. 53 subjects were randomized to the Treatment Phase. Of these, 39 subjects completed the study.

The results from the reviewer's primary analysis demonstrated the validity of the study by showing that each dose of Alprazolam had maximum drug liking statistically significantly greater than Placebo by 15 points. All doses of Cenobamate had significantly less maximum drug liking than each dose of Alprazolam. Cenobamate 200 mg had similar maximum drug liking to Placebo. However, it failed to reject the null hypothesis that the mean difference between Cenobamate 400 mg and Placebo was no less than 11 points with a p-value of 0.9745, which indicates that Cenobamate 400 mg was associated with higher drug liking than Placebo.

Per the CSS Pharmacologist Dr. Edward Hawkins's suggestion, the reviewer performed the secondary analysis for the Completers Population (N = 39) on global and positive effects: Overall Drug Liking E_{max}, Take Drug Again E_{max}, High E_{max}, and Good Drug Effects E_{max}. The hypotheses used in the secondary analysis were the same as those in the primary analysis, except the comparison between Cenobamate and Placebo. The reviewer performed a two-sided test with a test value 0 and type I error equal to 0.1 for this comparison. The secondary analysis results showed that the mean differences between Alprazolam 1.5 mg and Placebo, and between Alprazolam 3.0 mg and Placebo were statistically significantly greater than 15 points. The mean of each dose of Alprazolam was statistically significantly greater than that of all doses of Cenobamate, except the comparison between Alprazolam 1.5 mg and Cenobamate 400 mg for Take Drug Again E_{max}. Such comparison indicated that it failed to reject the null hypothesis that the mean of Alprazolam 1.5 mg was no greater than Cenobamate 400 mg for Take Drug Again E_{max} at significance level 0.05. In addition, each dose of Cenobamate had statistically significantly larger mean than Placebo on all these four endpoints.

After carefully examining the data of key secondary endpoints, the reviewer noticed that some subjects had the same responses across all time points for all treatments, and some subjects had large Placebo response. After eliminating subjects with similar responses at all time points across all treatments or large Placebo response, the numbers of subjects included in the sensitivity analysis were 35, 34, 33 and 34 for Overall Drug Liking E_{max}, Take Drug Again E_{max}, High E_{max}, and Good Drug Effects E_{max}, respectively. The reviewer's sensitivity analysis results were the same as secondary analysis results, except the comparison between Alprazolam 1.5 mg and Cenobamate 400

mg for Take Drug Again E_{max}. The null hypothesis of such comparison was rejected at significance level 0.05, indicating that the mean of Alprazolam 1.5 mg was also statistically significantly greater than that of Cenobamate 400 mg for Take Drug Again E_{max}. This distinction of results between the reviewer's sensitivity analysis and secondary analysis was due to the elimination of subjects who had similar responses across all treatments.

In conclusion, Drug Liking E_{max} of Cenobamate 200 mg did not differentiate from that of placebo, while Cenobamate 400 mg was associated with higher drug liking than Placebo. Cenobamate had global and positive effects significantly less than Alprazolam in all comparisons. However, these endpoints of Cenobamate were significantly greater than that of Placebo.

2. Review report on Study YKP3089C024

2.1. Overview

Study YKP3089C024 was a randomized, double-blind, double-dummy, 5-way crossover study to evaluate the abuse potential of Cenobamate relative to Alprazolam and placebo when administered orally in non-dependent, recreational drug users with sedative experience.

2.1.1. Objectives of the Study

Primary Objective

- To evaluate the abuse potential of single oral doses of cenobamate relative to alprazolam and placebo when administered to recreational drug users with sedative drug use experience.

Secondary Objective

- To evaluate the pharmacokinetics (PK), effects on performance, safety, and tolerability of single oral doses of cenobamate relative to alprazolam and placebo when administered to recreational drug users with sedative drug use experience.

2.1.2. Study Design

This was a single-dose, randomized, double-blind, active- and placebo-controlled, double-dummy, 10-sequence, 5-way crossover study to determine the abuse potential of cenobamate relative to alprazolam and placebo in recreational drug users with sedative drug use experience.

This study consisted of 4 phases: Screening, Qualification, Treatment, and Follow-up. Each subject participated in a medical screening visit (Visit 1), a 4-day (or 5-day) qualification visit (Visit 2), five 3-day (or 4-day) treatment periods (Visits 3 to 7), 2 follow-up visits (Visit 8 and 9; 2 and 4 weeks [± 2 days] after the last study drug administration), and 2 follow-up telephone calls (1 and 3 weeks [± 2 days] following the last study drug administration). If any AEs of concern were to be reported during the scheduled phone calls, an unscheduled follow-up visit would have been conducted.

Screening Phase

Subjects who provided informed consent underwent a standard medical screening to determine eligibility for the study. Within approximately 30 days of a standard medical screening, subjects who successfully completed the Screening phase returned to the CRU as inpatients to complete the Qualification phase.

Eligibility screening consisted of the assessments as presented in the schedule of assessments in Sponsor's Table 5, Section 9.5.1.

Qualification Phase

The Qualification phase comprised a Drug Discrimination Test to ensure that subjects were able to discriminate the drug effects of the positive control (alprazolam) when compared with placebo. During admission to the CRU, subjects were interviewed and assessed for continued eligibility for the study. Subjects who were eligible to continue remained as inpatients in the CRU. Subjects were randomized to receive single oral doses of each of the following treatments in a randomized, double-blind, crossover manner:

- Treatment Z: 2.0 mg alprazolam (2 × 1.0 mg alprazolam tablets)
- Treatment Y: placebo (2 × 100 mg lactose tablets)

Placebo and alprazolam tablets were over encapsulated for blinding purposes. Subjects were dosed with alprazolam or placebo on Day 1 and Day 2. Study drug administration occurred approximately 24 hours apart, as PD effects related to abuse potential were expected within several hours following dosing of alprazolam and have not been observed to carry over at 24 hours post-dose for "at the moment" measures. Subjects fasted for at least 8 hours pre-dose and for 4 hours post-dose. Pharmacodynamic and safety assessments were conducted as outlined in Sponsor's Table 5. At the discretion of the investigator, subjects were discharged after assessments were completed on Day 3, approximately 24 hours after the second qualification dose, to ensure the subject's safety. The Qualification phase data were unblinded and continued eligibility was determined upon data review as described in Sponsor's Section 9.3.3.

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 5 days. Eligible subjects who successfully completed the Qualification phase entered the Treatment phase. During admission to the CRU, subjects were interviewed and assessed for continued eligibility for the study. Subjects who were eligible to continue remained as inpatients in the CRU. Subjects were randomized to receive single oral doses of each of the following treatments in a randomized, double-blind, double-dummy fashion:

- Treatment A: placebo (4 × cenobamate-matched placebo tablets + 3 × alprazolam-matched placebo tablets)
- Treatment B: 1.5 mg alprazolam (3 × 0.5 mg alprazolam tablets + 4 × cenobamate-matched placebo tablets)
- Treatment C: 3.0 mg alprazolam (3 × 1.0 mg alprazolam tablets + 4 × cenobamate-matched placebo tablets)
- Treatment D: 200 mg cenobamate (2 × 100 mg cenobamate tablets + 2 × cenobamate-matched placebo tablets + 3 × alprazolam-matched placebo tablets)
- Treatment E: 400 mg cenobamate (4 × 100 mg cenobamate tablets + 3 × alprazolam-matched placebo tablets)

For each treatment, subjects swallowed a total of 7 pills containing the active drug and/or placebo in order to maintain the blind. Study drug administration occurred on Day 1 of each treatment period. Subjects fasted for at least 8 hours pre-dose and for 4 hours post-dose. Pharmacodynamic, PK, and safety assessments were conducted for up to 24 hours post-dose. At the discretion of the investigator, subjects were discharged after study assessments were completed on Day 2, approximately 24 hours after dosing, to ensure subject safety. Study drug administration in each treatment period was separated by a minimum washout interval of 16 days between dosing. If any AEs of concern were to be reported or if a subject was to report a rash or other signs or symptoms of hypersensitivity during the washout period, an unscheduled visit would have been promptly conducted.

Assessments during the treatment periods were performed as presented in the schedule of assessments in Sponsor's Table 6, Section 9.5.1.

Follow-up Phase

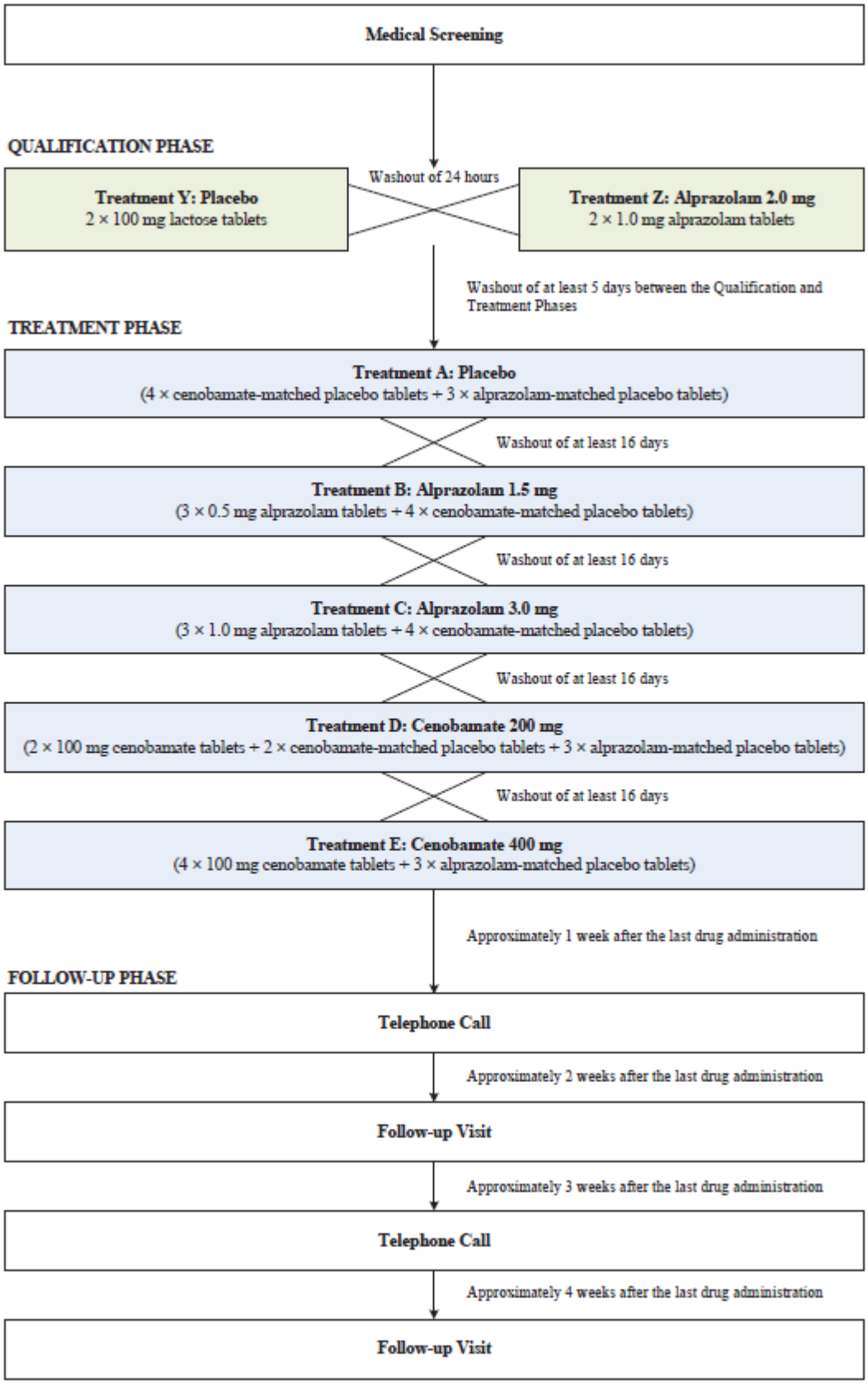
Subjects (including any subjects who discontinued early) returned to the CRU for follow-up visits approximately 2 and 4 weeks (± 2 days) following the last study drug administration. In addition, follow-up telephone calls were made 1 and 3 weeks (± 2 days) following the last study drug administration. If any AEs of concern were to be reported or if a subject was to report a rash or other signs or symptoms of hypersensitivity, an unscheduled visit would have been conducted promptly. Subjects were to undergo the follow-up procedures during any unscheduled visit and at the time of early discontinuation.

The chart on the next page (Sponsor's Figure 1) summarizes the design of the study.

2.1.3. Qualification Phase Eligibility Criteria

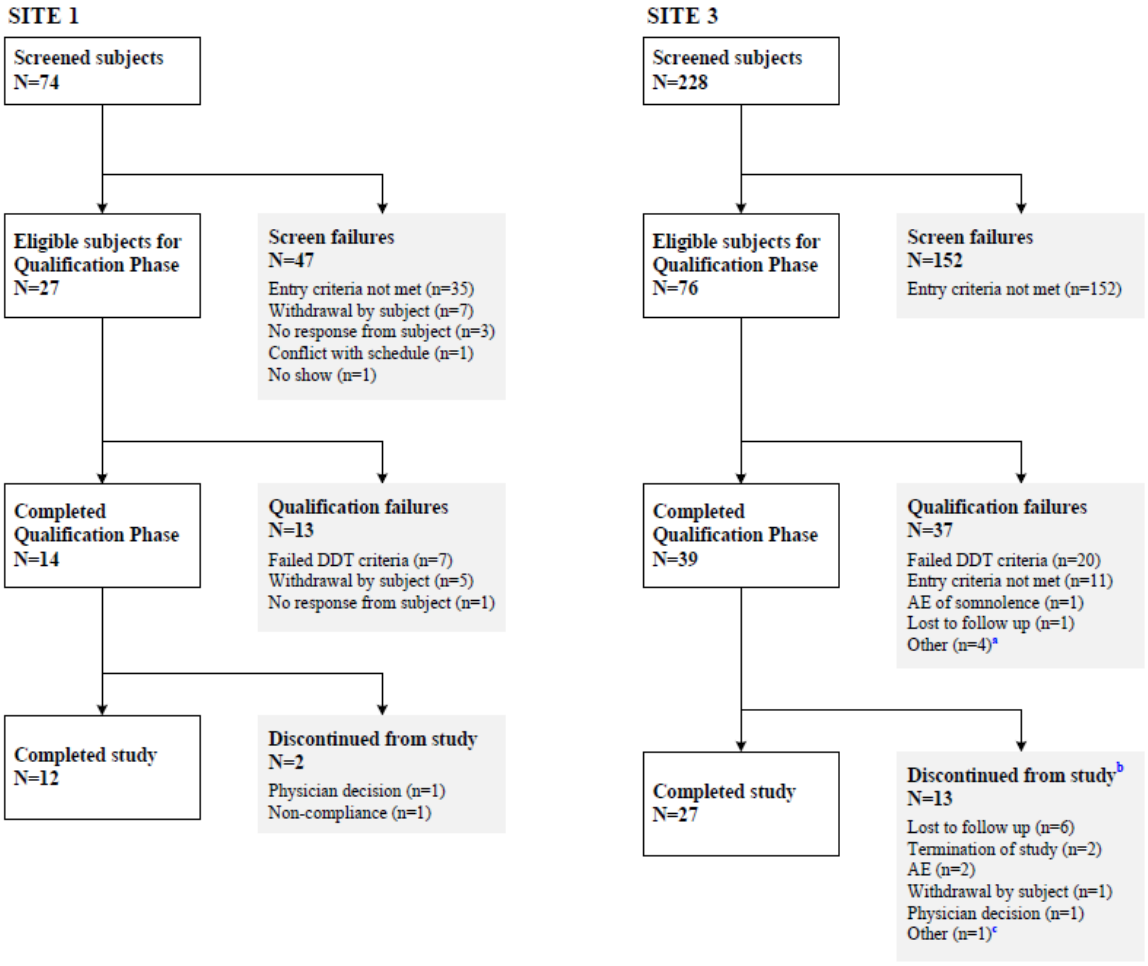
Subjects must have met the following qualification criteria to be eligible to enter the Treatment phase:

- Peak score in response to 2.0 mg alprazolam greater than that of placebo on Drug Liking (difference of at least 15 points) and score of at least 65 points for 2.0 mg alprazolam.
- Acceptable placebo response based on Drug Liking (score between 40 and 60 points, inclusive).
- Ability to complete the PD assessments and had acceptable overall responses as judged by the investigator or designee.
- Able to tolerate 2.0 mg alprazolam as judged by the investigator or designee based on available safety data (e.g., no emesis within 6 hours following dosing or unarousable sedation within the first 3 hours post-dose, i.e., score of 1 on the Observer's Assessment of Alertness/Sedation scale [OAA/S]).
- General behavior suggested that the subject could successfully complete the study, as judged by the research site staff.



2.1.4. Disposition of Subjects

The following chart (Sponsor's Figure 4) summarizes disposition of subjects.



Source: Tables 14.1.1.1 and 14.1.1.2
AE=adverse event, BP=blood pressure, DDT=Drug Discrimination Test, UDS=urine drug screen
[a] Other reasons for qualification visit failures included out-of-range BP (n=1), positive UDS (n=1), no show (n=1), failed VAS assessment (n=1).
[b] Subject 9332 completed the study per SAP definition for Completers Population, as the subject received all study treatments and completed all treatment periods in the Treatment phase. However, the subject was also discontinued from the study (ie, lost to follow-up).
[c] Other reason for early discontinuation included family emergency (n=1).

Site 1

A total of 74 subjects were screened for enrollment into the study and of these, 27 subjects were eligible for the Qualification phase. Nineteen subjects successfully completed the Drug Discrimination Test, while 7 subjects failed to meet the protocol-defined qualification criteria and 1 subject failed to respond to confirm their attendance.

Prior to the start of the Treatment phase, 5 subjects withdrew consent. A total of 14 subjects were randomized to treatment in the Treatment phase. One subject was discontinued due to physician decision (subject had increasing THC levels) and another subject was discontinued due to non-compliance.

Overall, a total of 12 subjects completed the study from Site 1.

Site 3

A total of 228 subjects were screened for enrollment into the study and of these, 76 subjects were eligible for the Qualification phase. Thirty-nine subjects successfully completed the Drug Discrimination Test, while 20 subjects failed to meet the protocol-defined qualification criteria, 11 subjects did not meet the entry criteria for the Qualification phase, 1 subject was unable to complete the PD assessments during the Qualification phase due to an AE of somnolence that was assessed by the investigator as moderate in severity, 1 subject was lost to follow up, 1 subject failed a VAS assessment, 1 subject had a clinically significant out-of-range blood pressure at pre-dose in the Qualification phase, 1 subject had a positive UDS result, and 1 subject did not show up as scheduled.

Of the 39 subjects who were randomized to the Treatment phase, 12 subjects were discontinued: 2 subjects were discontinued due to an AE 1 subject withdrew consent, 1 subject was lost to follow up, 1 subject was discontinued due to physician decision, study was terminated by the sponsor for 2 subjects, and 1 subject had a family emergency.

Overall, a total of 27 subjects completed the study from Site 3.

2.1.5. Pharmacodynamic Endpoints

Primary Endpoint

The primary PD endpoint is the Drug Liking visual analog scale (VAS) maximum (peak) effect (E_{max}).

Key Secondary Endpoints

- Balance of effects:
  - Drug Liking VAS (“at this moment”) minimum effect (E_{min}), time to E_{max} (TE_{max}), time to E_{min} (TE_{min}), and time-averaged area under the effect curve (TA_AUE)
- Global effects:
  - Overall Drug Liking (ODL) VAS (E_{max} and E_{min})
  - Take Drug Again (TDA) VAS (E_{max} and E_{min})
- Positive effects:
  - High VAS (E_{max}, TE_{max}, and TA_AUE)
  - Good Drug Effects VAS (E_{max}, TE_{max}, and TA_AUE)

Other Secondary Endpoints

- Positive effects:
  - Addiction Research Center Inventory Morphine-Benzedrine Group (ARCI MBG) scale (E_{max}, TE_{max}, and TA_AUE)
- Negative effects:
  - Bad Drug Effects VAS (E_{max}, TE_{max}, and TA_AUE)
  - ARCI LSD scale (E_{max}, TE_{max}, and TA_AUE)
- Sedative effects:
  - ARCI PCAG scale (E_{max}, TE_{max}, and TA_AUE)
  - Drowsiness/Alertness VAS (E_{max}, E_{min}, TE_{max}, TE_{min}, and TA_AUE)
- Other effects:
  - Any Effects VAS (E_{max}, TE_{max}, and TA_AUE)
  - Relaxation/Agitation VAS (E_{max}, E_{min}, TE_{max}, TE_{min}, and TA_AUE)
  - Dizziness VAS (E_{max}, TE_{max}, and TA_AUE)
  - Feeling Drunk VAS (E_{max}, TE_{max}, and TA_AUE)
- Objective and observer-rated measures of sedation and cognitive/psychomotor impairment:
  - Observer's Assessment of Alertness/Sedation (OAA/S) scale (E_{min} and TA_AUE of composite and sum scores)
  - Choice Reaction Time (CRT)
    - ◊ Motor Reaction Time (MRT) (maximum change from baseline [CFB_{max}] and baseline adjusted TA_AUE)
    - ◊ Recognition Reaction Time (RRT) (CFB_{max} and baseline adjusted TA_AUE)
    - ◊ Total Reaction Time (TRT) (CFB_{max} and baseline adjusted TA_AUE)
    - ◊ Percentage correct (minimum change from baseline [CFB_{min}] and baseline adjusted TA_AUE)
  - Divided Attention Test (DAT)
    - ◊ Root mean square (RMS) distance (E_{max} and CFB_{max})
    - ◊ Greatest distance (E_{max} and CFB_{max})
    - ◊ Response latency of correct responses (E_{max} and CFB_{max})
    - ◊ Number of false alarms (E_{max} and CFB_{max})
    - ◊ Percentage over road (E_{min} and CFB_{min})
    - ◊ Percentage of target hits (E_{min} and derived CFB_{min})
  - Sternberg Short-Term Memory (SSTM) Task
    - ◊ d'Prime pooled (E_{min} and CFB_{min})
    - ◊ Mean reaction time pooled for all valid responses (hit latency) (E_{max} and CFB_{max})

2.2. Sponsor's Analyses of the Pharmacodynamic Parameters

2.2.1. Statistical Methodologies Used in the Sponsor's Analyses

2.2.1.1. Analysis Population

The following analysis populations will be used in this study:

Randomized Population
The Randomized Population included all subjects who were assigned a randomization number in the Treatment phase.

Safety Population
The Safety Population included all randomized subjects who received any study treatment in the Treatment phase.

Pharmacodynamic (PD) Population
The PD Population included all subjects in the Safety Population who received any study treatments in the Treatment phase and who had no protocol deviations or other circumstances that would have excluded them from PD analysis.

Completers Population
The Completers Population included all subjects in the Safety Population who received all study treatments, completed all treatment periods in the Treatment phase, and had at least one Drug Liking score around the expected T_{max}, regardless of whether they had protocol deviations.

Reviewer's comments: The definition of the completer population should include the criterion that randomized subjects must have at least one response on the visual analog scale (VAS) for Drug Liking within 2 hours of T_{max} for each treatment in the study.

Pharmacokinetic (PK) Population
The PK Population included all subjects dosed with cenobamate at any dose level and had at least one measured PK concentration of cenobamate. Subjects who experienced emesis within 6 hours post-dose or did not receive the complete dose of the drug were flagged in the listings and removed from summary statistics and PK analyses. Pharmacokinetic samples obtained outside of the windows for a given nominal time may have been excluded from by-time point statistics, but used in PK parameters derivation (actual time used).

All PD analyses were performed using the Completers Population. The Completers Population included all randomized subjects who received all study treatments, completed all treatment periods in the Treatment Phase, and had at least one Drug Liking score around the expected T_{max}, regardless of whether they had protocol deviations.

2.2.1.2. Hypothesis Testing

The statistical analysis of this study addressed the following questions, with the tested hypotheses and contrasts defined as follows:

1. Does the positive control (C-alprazolam) produce mean responses that show greater abuse potential compared to placebo (P)?

$$H_0 : \mu_C - \mu_P \leq 5 \text{ vs. } H_a : \mu_C - \mu_P > 5$$

The study validity was confirmed by comparing the primary endpoint, Drug Liking VAS E_{max}, for each dose of the positive control against placebo. Statistically significant results for Hypothesis 1 confirmed the validity and sensitivity of the study. Hypothesis 1 was applied to the following contrasts:

- Alprazolam 1.5 mg (Treatment B) vs Placebo (Treatment A)
- Alprazolam 3.0 mg (Treatment C) vs Placebo (Treatment A)

Reviewer's comments: The reviewer suggests using 15 as the margin for the validation test, to be consistent with the value used in the Qualification Phase.

2. Does the test drug (T-cenobamate) produce mean responses that show less abuse potential compared to positive control (C)?

$$H_0 : \mu_C - \mu_T \leq 0 \text{ vs. } H_a : \mu_C - \mu_T > 0$$

The investigation of the abuse potential of the test drug, cenobamate, compared to the positive control, alprazolam, was determined by the results from the comparison of Drug Liking E_{max}. A statistically significant (P value < 0.05) difference for the comparison of cenobamate vs alprazolam supported the conclusion that cenobamate showed less abuse potential compared to alprazolam. Hypothesis 2 was applied to the following contrasts:

- Alprazolam 1.5 mg (Treatment B) vs Cenobamate 200 mg (Treatment D)
- Alprazolam 1.5 mg (Treatment B) vs Cenobamate 400 mg (Treatment E)
- Alprazolam 3.0 mg (Treatment C) vs Cenobamate 200 mg (Treatment D)
- Alprazolam 3.0 mg (Treatment C) vs Cenobamate 400 mg (Treatment E)

3. Does the test drug (T-cenobamate) produce mean responses that show similar abuse potential compared to placebo (P)?

$$H_0 : \mu_T - \mu_P \geq 11 \text{ vs. } H_a : \mu_T - \mu_P < 11$$

To investigate whether the test drug, cenobamate, had similar abuse potential compared to placebo, the null hypothesis was specified as the mean difference in Drug Liking $E_{max} \geq 11$ and the alternative hypothesis was specified as the mean difference < 11. A statistically significant (P value < 0.05) difference for the comparison of cenobamate vs placebo supported the conclusion that cenobamate produced a similar response profile to placebo. Hypothesis 3 was applied to the following contrasts:

- Cenobamate 200 mg (Treatment D) vs Placebo (Treatment A)
- Cenobamate 400 mg (Treatment E) vs Placebo (Treatment A)

In this study, the primary endpoint was Drug Liking VAS E_{max}, and the key secondary endpoints were Drug Liking VAS (E_{min} and TA_AUE), ODL VAS (E_{max} and E_{min}), TDA VAS (E_{max} and E_{min}), High VAS (E_{max} and TA_AUE), and Good Drug Effects VAS (E_{max} and TA_AUE). For PD

absolute values, derived endpoints, and paired differences, descriptive statistics and inferential analysis were analyzed for the Completers Population.

In addition, sensitivity analyses using the PD Population were conducted for Drug Liking VAS E_{max}, ODL VAS E_{max}, TDA VAS E_{max}, High VAS E_{max}, and Good Drug Effects VAS E_{max}. If any of the P values changed significance between populations, descriptive statistics and inferential analysis were to be provided in both populations for the primary and key secondary analyses.

These hypotheses were applied to the primary and key secondary endpoints.

Reviewer's comments: For the comparison between test drug and placebo, the test value 11 was studied only for the bipolar Drug Liking VAS. Therefore, a two-sided test with a test value 0 and type I error equal to 0.1 was performed to the comparison between test drug and placebo for key secondary analyses.

For PD-derived endpoints that were not primary or key secondary endpoints (i.e., ARCI scales, Bad Drug Effects VAS, Drowsiness/Alertness VAS, Relaxation/Agitation VAS, Dizziness VAS, Feeling Drunk VAS, OAA/S, CRT, DAT, SSTM task), the following hypotheses were used:

1. $H_0 : \mu_C - \mu_P = 0$ vs. $H_a : \mu_C - \mu_P \neq 0$
2. $H_0 : \mu_C - \mu_T = 0$ vs. $H_a : \mu_C - \mu_T \neq 0$
3. $H_0 : \mu_T - \mu_P = 0$ vs. $H_a : \mu_T - \mu_P \neq 0$

The significance level of P value < 0.05 was used for one-sided tests and the significant level of P value < 0.025 was used for two-sided tests. Multiple comparison adjustments were not made.

Reviewer's comments: For two-sided tests, the significance level should also be 0.05 instead of 0.025, which means each tail has the type I error of 0.025.

2.2.1.3. Statistical Methodologies

All of the primary and secondary analyses were performed for the Completers Population. Pharmacodynamic data at each time point were summarized by descriptive statistics, including mean, standard deviation (SD), standard error (SE), minimum, 25th percentile (Q_1), median, 75th percentile (Q_3), and maximum. Pharmacodynamic data were presented graphically (where appropriate) for the Completers Population.

For primary and key secondary PD endpoints (E_{max}, E_{min}, TA_AUE) in the Treatment phase, treatment comparisons were made between alprazolam and placebo, each cenobamate dose and alprazolam, and each cenobamate dose and placebo. The treatment comparison analysis was performed using a mixed-effects model for a crossover study. The model included treatment, period, sequence, site, and first-order carryover effect as fixed effects, baseline (pre-dose) measurement as covariate where assessed, and subject nested within treatment sequence as a random effect.

Reviewer's comments: Use subject as random effect, instead of subject nested within treatment sequence, by following 2017 FDA Guidance (Assessment of Abuse Potential of Drugs Guidance for Industry – FDA). However, in this situation, one subject was only assigned one sequence, hence using subject nested within treatment sequence as random effect is equivalent to using subject as random effect.

Carryover effect was determined as the treatment administered in the previous treatment period; for treatment period 1, placebo (Treatment A) was used. A minimum interval of 7 days between each dosing in the Treatment phase was implemented to ensure a suitable PK washout in order to minimize the potential for carryover effects. If the carryover effect was found to be non-significant at the 25% level, then the term was to be dropped from the analysis model.

Least-squares means (LSMs), standard errors (SEs), and 95% confidence intervals (CIs) for treatments and pairwise comparisons were derived from the mixed-effects model. P values were provided for the effects and the contrasts.

All analyses were investigated against the statistical assumptions implicit within that analysis; serious violation of those assumptions (e.g., distributional violations) would have resulted in a changed analysis to account for the true apparent features of the data. The residuals from the mixed-effect model were investigated for normality using the Shapiro-Wilk W-test. Parameters were analyzed as having a normal distribution if the probability values were ≥ 0.05. If this criterion was not met, each paired difference would be investigated for normality using the Shapiro-Wilk W-test. If the P value for the distribution of the paired difference was ≥ 0.05 or the distribution was relatively symmetric (skewness = −½ to ½), a paired t test would be used. Means, SE, and one-sided 95% CIs for treatment differences would be presented. P values would be provided for the contrasts from the paired t tests.

Reviewer's comments: Besides the normality assumption, the assumption of homogeneity of variance should also be examined.

If the paired differences were not normally distributed or quite symmetric, pairwise treatment comparisons were to be assessed using the sign test on the within-subject differences. For this test, the margins, $\delta_1 = 5$ and $\delta_3 = 11$, were added to the respective paired difference before they could be tested. The one-sided P value would be P/2, where P is the two-sided P value output in SAS. If the estimated median was in the opposite direction of the alternative hypothesis, then the one-sided P value would be a large number. In this case, the one-sided P value would be calculated as $1 - (P/2)$. If the estimated median was equal to the margins (i.e., $\delta_1 = 5$, $\delta_2 = 0$, and $\delta_3 = 11$), but the test statistics was in the opposite direction of the alternative hypothesis, then the one-sided P value would be calculated as $1 - (P/2)$. Median, first quantile (Q_1) and third quantile (Q_3), two-sided 95% CI, and P value for each treatment difference were presented.

2.2.1.4. Handling of Dropouts or Missing Data

Missing concentration data for all subjects who were administered the scheduled study treatments were considered as non-informative missing and were not imputed.

The rules for the derivation of AUC and for the individual plasma concentration vs time curves are outlined in the SAP (Sponsor's Appendix 16.1.9) for missing or BLQ plasma concentration values. No further imputations were applied to any missing values.

2.2.2. Sponsor's Summary and Conclusions

The validity of the study was confirmed; the mean difference in Drug Liking VAS E_{max} was statistically significant between alprazolam (1.5 mg and 3.0 mg) and placebo. When compared to alprazolam 1.5 mg and 3.0 mg, cenobamate 200 mg and 400 mg was associated with a significantly lower Drug Liking VAS E_{max} indicating that cenobamate was less liked by the recreational sedative users. When compared to placebo, cenobamate 200 mg was associated with similar subjective "at the moment" drug liking ratings throughout the assessment period, while cenobamate 400 mg was associated with higher subjective "at the moment" drug liking.

Key secondary endpoints included Drug Liking VAS E_{min} as well as measures of global effects (ODL and TDA) and positive drug effects (Good Effects VAS and High VAS). Drug Liking E_{min} (maximum "disliking") were similar between the active treatments (both doses of alprazolam and cenobamate) and placebo. Cenobamate 200 mg and 400 mg were associated with significantly lower overall drug liking compared to both doses of alprazolam. Additionally, other than for cenobamate 400 mg vs alprazolam 1.5 mg, cenobamate was also associated with a significantly lower stated preference for taking the drug again when compared to alprazolam. Although cenobamate 200 mg and 400 mg were associated with increased overall drug liking compared to placebo, mean peak responses to cenobamate were below to those reported following alprazolam administration. Assessment of the willingness to take the drug again showed similar responses for cenobamate 200 mg and placebo, and an increased preference for taking the drug again for cenobamate 400 mg compared to placebo. While responses on High VAS and Good Drug Effects VAS for both doses of cenobamate were associated with significant positive effects compared to placebo, these effects were significantly less pronounced relative to alprazolam 1.5 mg and 3.0 mg.

Based on the evaluation of the primary and secondary measures, both doses of cenobamate showed an abuse potential profile that were significantly lower compared to alprazolam in a population of recreational sedative users. The lower dose of cenobamate (200 mg) was similar to placebo on the primary measure (Drug Liking E_{max}) and on the key secondary measure of TDA. Although cenobamate 400 mg did differentiate from placebo on the primary and key secondary measures related to abuse potential, this study demonstrated that even with dose escalation, cenobamate 400 mg showed significantly decreased peak effects even when compared to the lowest dose of alprazolam (1.5 mg) on the majority of these measures. Furthermore, cenobamate was not associated with significant impairing effects on measures of cognition and psychomotor tasks, unlike alprazolam, and was associated with fewer AEs such as somnolence, euphoric mood, and

feeling of relaxation. Single doses of cenobamate 200 mg and 400 mg were well tolerated. Plasma concentrations of cenobamate observed in recreational sedative users were consistent with those measured in previous cenobamate clinical studies conducted in healthy subjects.

2.3. Data Location

The dataset used in the reviewer's analysis is located at

\\cdsesub1\evsprod\NDA212839\0001\m5\datasets\ykp3089c024\analysis\adam\datasets\adpd.xpt

2.4. Reviewer's Assessment

In this report, the reviewer used the following notations for treatments in Study YKP3089C024:

P – Placebo
A1.5 – Alprazolam 1.5 mg
A3.0 – Alprazolam 3.0 mg
C200 – Cenobamate 200 mg
C400 – Cenobamate 400 mg

2.4.1. Primary Analysis

The reviewer's primary analysis was performed using the Completers Population.

2.4.1.1. Descriptive Statistics

We first examined the maximum drug liking from each subject in the Qualification Phase, as shown in Figure 1.

Note that the orange line on the heat map separates females from males. The notations for treatments in Qualification Phase are as below:

P_Q – Placebo
A2.0 – Alprazolam 2.0mg

Figure 1 shows a successful selection for qualified subjects based on the selection criteria in the Qualification Phase except Subject (b) (6) Subject (b) (6) has the peak score in response to Alprazolam 2.0mg less than that of Placebo on drug liking. However, in Section 11.4.1.1 of Sponsor's study report, they stated that:

Subject (b) (6) *had one outlier response to placebo 30 minutes post-dose. Given that this subject demonstrated good discrimination between placebo and alprazolam at all other time points, and his overall performance was consistent with the expected response patterns, the subject was recommended to pass the qualification criteria.*

Therefore, the reviewer kept Subject (b) (6) for further analysis.

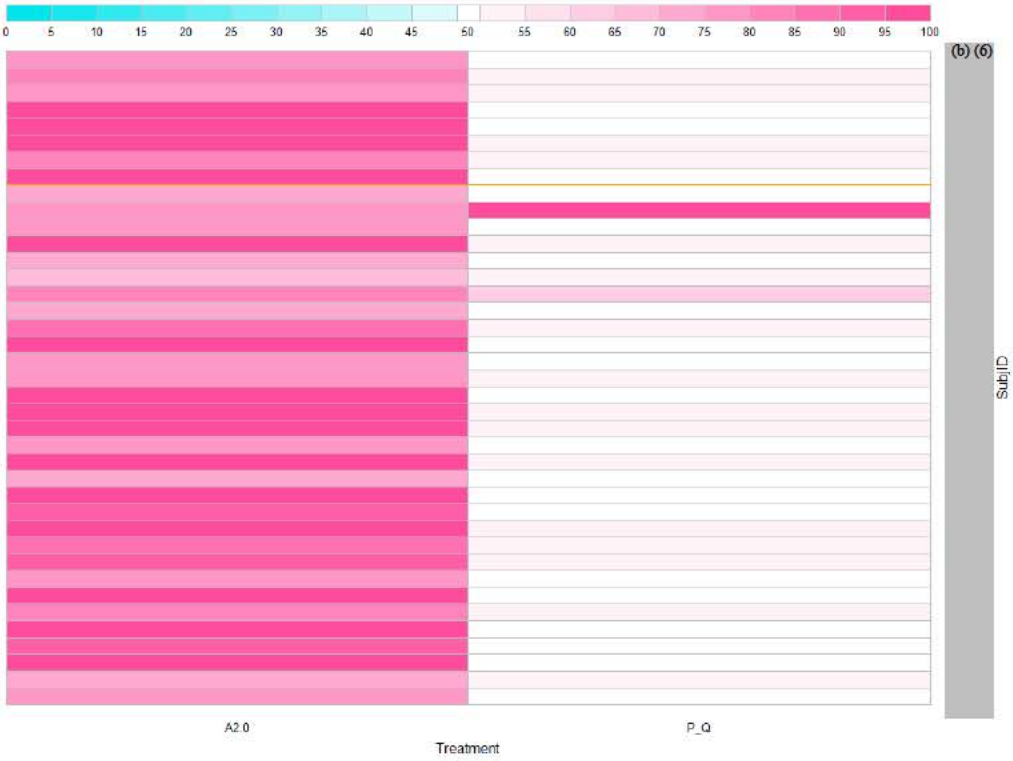


Figure 1: Heat Map by Treatment for Drug Liking E_{max} in the Qualification Phase (N = 39)

Table 1 summarizes the mean, standard deviation (SD), minimum (Min), the first quartile (Q_1), median (Med), the third quartile (Q_3), and maximum (Max) for the 5 treatments in the Treatment Phase for the primary endpoint Drug Liking E_{max}.

Table 1: Summary Statistics for Drug Liking E_{max} (N = 39)

TRT	Mean	SD	Min	Q_1	Med	Q_3	Max
P	52.3	5.3	50	50	51	51	72
A1.5	79.5	14.3	52	68	77	96	100
A3.0	85.3	13.5	57	74	87	99	100
C200	60.8	14.6	50	51	52	69	100
C400	68.8	16.5	50	52	68	77	100

As summarized in Table 1, there was some difference in means of maximum drug liking between the lower dose of Cenobamate and Placebo, while larger difference between the higher dose of Cenobamate and Placebo. The means of two doses of Alprazolam were 79.5 and 85.3. The reviewer examined data from the Qualification Phase and found that mean of maximum liking of Alprazolam 2.0 mg was 87.7 (SD = 10.9), which was similar to the results of Alprazolam 1.5 mg and 3.0 mg in the Treatment Phase. Detailed maximum drug liking from each subject in the Treatment Phase is shown in Figure 2.

Figure 2: Heat Map by Treatment for Drug Liking E_{max} in the Treatment Phase (N = 39)

In the Treatment Phase, subjects responded well to both Alprazolam 1.5 mg and 3.0 mg. Only 1 out of 39 subjects did not respond (maximum liking < 55) to Alprazolam 1.5 mg, and 3 subjects had maximum drug liking to placebo greater than 60.

Figure 3 is the mean time course profiles by treatment for Drug Liking VAS. Data were collected at hours 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, and 24. By carefully examining the data, missing responses exist for treatment Alprazolam 3.0 mg. Subject (b) (6) did not have responses at time points 0.5, 1, 2, and 2.5 hours post dose, Subject (b) (6) did not respond at 0.5, 1, 1.5, 2, 2.5, 3.5, and 4 hours post dose, Subject (b) (6) did not have response at 3 hours post dose, Subject (b) (6) had missing responses at 2.5 and 3 hours post dose, while Subject (b) (6) did not respond at 2 hours post dose. Detailed Drug Liking VAS at each time point from each subject in the Treatment Phase is shown in Figure 4.

Therefore, at the time points with missing responses, the mean Drug Liking VAS was averaged by non-missing values. The peak mean responses for Alprazolam 1.5 mg and 3.0 mg were 70.6 and 71.8, respectively, reached at 2 hours post dose. The peak mean responses for Cenobamate 200 mg and 400 mg were 56 and 64, reached at 1.5 and 1-hour post dose, respectively. Thus, Cenobamate reached the peak value faster than Alprazolam. From Figure 3, one may notice that the mean time course profiles of Cenobamate 200 mg and 400 mg were lower than both doses of Alprazolam after peak. However, both doses of Cenobamate still have relatively obvious separation from the mean time course profile of Placebo.

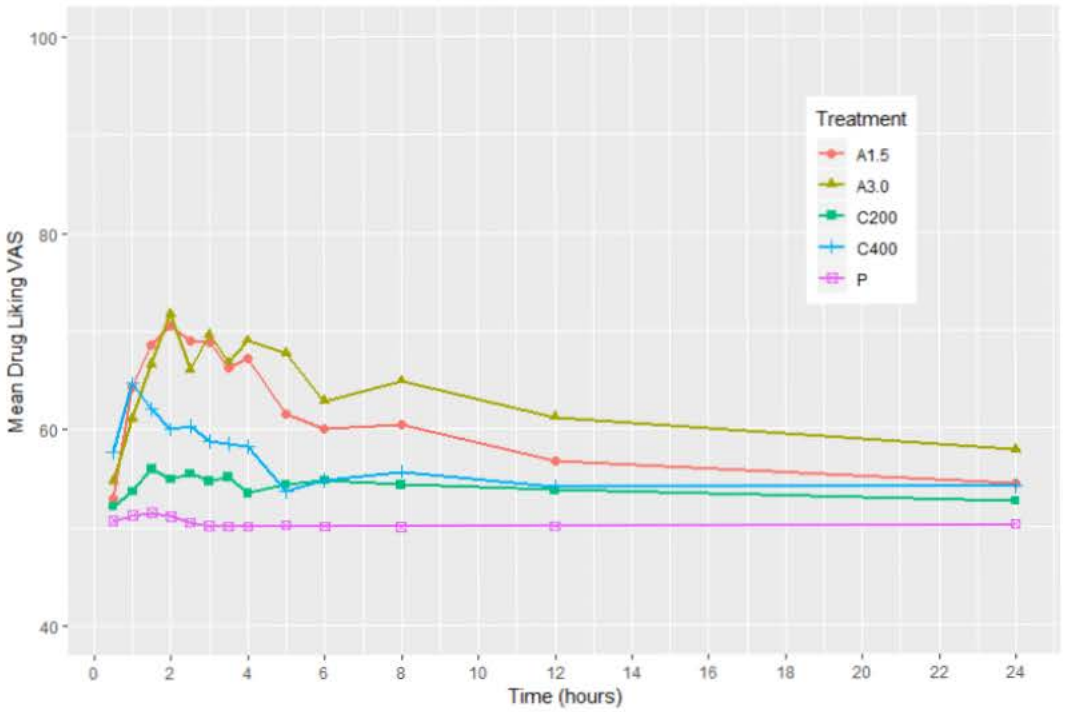


Figure 3: The Mean Time Course Profiles on Drug Liking VAS by Treatment (N = 39)

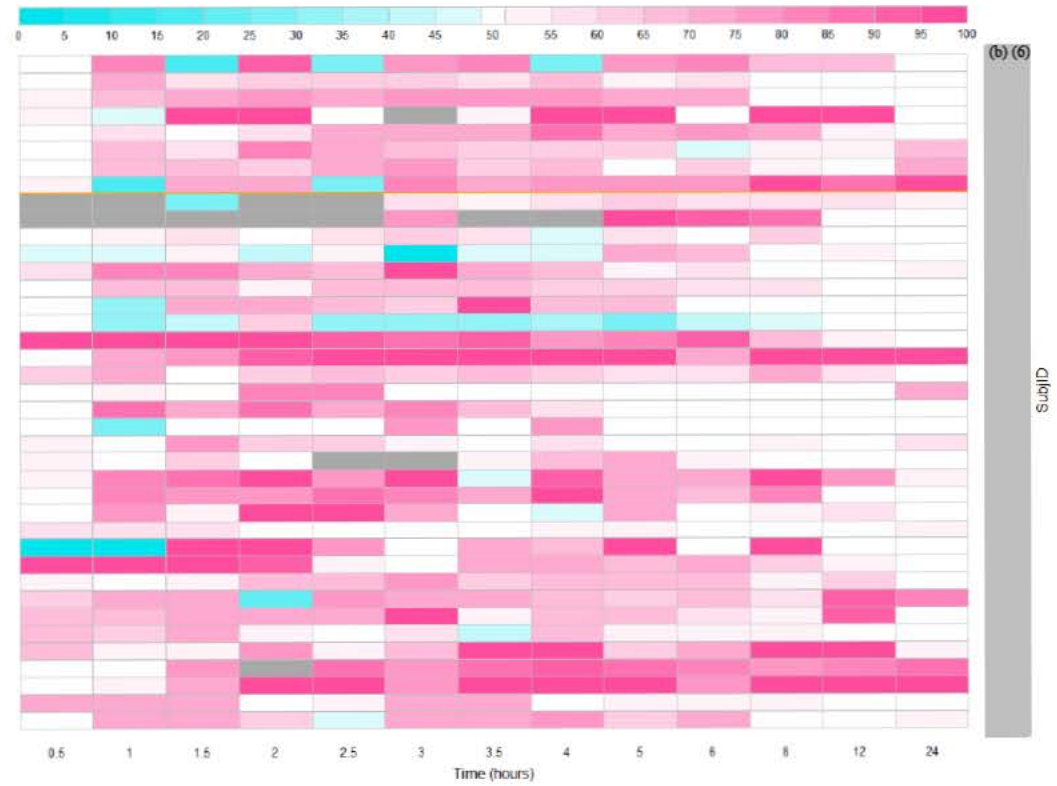


Figure 4: Heat Map by Time Point for Drug Liking VAS in the Treatment Phase (N = 39)

2.4.1.2. Statistical Testing

To evaluate abuse potential of Cenobamate, the following comparisons were performed for the primary endpoint, Drug Liking E_{max}.

1. A1.5 versus P
2. A3.0 versus P
3. A1.5 versus C200
4. A1.5 versus C400
5. A3.0 versus C200
6. A3.0 versus C400
7. C200 versus P
8. C400 versus P

The comparisons #1 and #2 were for the study validation. The comparisons #3 – #6 were for investigation of the abuse potential of the test drug Cenobamate, compared to the positive control Alprazolam. The comparisons #7 and #8 were to investigate whether the test drug Cenobamate had similar abuse potential compared to Placebo.

The statistical model used in the reviewer's primary analysis was a mixed-effects model which included treatment, period, sequence, site, and first-order carryover effect as fixed effects, subject as a random effect. With heteroscedasticity adjustment, the residuals from the mixed-effects model, excluding the carryover effects, are investigated for normality using the Shapiro-Wilk W-test. The results are presented in Table 2.

Table 2: Results from the W-test on Residuals for Drug Liking E_{max} (N = 39)

Endpoints	N	Skewness	W Statistic	p-value
Drug Liking E_{max}	39	0.60	0.9746	0.0013

The Shapiro-Wilk W-test on the residuals was statistically significant for Drug Liking E_{max} with a p-value 0.0013. Therefore, the normality assumption of the mixed-effects model was not satisfied, the distribution of the paired difference for each contrast was further examined. Table 3 shows skewness, W statistic, and p-value of the Shapiro-Wilk W-test for Drug Liking E_{max} on each paired difference.

As summarized in Table 3, the p-values of the W-test were greater than 0.05 for the paired differences between Alprazolam 1.5 mg and Placebo, and Alprazolam 3.0 mg and Cenobamate 400mg. The distribution was relatively symmetric (skewness = -0.5 to 0.5) for the paired differences between Alprazolam 1.5 mg and Placebo, Alprazolam 3.0 mg and Placebo, Alprazolam 3.0 mg and Cenobamate 200mg, Alprazolam 3.0 mg and Cenobamate 400mg, and Cenobamate 400mg and Placebo. Thus, for comparisons with paired differences that were not significantly departure from normal (W-test p-value $\geq$ 0.05) or the distribution was relatively symmetric

(skewness = -0.5 to 0.5), a paired *t*-test was used. Otherwise, for comparisons (see in red) with paired differences that were significantly departure from normal (W-test p-value < 0.05) and skewed (skewness < -0.5 or > 0.5), the sign test was performed.

Table 3: Results from the W-test on Paired Difference for Drug Liking E_{max} (N = 39)

Comparison	Skewness	W Statistic	p-value
A1.5 – P	0.24	0.9482	0.0717
A3.0 – P	-0.18	0.9298	0.0177
A1.5 – C200	0.52	0.9138	0.0056
A1.5 – C400	1.11	0.8599	0.0002
A3.0 – C200	0.01	0.9429	0.0474
A3.0 – C400	0.50	0.9462	0.0612
C200 – P	1.18	0.8371	< 0.0001
C400 – P	0.38	0.9304	0.0185

Based on the 2017 FDA Guidance (Assessment of Abuse Potential of Drugs Guidance for Industry – FDA), the following hypotheses were investigated:

1. $H_0 : \mu_C - \mu_P \le \delta_1$ vs. $H_a : \mu_C - \mu_P > \delta_1$,
2. $H_0 : \mu_C - \mu_T \le \delta_2$ vs. $H_a : \mu_C - \mu_T > \delta_2$, and
3. $H_0 : \mu_T - \mu_P \ge \delta_3$ vs. $H_a : \mu_T - \mu_P < \delta_3$,

where *C*, *T* and *P* denote Alprazolam, Cenobamate and Placebo; $\delta_1 = 15$ in order to be consistent with the value used in the Qualification Phase, $\delta_2 = 0$ (same as what the sponsor did), and $\delta_3 = 11$ (*Chen and Bonson, 2013*) in the primary analysis.

Table 4 summarizes the results from the reviewer's primary analysis. The reviewer's primary analysis showed that for Drug Liking E_{max},

- the mean differences between Alprazolam 1.5 mg and Placebo, and between Alprazolam 3.0 mg and Placebo were statistically significantly greater than 15 points, confirming the study validity;
- the mean of each dose of Alprazolam was statistically significantly greater than that of all doses of Cenobamate;
- the mean difference between Cenobamate 200 mg and Placebo was statistically significantly less than 11 points;
- it failed to reject the null hypothesis that the mean difference between Cenobamate 400 mg and Placebo was no less than 11 points with a p-value of 0.9745, which indicates that Cenobamate 400 mg has higher Drug Liking E_{max} than Placebo.

Table 4: Primary Analysis Results on Drug Liking E_{max} (N = 39)

Pairwise Comparison	Mean Diff /Med Diff	StdErr /IQR	p-value	95% CI	
				LCL	UCL
A1.5 – P	27.2	2.1	< 0.0001	23.7	Infty
A3.0 – P	33.0	2.0	< 0.0001	29.6	Infty
A1.5 – C200†	15.0	5, 27	< 0.0001	10.0	Infty
A1.5 – C400†	6.0	0, 18	0.0007	0	Infty
A3.0 – C200	24.5	2.6	< 0.0001	20.1	Infty
A3.0 – C400	16.5	2.5	< 0.0001	12.2	Infty
C200 – P†	1.0	0, 14	0.0038	-Infty	6.0
C400 – P	16.5	2.7	0.9745	-Infty	21.1

† The sign test was performed. The median difference and the interquartile range as well as the distribution free 95% confidence interval of the median difference are listed.

2.4.2. Secondary Analysis

The sponsor pre-specified many key secondary endpoints. Per the CSS Pharmacologist Dr. Edward Hawkins's suggestion, Overall Drug Liking E_{max}, Take Drug Again E_{max}, High E_{max}, and Good Drug Effects E_{max} were included in the reviewer's secondary analysis. Note that Overall Drug Liking E_{max} and Take Drug Again E_{max} were on a bipolar visual analog scale, while High E_{max} and Good Drug Effects E_{max} were on a unipolar visual analog scale. Also note that pre-dose responses were collected for High VAS, thus E_{max} was derived based on change from pre-dose response for High VAS.

2.4.2.1. Descriptive Statistics

Figures 5 – 8 are the heat maps by treatment for Overall Drug Liking E_{max}, Take Drug Again E_{max}, High E_{max} and Good Drug Effects E_{max} in the Treatment Phase.

Figure 5: Heat Map by Treatment for Overall Drug Liking E_{max} in the Treatment Phase (N = 39)

Figure 6: Heat Map by Treatment for Take Drug Again E_{max} in the Treatment Phase (N = 39)

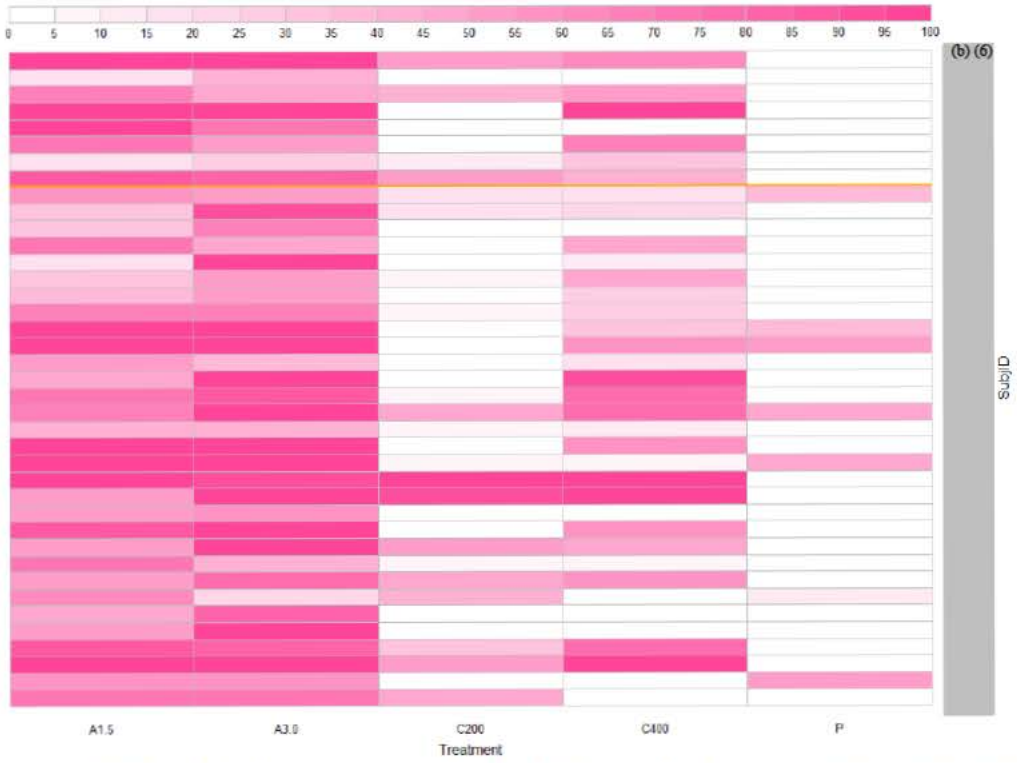


Figure 7: Heat Map by Treatment for High E_{max} in the Treatment Phase (N = 39)

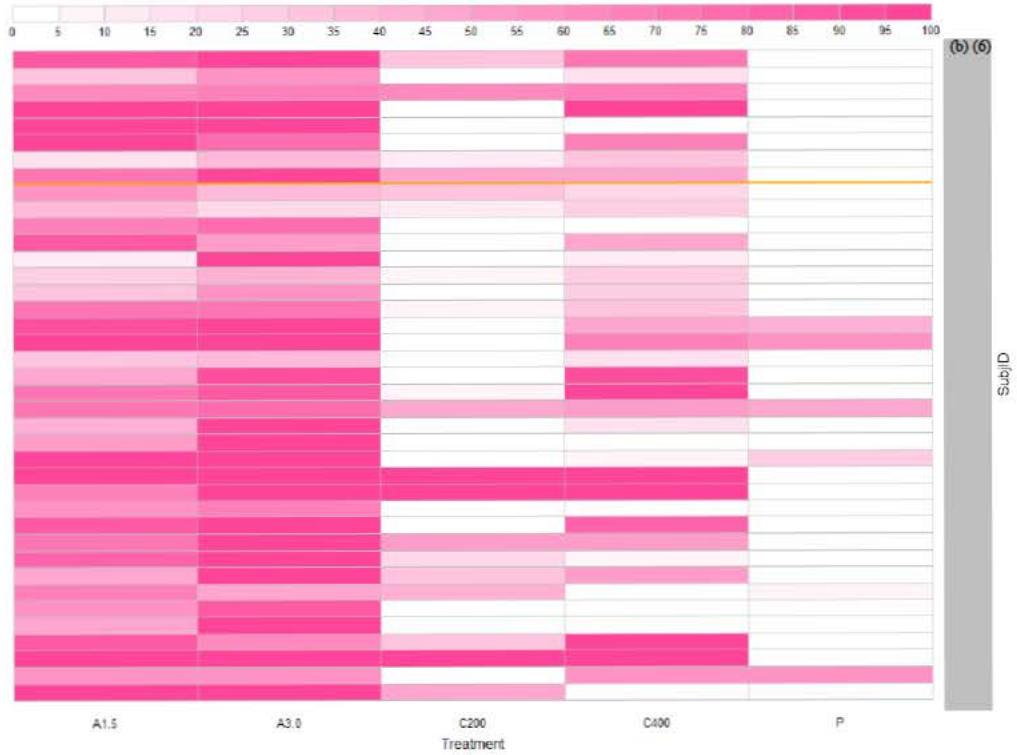


Figure 8: Heat Map by Treatment for Good Drug Effects E_{max} in the Treatment Phase (N = 39)

The reviewer did the secondary analysis for the Completers Population (N = 39). Table 5 summarizes the mean, standard deviation (SD), minimum (Min), the first quartile (Q_1), median (Med), the third quartile (Q_3), and maximum (Max) for the 5 treatments in the study for the secondary endpoint Overall Drug Liking E_{max}, Take Drug Again E_{max}, High E_{max}, and Good Drug Effects E_{max}.

Table 5: Summary Statistics for Overall Drug Liking E_{max}, Take Drug Again E_{max}, High E_{max} and Good Drug Effects E_{max} (N = 39)

Measure	TRT	Mean	SD	Min	Q_1	Med	Q_3	Max
Overall Drug Liking E_{max}	P	53.0	8.5	50	50	50	50	90
	A1.5	81.2	18.8	26	73	81	99	100
	A3.0	84.9	18.5	27	75	92	100	100
	C200	62.2	16.7	47	50	51	74	100
	C400	69.4	18.9	45	51	69	77	100
Take Drug Again E_{max}	P	53.0	9.5	50	50	50	51	100
	A1.5	80.7	21.0	31	69	80	100	100
	A3.0	84.1	20.7	24	72	91	100	100
	C200	61.3	17.9	43	50	51	70	100
	C400	69.1	23.2	0	50	69	100	100
High E_{max}	P	8.1	17.4	0	0	0	2	55
	A1.5	65.6	25.8	16	49	67	87	100
	A3.0	75.2	24.0	24	54	82	99	100
	C200	19.6	26.7	0	0	6	45	100
	C400	40.0	33.8	0	9	35	62	100
Good Drug Effects E_{max}	P	6.7	16.4	0	0	0	1	59
	A1.5	67.8	25.6	11	49	70	89	100
	A3.0	79.6	23.7	24	59	91	100	100
	C200	21.2	29.7	0	1	4	35	100
	C400	42.9	35.6	0	9	33	70	100

The bar charts for Overall Drug Liking VAS and Take Drug Again VAS as well as the mean time course profiles by treatment for High E_{max} and Good Drug Effects E_{max} are presented in Figures 9 – 12, respectively.

By average, the mean Overall Drug Liking responses for Alprazolam 1.5 mg and 3.0 mg were much greater than each dose of Cenobamate at both Hours 12 and 24. The responses for the higher dose of Alprazolam was slightly greater than the lower dose, while Cenobamate showed the same phenomenon. The responses for Placebo were around 50 at both 12 and 24 hours post dose. Similar results were also observed for the mean Take Drug Again VAS.

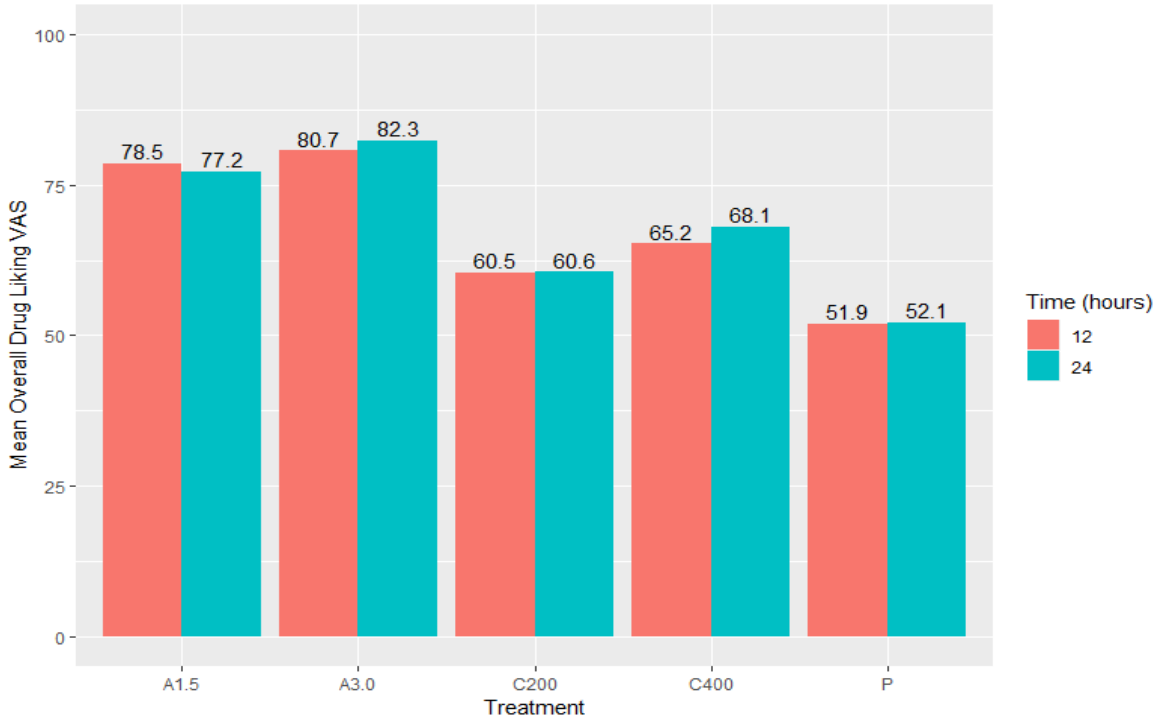


Figure 9: Mean Responses at Hours 12 and 24 by Treatment for Overall Drug Liking VAS (N = 39)

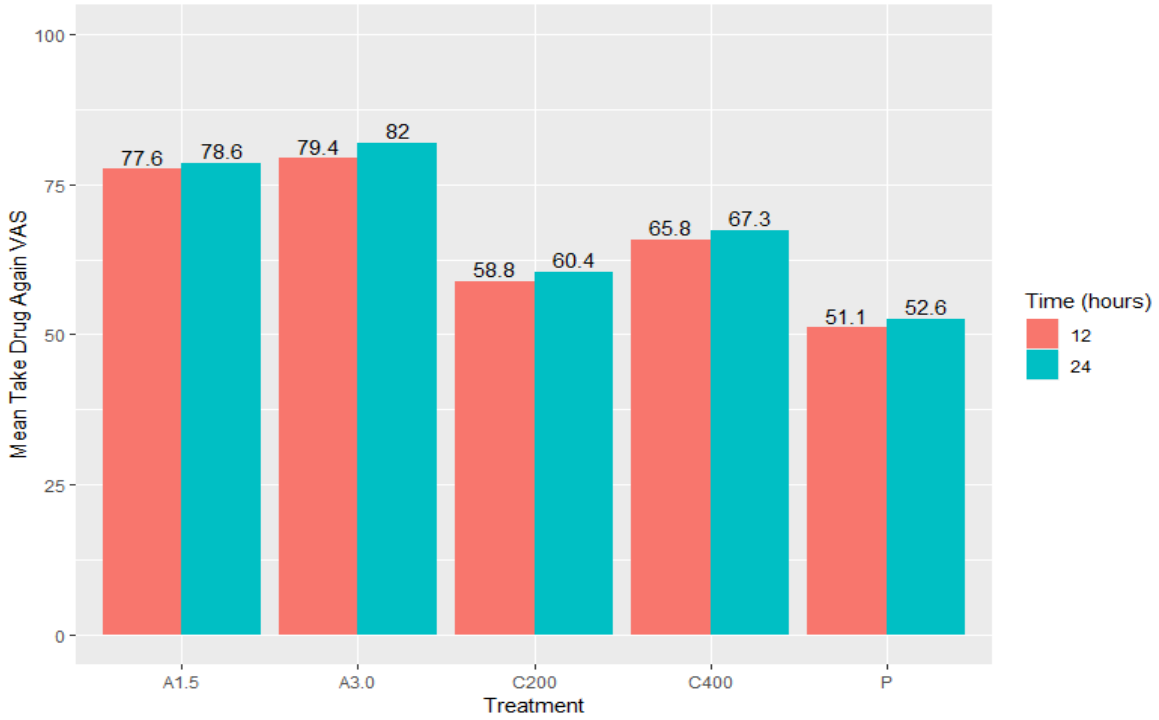


Figure 10: Mean Responses at Hours 12 and 24 by Treatment for Take Drug Again VAS (N = 39)

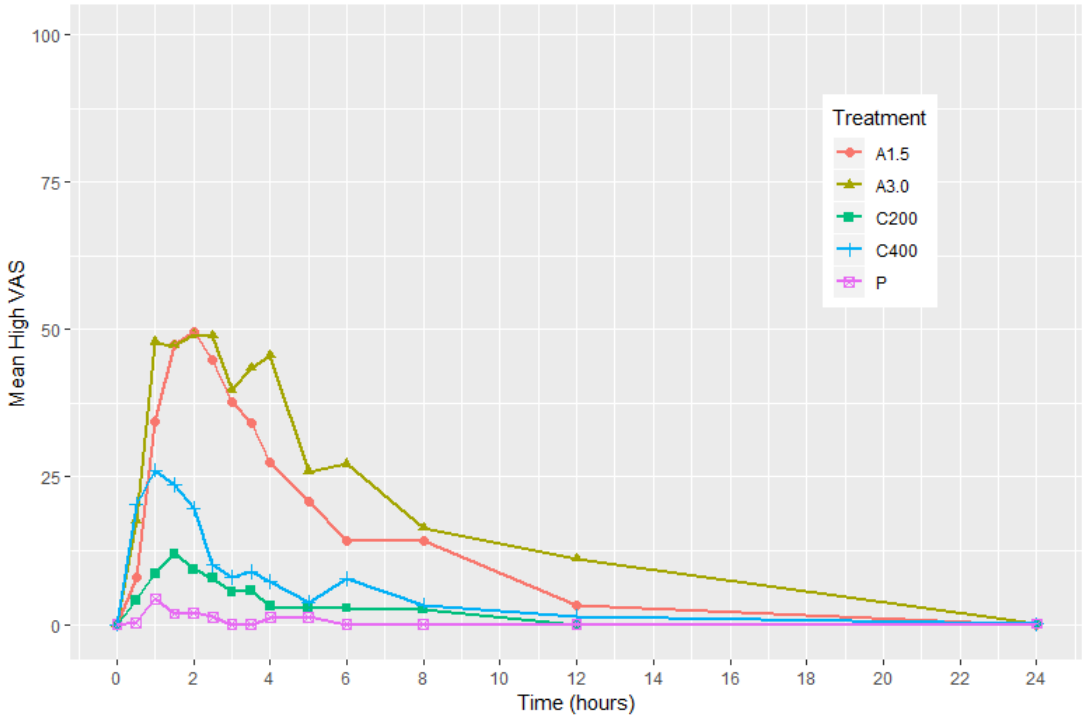


Figure 11: The Mean Time Course Profiles on High VAS by Treatment (N = 39)

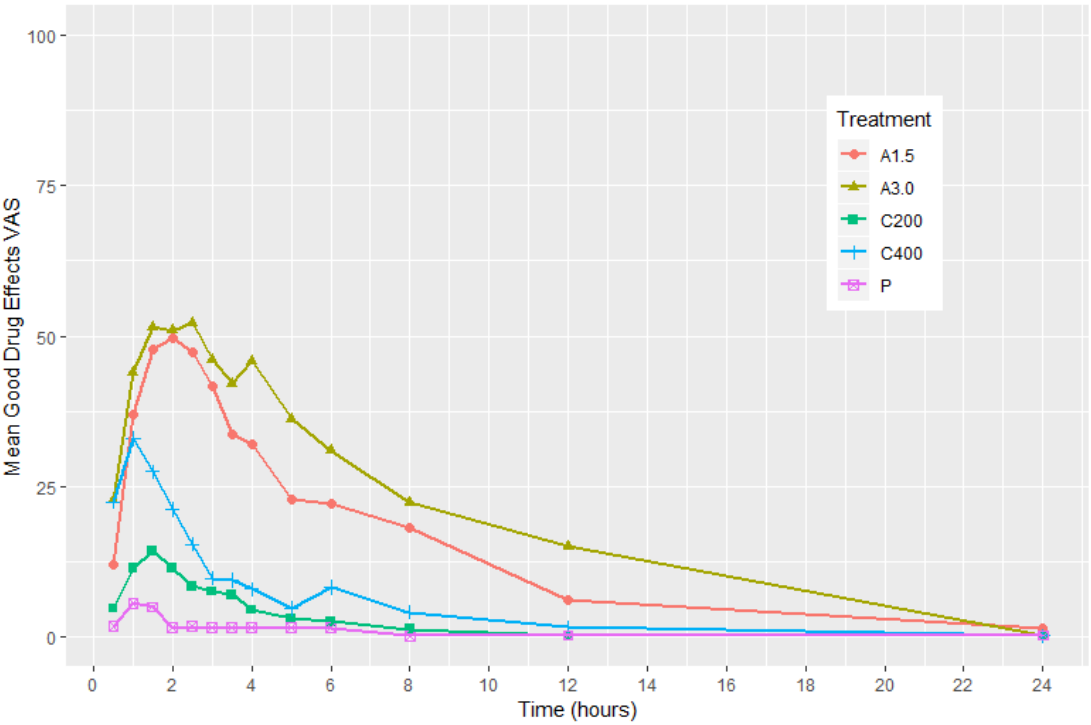


Figure 12: The Mean Time Course Profiles on Good Drug Effects VAS by Treatment (N = 39)

For High VAS, the peak mean responses for Alprazolam 1.5 mg and 3.0 mg were 49.7 and 49.2, respectively, reached at 2 hours post dose; Cenobamate 200 mg and 400 mg reached the peak mean response of 11.9 at 1.5 hours post dose, and 26.1 at 1-hour post dose, respectively. While for Good Drug Effects VAS, the peak mean responses for Alprazolam 1.5 mg and 3.0 mg were 49.7 reached at 2 hours post dose, and 52.1 reached at 2.5 hours post dose, respectively; Cenobamate 200 mg and 400 mg reached the peak mean response of 14.2 at 1.5 hours post dose, and 32.9 at 1-hour post dose, respectively. Thus, Cenobamate reached the peak value faster than Alprazolam.

For both High VAS and Good Drug Effects VAS, the mean time course profiles of Cenobamate 200 mg and 400 mg were lower than each dose of Alprazolam after peak. However, both doses of Cenobamate still have relatively obvious separation from the mean time course profile of Placebo.

2.4.2.2. Statistical Testing

The statistical model used in the reviewer's secondary analysis was a mixed-effects model which included treatment, period, sequence, site, and first-order carryover effect as fixed effects, subject as a random effect. For the High E_{max}, pre-dose responses were collected, thus also included as a covariate in the model. With heteroscedasticity adjustment, the residuals from the mixed-effects model, excluding the carryover effects, are investigated for normality using the Shapiro-Wilk W-test. The results are presented in Table 6.

Table 6: Results from the W-test on Residuals for Overall Drug Liking E_{max}, Take Drug Again E_{max}, High E_{max} and Good Drug Effects E_{max} (N = 39)

Endpoints	Skewness	W Statistic	p-value
Overall Drug Liking E_{max}	-0.20	0.9919	0.3544
Take Drug Again E_{max}	-0.61	0.9716	0.0005
High E_{max}	0.26	0.9915	0.3098
Good Drug Effects E_{max}	0.39	0.9859	0.0494

The p-values of the W-test in Table 6 indicate that the residuals were approximately normally distributed for Overall Drug Liking E_{max} and High E_{max}. When including first-order carryover effect in the model, the p-value for the carryover effect was greater than 0.25. Hence, the first-order carryover effect was found to be non-significant at the 0.25 level, then the term was to be dropped from the analysis model. Table 7 shows the least square mean and standard error of each treatment for Overall Drug Liking E_{max} and High E_{max}.

Table 7: Least Square Mean Estimation for Overall Drug Liking E_{max} and High E_{max} (N = 39)

TRT	Overall Drug Liking E_{max}		High E_{max}	
	LSMean	StdErr	LSMean	StdErr
P	51.5	1.8	6.4	3.6
A1.5	79.6	2.8	63.8	4.1
A3.0	83.4	3.0	73.1	3.9
C200	60.6	2.6	16.9	4.7
C400	67.9	3.0	38.3	5.4

The hypotheses used in the secondary analysis were the same as those in the primary analysis, except the comparison between Cenobamate and Placebo. Note that the test value 11 for this comparison was studied only for the bipolar Drug Liking VAS. Also note that for a fixed sample size, increasing the type I error will decrease the type II error. Therefore, a two-sided test with a test value 0 and type I error equal to 0.1 was performed, and the 90% confidence interval was also calculated for this comparison. Table 8 summarizes the results from the reviewer's secondary analysis for Overall Drug Liking E_{max} and High E_{max}.

Table 8: Secondary Analysis Results on Overall Drug Liking E_{max} and High E_{max} (N = 39)

Measure	Pairwise Comparison	LSmean Diff	StdErr	p-value	95% CI / 90% CI	
					LCL	UCL
Overall Drug Liking E_{max}	A1.5 – P	28.1	2.8	< 0.0001	23.5	Infty
	A3.0 – P	31.9	3.0	< 0.0001	26.9	Infty
	A1.5 – C200	19.0	3.3	< 0.0001	13.5	Infty
	A1.5 – C400	11.7	3.7	0.0012	5.6	Infty
	A3.0 – C200	22.8	3.5	< 0.0001	17.0	Infty
	A3.0 – C400	15.5	3.8	< 0.0001	9.1	Infty
	C200 – P*	9.1	2.5	0.0008	4.9	13.4
	C400 – P*	16.5	3.0	< 0.0001	11.4	21.5
High E_{max}	A1.5 – P	57.4	4.3	< 0.0001	50.1	Infty
	A3.0 – P	66.7	4.1	< 0.0001	59.7	Infty
	A1.5 – C200	46.9	5.3	< 0.0001	38.0	Infty
	A1.5 – C400	25.5	5.9	< 0.0001	15.6	Infty
	A3.0 – C200	56.1	5.1	< 0.0001	47.6	Infty
	A3.0 – C400	34.8	5.8	< 0.0001	25.1	Infty
	C200 – P*	10.6	4.9	0.0354	2.4	18.7
	C400 – P*	31.9	5.6	< 0.0001	22.5	41.2

* Two-sided test was performed.

Table 6 also shows that the W-test was statistically significant (p-value < 0.05) for Take Drug Again E_{max} and Good Drug Effects E_{max}. Therefore, the normality assumption of the mixed-effects model was not satisfied, the distribution of the paired differences for these two endpoints was further examined. Table 9 shows skewness, W statistic, and p-value of the Shapiro-Wilk W-test for Take Drug Again E_{max} and Good Drug Effects E_{max} on each paired difference.

Table 9: Results from the W-test on Paired Difference for Take Drug Again E_{max} and Good Drug Effects E_{max} (N = 39)

Measure	Comparison	Skewness	W Statistic	p-value
Take Drug Again E_{max}	A1.5 – P	-0.58	0.8860	0.0009
	A3.0 – P	-1.08	0.8390	< 0.0001
	A1.5 – C200	-0.14	0.9293	0.0171
	A1.5 – C400	1.48	0.8377	< 0.0001
	A3.0 – C200	-0.77	0.8959	0.00017
	A3.0 – C400	0.42	0.9434	0.0494
	C200 – P	1.28	0.7670	< 0.0001
	C400 – P	-0.16	0.9016	0.0025
Good Drug Effects E_{max}	A1.5 – P	-0.26	0.9612	0.1950
	A3.0 – P	-0.74	0.8614	0.0002
	A1.5 – C200	-0.01	0.9627	0.2199
	A1.5 – C400	0.42	0.9703	0.3822
	A3.0 – C200	-0.40	0.9038	0.0028
	A3.0 – C400	0.32	0.9217	0.0098
	C200 – P	0.67	0.8759	0.0005
	C400 – P	0.56	0.8835	0.0008

As summarized in Table 9, for comparisons with paired differences that were not significantly departure from normal (W-test p-value ≥ 0.05) or the distribution was relatively symmetric (skewness = -0.5 to 0.5), a paired *t*-test was used. Otherwise, for comparisons (see in red) with paired differences that were significantly departure from normal (W-test p-value < 0.05) and skewed (skewness < -0.5 or > 0.5), the sign test was performed. Table 10 summarizes the results from the reviewer's secondary analysis for Take Drug Again E_{max} and Good Drug Effects E_{max}.

Table 10: Secondary Analysis Results on Take Drug Again E_{max} and Good Drug Effects E_{max} (N = 39)

Measure	Pairwise Comparison	Mean Diff /Med Diff	StdErr /IQR	p-value	95% CI / 90% CI	
					LCL	UCL
Take Drug Again E_{max}	A1.5 – P†	28.0	15, 49	0.0013	24.0	Infty
	A3.0 – P†	38.0	21, 50	< 0.0001	26.0	Infty
	A1.5 – C200	19.4	3.6	< 0.0001	13.3	Infty
	A1.5 – C400†	0.0	-1, 18	0.0925	0	Infty
	A3.0 – C200†	25.0	1, 49	< 0.0001	20.0	Infty
	A3.0 – C400	15.0	4.5	0.0009	7.4	Infty
	C200 – P*†	1.0	0, 14	0.0094	0	2.0
	C400 – P*	16.1	3.7	0.0001	9.9	22.4
Good Drug Effects E_{max}	A1.5 – P	61.2	4.4	< 0.0001	53.8	Infty
	A3.0 – P†	79.0	51, 99	< 0.0001	66.0	Infty
	A1.5 – C200	46.6	5.3	< 0.0001	37.7	Infty
	A1.5 – C400	24.9	5.6	< 0.0001	15.4	Infty
	A3.0 – C200	58.3	5.5	< 0.0001	49.1	Infty
	A3.0 – C400	36.6	6.2	< 0.0001	26.3	Infty
	C200 – P*†	1.0	0, 33	0.0014	0	11.0
	C400 – P*†	27.0	0, 70	< 0.0001	11.0	48.0

* Two-sided test was performed.
† The sign test was performed. The median difference and the interquartile range as well as the distribution free 95% / 90% confidence interval of the median difference are listed.

The results from the reviewer's secondary analysis showed that for Overall Drug Liking E_{max}, Take Drug Again E_{max}, High E_{max} and Good Drug Effects E_{max},

- the mean differences between Alprazolam 1.5 mg and Placebo, and between Alprazolam 3.0 mg and Placebo were statistically significantly greater than 15 points;
- the mean of each dose of Alprazolam was statistically significantly greater than that of all doses of Cenobamate, **except the comparison between Alprazolam 1.5 mg and Cenobamate 400 mg for Take Drug Again E_{max};**
- each dose of Cenobamate had statistically significantly larger mean than Placebo.

2.4.3. Sensitivity Analysis

After carefully examining the data for key secondary endpoints, the reviewer found that

- Subjects [redacted] responded 50 or 51 points for all treatments to both Overall Drug Liking and Take Drug Again at all time points; Subject [redacted] responded 50 or 51 points for all treatments to Take Drug Again at all time points;
- Subject [redacted] had maximum Overall Drug Liking and Take Drug Again greater or equal to 90 for all treatments;
- Subject [redacted] responded less than 32 points to both doses of Alprazolam, and responded 50 points for Cenobamate and Placebo at all time points, for Overall Drug Liking and Take Drug Again.
- Subjects [redacted] responded neutral score to one dose of Alprazolam;
- Subjects [redacted] had a maximum High greater than 40 points to Placebo, and a maximum Good Drug Effects greater than 25 points to Placebo; Subject [redacted] had a maximum High equal to 40 points to Placebo.

These same responses to all treatments and large placebo responses would reduce the mean difference between Alprazolam and Placebo, hence made it difficult to show significant difference between positive control and placebo. These issues may also reduce the mean difference between Alprazolam and Cenobamate, which might lead to no significance of relative abuse potential of positive control compared to the test drug. In addition, these issues would reduce the mean difference between Cenobamate and Placebo, which made it easier to show no much difference in means between test product and placebo. To make some sense from the existing data, the reviewer's sensitivity analysis eliminated the following subjects for each secondary endpoint:

1. Overall Drug Liking E_{max}: Subjects [redacted]
2. Take Drug Again E_{max}: Subjects [redacted]
3. High E_{max}: Subjects [redacted]
4. Good Drug Effects E_{max}: Subjects [redacted]

After eliminating subjects with similar responses at all time points across all treatments or large Placebo response, the numbers of subjects included in the sensitivity analysis were 35, 34, 33 and 34 for Overall Drug Liking E_{max}, Take Drug Again E_{max}, High E_{max}, and Good Drug Effects E_{max}, respectively.

2.4.3.1. Descriptive Statistics

Table 11 summarizes the mean, standard deviation (SD), minimum (Min), the first quartile (Q_1), median (Med), the third quartile (Q_3), and maximum (Max) for the 5 treatments in the study for the secondary endpoint Overall Drug Liking E_{max}, Take Drug Again E_{max}, High E_{max}, and Good Drug Effects E_{max}.

Table 11: Summary Statistics for Overall Drug Liking E_{max}, Take Drug Again E_{max}, High E_{max} and Good Drug Effects E_{max}

Measure	TRT	Mean	SD	Min	Q_1	Med	Q_3	Max
Overall Drug Liking E_{max} N = 35	P	52.2	6.2	50	50	50	50	72
	A1.5	84.2	15.4	50	74	86	100	100
	A3.0	88.2	14.0	51	77	98	100	100
	C200	62.2	16.1	47	50	54	74	100
	C400	70.2	18.4	45	51	71	77	100
Take Drug Again E_{max} N = 34	P	51.9	5.9	50	50	50	51	78
	A1.5	84.3	18.0	34	74	91	100	100
	A3.0	88.5	15.9	34	76	97.5	100	100
	C200	61.5	17.6	43	50	51	70	100
	C400	70.4	23.4	0	50	69	100	100
High E_{max} N = 33	P	0.8	2.3	0	0	0	1	12
	A1.5	62.9	25.8	16	47	65	86	100
	A3.0	73.5	24.2	24	54	80	98	100
	C200	21.0	27.9	0	0	7	45	100
	C400	41.2	34.7	0	10	42	62	100
Good Drug Effects E_{max} N = 34	P	0.7	1.8	0	0	0	1	10
	A1.5	65.4	25.8	11	48	67	88	100
	A3.0	78.6	24.5	24	59	90.5	100	100
	C200	22.7	30.7	0	1	7	35	100
	C400	42.4	37.3	0	9	31.5	72	100

The bar charts for Overall Drug Liking VAS and Take Drug Again VAS as well as the mean time course profiles by treatment for High E_{max} and Good Drug Effects E_{max} are presented in Figures 13 – 16, respectively.

By average, the mean Overall Drug Liking responses for Alprazolam 1.5 mg and 3.0 mg were much greater than each dose of Cenobamate at both Hours 12 and 24. The responses for the higher dose of Alprazolam was slightly greater than the lower dose, while Cenobamate showed the same phenomenon. The responses for Placebo were around 50 at both 12 and 24 hours post dose. Similar results were also observed for the mean Take Drug Again VAS.

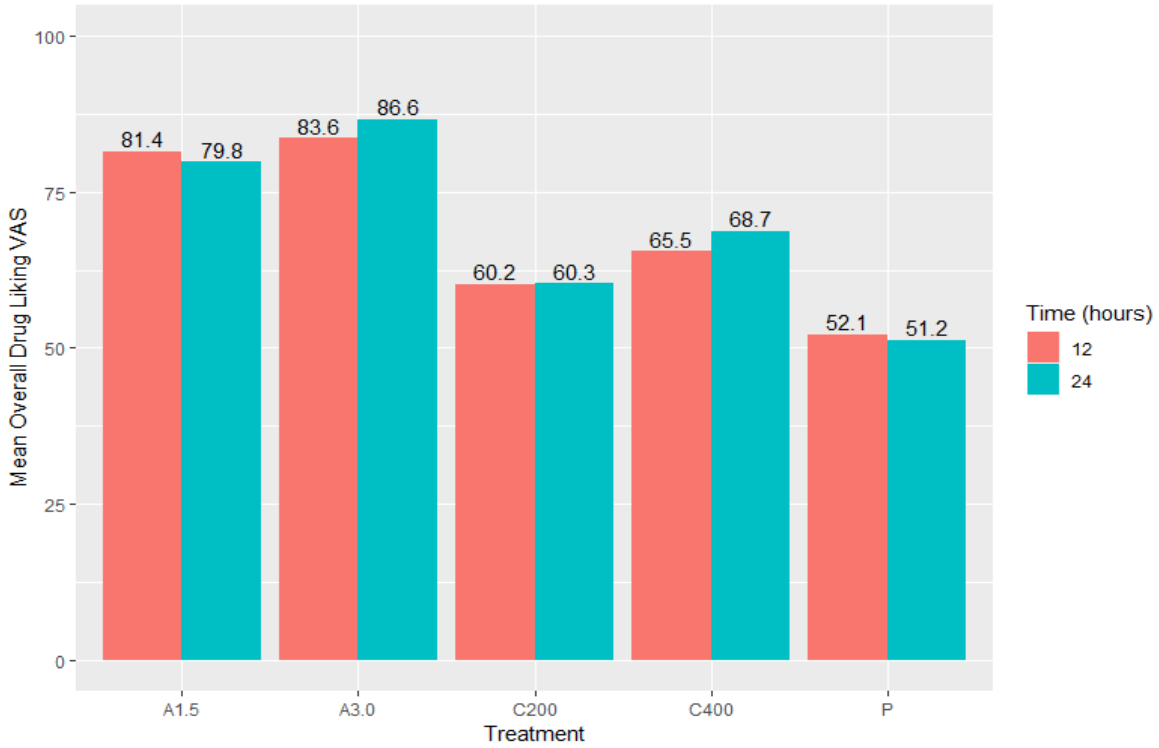


Figure 13: Mean Responses at Hours 12 and 24 by Treatment for Overall Drug Liking VAS (N = 35)

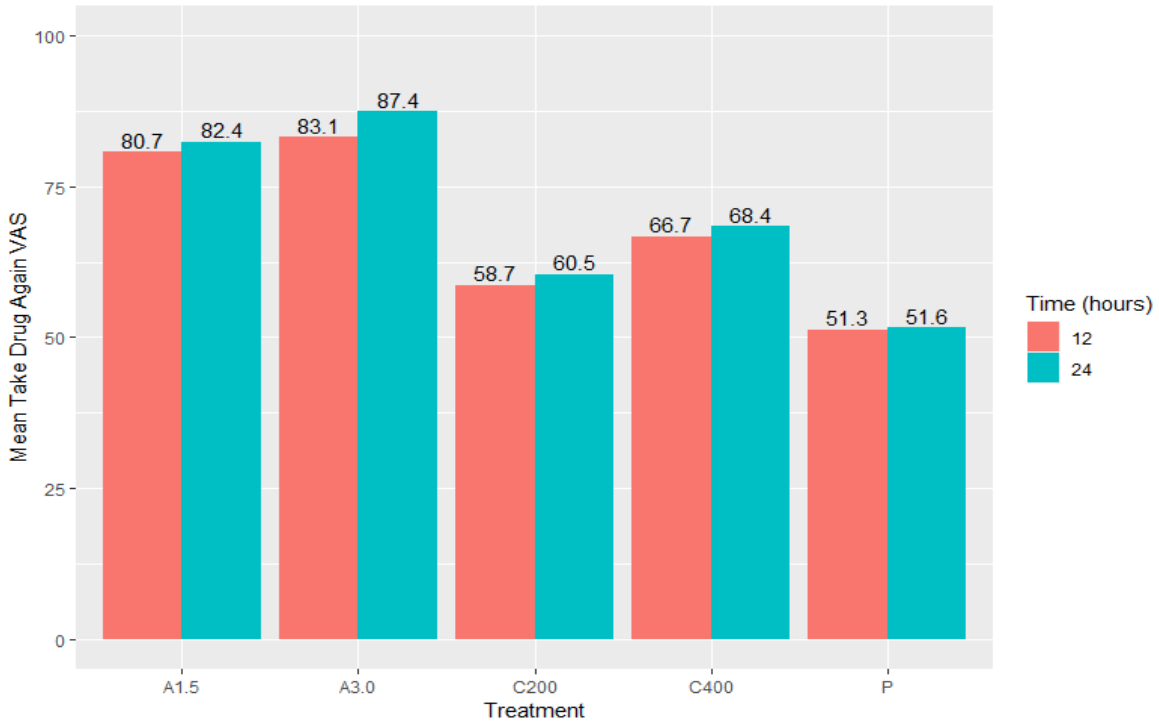


Figure 14: Mean Responses at Hours 12 and 24 by Treatment for Take Drug Again VAS (N = 34)

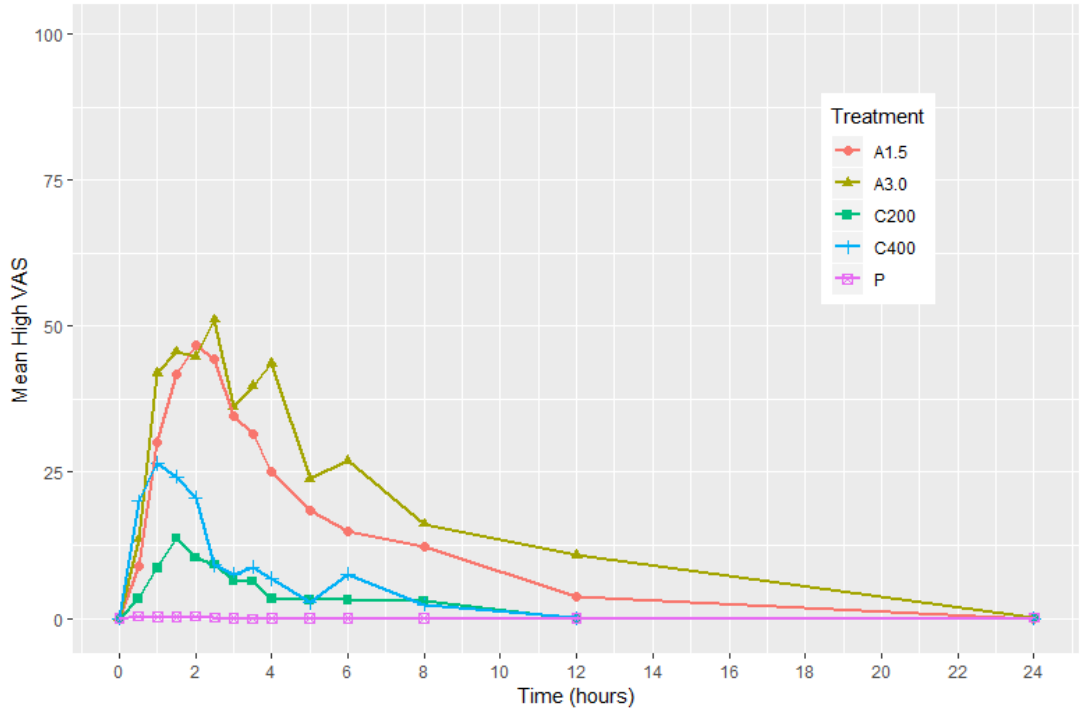


Figure 15: The Mean Time Course Profiles on High VAS by Treatment (N = 33)

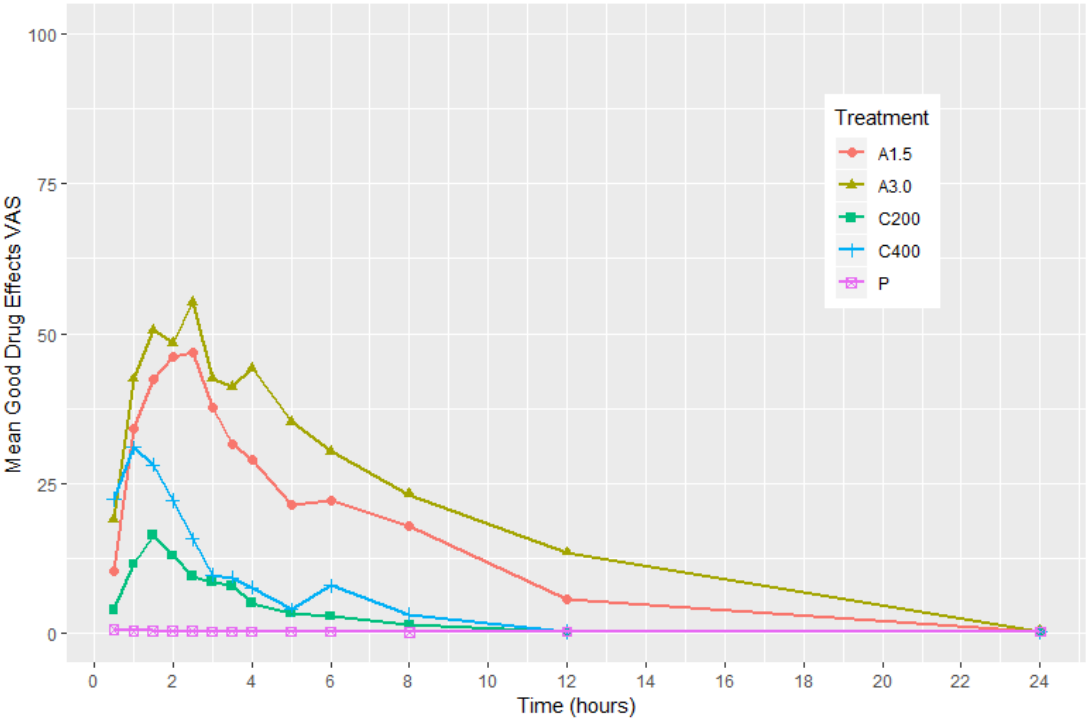


Figure 16: The Mean Time Course Profiles on Good Drug Effects VAS by Treatment (N = 34)

For High VAS, the peak mean responses for Alprazolam 1.5 mg and 3.0 mg were 46.9 reached at 2 hours post dose, and 51.1 reached at 2.5 hours post dose, respectively; Cenobamate 200 mg and 400 mg reached the peak mean response of 13.7 at 1.5 hours post dose, and 26.5 at 1-hour post dose, respectively. While for Good Drug Effects VAS, the peak mean responses for Alprazolam 1.5 mg and 3.0 mg were 46.7 and 55.2, respectively, reached at 2.5 hours post dose; Cenobamate 200 mg and 400 mg reached the peak mean response of 16.3 at 1.5 hours post dose, and 30.9 at 1-hour post dose, respectively. Thus, Cenobamate reached the peak value faster than Alprazolam.

For both High VAS and Good Drug Effects VAS, the mean time course profiles of Cenobamate 200 mg and 400 mg were lower than each dose of Alprazolam after peak. However, both doses of Cenobamate still have relatively obvious separation from the mean time course profile of Placebo.

2.4.3.2. Statistical Testing

The statistical model used in the reviewer's sensitivity analysis was a mixed-effects model which included treatment, period, sequence, site, and first-order carryover effect as fixed effects, subject as a random effect. For the High E_{max}, pre-dose responses were collected, thus also included as a covariate in the model. With heteroscedasticity adjustment, the residuals from the mixed-effects model, excluding the carryover effects, are investigated for normality using the Shapiro-Wilk W-test. The results are presented in Table 12.

Table 12: Results from the W-test on Residuals for Overall Drug Liking E_{max}, Take Drug Again E_{max}, High E_{max} and Good Drug Effects E_{max}

Endpoints	N	Skewness	W Statistic	p-value
Overall Drug Liking E_{max}	35	0.12	0.9938	0.6768
Take Drug Again E_{max}	34	-0.50	0.9620	0.0001
High E_{max}	33	0.39	0.9821	0.0318
Good Drug Effects E_{max}	34	0.51	0.9767	0.0058

The p-values of the W-test in Table 12 indicate that the residuals were approximately normally distributed for Overall Drug Liking E_{max}. When including first-order carryover effect in the model, the p-value for the carryover effect was greater than 0.25. Hence, the first-order carryover effect was found to be non-significant at the 0.25 level, then the term was to be dropped from the analysis model. Table 13 shows the least square mean and standard error of each treatment for Overall Drug Liking E_{max}.

Table 13: Least Square Mean Estimation for Overall Drug Liking E_{max} (N = 35)

TRT	LSMean	StdErr
P	51.3	1.3
A1.5	83.4	2.4
A3.0	87.4	2.4
C200	61.0	2.6
C400	69.3	3.2

The hypotheses used in the sensitivity analysis were the same as those in the primary analysis, except the comparison between Cenobamate and Placebo. Note that the test value 11 for this comparison was studied only for the bipolar Drug Liking VAS. Also note that for a fixed sample size, increasing the type I error will decrease the type II error. Therefore, a two-sided test with a test value 0 and type I error equal to 0.1 was performed, and the 90% confidence interval was also calculated for this comparison. Table 14 summarizes the results from the reviewer's sensitivity analysis for Overall Drug Liking E_{max}.

Table 14: Sensitivity Analysis Results on Overall Drug Liking E_{max} (N = 35)

Pairwise Comparison	LSmean Diff	StdErr	p-value	95% CI / 90% CI	
				LCL	UCL
A1.5 – P	32.1	2.4	< 0.0001	28.0	Infty
A3.0 – P	36.1	2.5	< 0.0001	31.9	Infty
A1.5 – C200	22.5	3.4	< 0.0001	16.8	Infty
A1.5 – C400	14.2	3.8	0.0002	7.8	Infty
A3.0 – C200	26.4	3.4	< 0.0001	20.7	Infty
A3.0 – C400	18.1	3.8	< 0.0001	11.7	Infty
C200 – P*	9.7	2.7	0.0009	5.2	14.2
C400 – P*	18.0	3.2	< 0.0001	12.5	23.4

* Two-sided test was performed.

Table 12 also shows that the W-test was statistically significant (p-value < 0.05) for Take Drug Again E_{max}, High E_{max}, and Good Drug Effects E_{max}. Therefore, the normality assumption of the mixed-effects model was not satisfied, the distribution of the paired differences for these three endpoints was further examined. Table 15 shows skewness, W statistic, and p-value of the Shapiro-Wilk W-test for Take Drug Again E_{max}, High E_{max}, and Good Drug Effects E_{max} on each paired difference.

Table 15: Results from the W-test on Paired Difference for Take Drug Again E_{max}, High E_{max}, and Good Drug Effects E_{max}

Measure	Comparison	Skewness	W Statistic	p-value
Take Drug Again E_{max} N = 34	A1.5 – P	-0.85	0.8705	0.0008
	A3.0 – P	-1.47	0.8079	< 0.0001
	A1.5 – C200	-0.42	0.9268	0.0253
	A1.5 – C400	1.33	0.8619	0.0005
	A3.0 – C200	-1.21	0.8605	0.0005
	A3.0 – C400	0.23	0.9468	0.0984
	C200 – P	1.07	0.8104	< 0.0001
	C400 – P	-0.43	0.9081	0.0076
High E_{max} N = 33	A1.5 – P	-0.05	0.9416	0.0756
	A3.0 – P	-0.56	0.9025	0.0062
	A1.5 – C200	-0.10	0.9767	0.6823
	A1.5 – C400	0.03	0.9844	0.9040
	A3.0 – C200	-0.22	0.9589	0.2402
	A3.0 – C400	0.43	0.9458	0.1004
	C200 – P	1.41	0.7610	< 0.0001
	C400 – P	0.31	0.9267	0.0282
Good Drug Effects E_{max} N = 34	A1.5 – P	-0.27	0.9531	0.1518
	A3.0 – P	-0.79	0.8206	< 0.0001
	A1.5 – C200	0.05	0.9749	0.6069
	A1.5 – C400	0.44	0.9688	0.4282
	A3.0 – C200	-0.35	0.9106	0.0089
	A3.0 – C400	0.31	0.9177	0.0140
	C200 – P	1.53	0.7405	< 0.0001
	C400 – P	0.39	0.8883	0.0023

As summarized in Table 15, for comparisons with paired differences that were not significantly departure from normal (W-test p-value $\geq$ 0.05) or the distribution was relatively symmetric (skewness = -0.5 to 0.5), a paired *t*-test was used. Otherwise, for comparisons (see in red) with paired differences that were significantly departure from normal (W-test p-value < 0.05) and skewed (skewness < -0.5 or > 0.5), the sign test was performed. Table 16 summarizes the results from the reviewer's sensitivity analysis for Take Drug Again E_{max}, High E_{max}, and Good Drug Effects E_{max}.

Table 16: Sensitivity Analysis Results on Take Drug Again E_{max}, High E_{max}, and Good Drug Effects E_{max}

Measure	Pairwise Comparison	Mean Diff /Med Diff	StdErr /IQR	p-value	95% CI / 90% CI	
					LCL	UCL
Take Drug Again E_{max} N = 34	A1.5 – P†	30.0	23, 49	< 0.0001	27.5	Infty
	A3.0 – P†	39.0	26, 50	< 0.0001	36.0	Infty
	A1.5 – C200	22.8	3.8	< 0.0001	16.4	Infty
	A1.5 – C400†	4.5	0, 31	0.0378	0	Infty
	A3.0 – C200†	27.0	19, 49	< 0.0001	22.0	Infty
	A3.0 – C400	18.1	4.9	0.0004	9.9	Infty
	C200 – P*†	1.0	0, 19	0.0094	0	5.0
	C400 – P*	18.4	4.1	< 0.0001	11.5	25.4
High E_{max} N = 33	A1.5 – P	62.0	4.6	< 0.0001	54.3	Infty
	A3.0 – P†	75.0	52, 97	< 0.0001	58.0	Infty
	A1.5 – C200	41.9	5.5	< 0.0001	32.6	Infty
	A1.5 – C400	21.6	5.6	0.0002	12.2	Infty
	A3.0 – C200	52.5	5.5	< 0.0001	43.1	Infty
	A3.0 – C400	32.2	5.4	< 0.0001	23.1	Infty
	C200 – P*†	7.0	0, 43	< 0.0001	1.0	17.0
	C400 – P*	40.4	6.2	< 0.0001	30.0	50.8
Good Drug Effects E_{max} N = 34	A1.5 – P	64.7	4.4	< 0.0001	57.2	Infty
	A3.0 – P†	90.5	59, 99	< 0.0001	71.0	Infty
	A1.5 – C200	42.6	5.4	< 0.0001	33.4	Infty
	A1.5 – C400	23.0	6.1	0.0003	12.8	Infty
	A3.0 – C200	55.9	5.9	< 0.0001	46.0	Infty
	A3.0 – C400	36.3	6.8	< 0.0001	24.8	Infty
	C200 – P*†	6.5	0, 34	< 0.0001	1.0	22.5
	C400 – P*	41.7	6.5	< 0.0001	30.7	52.6

* Two-sided test was performed.
† The sign test was performed. The median difference and the interquartile range as well as the distribution free 95% / 90% confidence interval of the median difference are listed.

The results from the reviewer's sensitivity analysis showed that for Overall Drug Liking E_{max}, Take Drug Again E_{max}, High E_{max} and Good Drug Effects E_{max},

- the mean differences between Alprazolam 1.5 mg and Placebo, and between Alprazolam 3.0 mg and Placebo were statistically significantly greater than 15 points;
- the mean of each dose of Alprazolam was statistically significantly greater than that of all doses of Cenobamate;
- each dose of Cenobamate had statistically significantly larger mean than Placebo.

3. Conclusion

The reviewer's primary analysis was conducted on Drug Liking E_{max}. The means of maximum drug liking of both Alprazolam 1.5 mg and 3.0 mg (79.5 and 85.3) were statistically significantly greater than 15 points to that of Placebo (52.3), which demonstrated the validity of the study. The differences of maximum drug liking between both doses of Alprazolam and each dose of Cenobamate were statistically greater than 0 to 20.1 points. The mean difference between Cenobamate 200 mg and Placebo was statistically significantly less than 11 points. However, it failed to reject the null hypothesis that the mean difference between Cenobamate 400 mg and Placebo was no less than 11 points with a p-value of 0.9745, which indicates that Cenobamate 400 mg was associated with higher drug liking than Placebo.

The reviewer's secondary analysis was on Overall Drug Liking E_{max}, Take Drug Again E_{max}, High E_{max}, and Good Drug Effects E_{max}. Note that High E_{max} and Good Drug Effects E_{max} were on unipolar scale. The reviewer did the secondary analysis for the Completers Population (N = 39), which showed that the mean differences between Alprazolam 1.5 mg and Placebo, and between Alprazolam 3.0 mg and Placebo were statistically significantly greater than 15 points. The mean of each dose of Alprazolam was statistically significantly greater than that of all doses of Cenobamate, except the comparison between Alprazolam 1.5 mg and Cenobamate 400 mg for Take Drug Again E_{max}. Such comparison indicated that it failed to reject the null hypothesis that the mean of Alprazolam 1.5 mg was no greater than Cenobamate 400 mg for Take Drug Again E_{max} at significance level 0.05. In addition, each dose of Cenobamate had statistically significantly larger mean than Placebo.

By carefully examining the data of key secondary endpoints, the reviewer noticed that some subjects had the same responses across all time points for all treatments, and some subjects had large Placebo response. These same responses to all treatments and large placebo responses would reduce the mean difference between Alprazolam and Placebo, hence made it difficult to show significant difference between positive control and placebo. These issues may also reduce the mean difference between Alprazolam and Cenobamate, which might lead to no significance of relative abuse potential of positive control compared to the test drug. Moreover, these issues would reduce the mean difference between Cenobamate and Placebo, which made it easier to show no much difference in means between test product and placebo. After eliminating subjects with large Placebo response or similar responses at all time points across all treatments, the reviewer's sensitivity analysis results were the same as secondary analysis results, except the comparison between Alprazolam 1.5 mg and Cenobamate 400 mg for Take Drug Again E_{max}. The null hypothesis of such comparison was rejected at significance level 0.05, indicating that the mean of Alprazolam 1.5 mg was also statistically significantly greater than that of Cenobamate 400 mg for Take Drug Again E_{max}. This distinction of results between the reviewer's sensitivity analysis and secondary analysis was due to the elimination of subjects who had similar responses across all treatments.

In conclusion, Drug Liking E_{max} of Cenobamate 200 mg did not differentiate from that of Placebo, while Cenobamate 400 mg was associated with higher drug liking than Placebo. Cenobamate had global and positive effects (Overall Drug Liking E_{max}, Take Drug Again E_{max}, High E_{max}, and Good

Drug Effects E_{max}) significantly less than Alprazolam in all comparisons. However, these effects of Cenobamate were significantly greater than those of Placebo.

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