CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

Addendum to Statistical Review and Evaluation

NDA 205,836

This addendum is to correct the % reduction in seizure frequencies reported by the sponsor and to provide the details of the recalculations of the % reduction in seizure frequency to be displayed in the Clinical Studies section of the label.

The primary efficacy endpoint for the 3 efficacy studies (N01252, N01253, and N01358) was seizure frequency. According to the Statistical Analysis Plan (SAP), seizure frequency in Studies N01252 and N01253 was calculated and analyzed on a per 7-day basis while seizure frequency for Study N01358 was calculated and analyzed on a per 28-day basis. Also specified in the SAP, that a log transformation of log(x+1) (x being the seizure frequency) was to be performed to the seizure data for analysis due to the expected skewness of the seizure data. Using x+1 instead of x in the transformation was to avoid x being 0. In order to get the estimated seizure frequency from the primary model, a least square mean (LSM) of log(x+1) was obtained from the analysis model first, followed by an exponential back transformation and subtraction of 1 required to get the LSM of x. This is true for both 7-day and 28-day seizure frequency.

In the results reported in the Clinical Study Report, correct seizure frequencies were reported, i.e., 1 was subtracted from the estimate of seizure frequency. However, in calculating the % reduction of seizure frequency, the definition giving by the SAP did not include the subtraction of 1 as shown in the following formula:

$$\%\,\text{Reduction / PBO} = 100 \times \frac{\exp[\text{LSMean(PBO)}] - \exp[\text{LSMean(BRV)}]}{\exp[\text{LSMean(PBO)}]}$$

The obtained estimates of the % reduction were thus smaller than what actually should be, and this affected the % reduction in 7-day seizure frequency more than it did for the % reduction of 28-day seizure frequency. In a response from the sponsor (SN 0052 dated November 20, 2015) to our questions, the sponsor stated that the above formula was used because it could be applied to derive back-transformed confidence intervals based on the lower and upper confidence limits for the differences in LS means on the log-transformed scale.

In order to obtain the correct numbers of the % reduction of seizure frequency, the % reductions were recalculated as follows:

1. The LS Means from the model in log scale were back transformed by exponential (exp) to original scale;

2. Subtraction of 1 was performed to the LS Means estimate of x+1 (x being the seizure frequency);

3. The % reduction was thus obtained from the following formula:

$$\% \text{ Reduction / PBO} = 100 \times \frac{\exp[\text{LS Mean(PBO)}] - \exp[\text{LS Mean(BRV)}]}{\exp[\text{LS Mean(PBO)}] - 1}$$

Note that the subtractions of 1 for exp[LS Mean(PBO)] and exp[LS Mean(BRV)] in the numerator canceled out. The difference of the two formulae above was the subtraction of 1 in the denominator.

The following table presents the correctly recalculated % reduction of seizure frequency for the 3 efficacy studies. In theory, the % reduction in seizure frequency is independent of the duration (7-day or 28-day seizure frequency).

Table 1 Recalculated % reduction in seizure frequency (corrections are highlighted)

	Placebo			**BRV**		
		5 mg	**20 mg**	**50 mg**	**100 mg**	**100 mg**
N01252 N % Reduction in seizure frequency	100	NA	99 9.9	99 9.5	100 17.0	NA
N01253 N % Reduction in seizure frequency	96	96 -1.2	99 5.4	101 16.9	NA	NA
N01358 N % Reduction in seizure frequency	259	NA	NA	NA	252 25.2	249 25 (b) (4)

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01/15/2016

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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

sNDA/BLA Serial Number:	205836
Drug Name:	Brivaracetam
Indication(s):	Partial Onset Seizures
Applicant:	UCB Inc.
Date(s):	Date of Submission: November 22, 2014 PDUFA Due Date: November 20, 2015
Review Priority:	Standard Review
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Sharon Yan, Ph.D.
Concurring Reviewers:	Kun Jin, Ph.D., Team Leader James Hung, Ph.D., Director
Medical Division:	Neurology
Clinical Team:	Steven Dinsmore, M.D., Clinical Reviewer Norman Hershkowitz, M.D., Team Leader Eric Bastings, M.D., Deputy Director Billy Dunn, M.D., Acting Director
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1 EXECUTIVE SUMMARY

Three pivotal, fixed-dose, randomized, double-blind, placebo-controlled studies were conducted to establish the efficacy of Brivaracetam in patients with (b) (4) partial onset seizures (b) (4)

The three trials N01252, N01253, and N01358 evaluated Brivaracetam (BRV) at daily doses from 5 mg to 200 mg against placebo. Although none of the tested BRV doses had duplicated positive efficacy in 2 or more of the trials, the data strongly suggested that BRV 100 mg/day and 200 mg/day were effective. The effectiveness of BRV 50 mg/day could not be conclusively determined as statistical significance was reached in Study N01253, but not in N01252. BRV at doses below 50 mg daily did not show effectiveness.

Concomitant use of levetiracetam (LEV) appeared to be a confounding factor as patients who took LEV as concomitant antiepileptic drug (AED) (occurred in 20% of patients in N01252 and N01253) did not seem to have reduction in seizure frequency as seen in patients who were not using LEV as concomitant AED.

In trial N01252, BRV at doses 20 mg, 50 mg, and 100 mg were tested against placebo. The primary outcome did not achieve statistical significance based on the sequential testing procedure, which required statistical significance at the 0.05 level for BRV 50mg versus placebo prior to the testing of BRV 100mg and BRV 20mg in sequence. The comparison of BRV 100mg/day versus PBO was nominally statistically significant with an 11.7% reduction of seizure frequency over PBO (p=0.037).

In trial N01253, BRV at doses 5 mg, 20 mg, and 50 mg were tested against placebo. The effect of BRV 50 mg achieved statistical significance (p=0.025).

Trial N01358 was initiated after the completion of N01252 and N01253. Patients using LEV as concomitant AED were excluded from the trial after the findings in N01252 and N01253 that LEV was a potential confounding factor. Both of the tested doses Brivaracetam 100 mg and 200 mg achieved statistical significance in efficacy as compared to placebo ($p < .001$for both doses).

2 INTRODUCTION

2.1 Overview

The clinical development of BRV with oral formulations in subjects 16 years of age and older with POS is composed of 2 dose-ranging studies, 3 pivotal Phase 3 studies and 1 safety study. The evidence for efficacy of BRV for treatment of POS are supported by 3 pivotal phase-3 studies N01252, N01253, and N01358, which are included in this review. The three pivotal studies were randomized, double-blind, placebo-controlled, fixed-dose, multicenter studies in adults (≥16 years) with refractory POS with or without secondary generalization. The 3 studies

were designed to evaluate the efficacy and safety of twice-daily oral administration of BRV 5mg/day to 200mg/day.

Study N01252, conducted in Europe and India, evaluated the efficacy and safety of twice-daily oral administration of BRV tablets at doses of 20mg/day, 50mg/day, and 100mg/day. Because both BRV and LEV were known to bind to the same SV2A binding site, the number of subjects using LEV as concomitant AED was limited to 20% of the total study population. Subjects completed an 8-week prospective Baseline Period followed by a 12-week Treatment Period during which they received randomized study drug without up-titration.

N01253 was a global study, with design similar to N01252. The study evaluated BRV tablets at doses of 5mg/day, 20mg/day, and 50mg/day. Like N01252, the number of subjects taking LEV at the time of study entry was limited to 20% of randomized subjects.

N01358, conducted after the completion of N01252 and N01253, was a global study with design similar to Studies N01252 and N01253, and evaluated BRV tablets at doses of 100mg/day and 200mg/day. Subjects who were receiving LEV within 90 days prior to study entry were excluded from this study.

A summary of the phase-3 pivotal studies are presented in Table 1.

Table 1 List of studies included in this review

Study	Phase and Design	Duration of treatment	Dosage	Comparator	# of Subjects randomized	Study Population
Protocol N01252	Phase 3, randomized, double-blind, PBO-controlled in Europe and India	12 weeks	20 mg/day, 50 mg/day, 100 mg/day	Exit rate estimated from historical data	399	Patients with POS; < 20% LEV user
Protocol N01253	Phase 3, randomized, double-blind, PBO-controlled conducted globally	12 weeks	5 mg/day, 20 mg/day, 50 mg/day	Exit rate estimated from historical data	400	Patients with POS; < 20% LEV user
Protocol N01358	Phase 3, randomized, double-blind, PBO-controlled conducted globally	12 weeks	100 mg/day, 200 mg/day		768	Patients with POS; excludes patients using LEV at entry

2.2 Data Sources

All documents reviewed for this NDA submission are in electronic form with eCTD format. The electronic files are compatible with eCTD viewer software Global Summit. Both raw and derived datasets are included in the submission. The SAS programs for primary and secondary analyses are also included. The path to CDER Electronic Document Room for documents of this NDA is listed below:

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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

No data issues were identified.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

The three studies, N01252, N01253 and N01358, were similarly designed with the same primary objective but studied different dosage of BRV.

The primary objective of the three studies were to evaluate the efficacy of BRV as compared to placebo in reducing seizure frequency in subjects with partial onset seizures not fully controlled despite optimal treatment with 1 to 2 concomitant AEDs.

The three pivotal studies were randomized, double-blind, parallel-group, placebo-controlled studies to determine efficacy and safety of BRV in subjects of at least 16 years old with partial onset seizures (POS). Eligible subjects were enrolled and entered an 8-week Baseline Period. Subjects who had at least 8 POS whether or not secondarily generalized during the 8-Week Baseline Period were randomized in equal numbers to one of the dose groups or placebo for each studies described in Table 2. Subjects received full dose of the randomized treatment without titration. The Treatment Period lasted 12 weeks. At the end of the Treatment Period, the subject either entered a long term follow-up (LTFU) study, or entered a Down-Titration Period of 1 to 4 weeks depending on the study, followed by a 2-week Study Drug-Free Period.

The use of concomitant LEV was limited to 20% of the subjects in N01252 and N01253. Because the use of concomitant LEV was later determined to be a potential confounding factor in N01252 and N01253, and it was recognized that LEV and BRV had a similar mechanism of action, patients receiving concomitant LEV within 90 days prior to study entry were excluded from N01358. The following table presents a summary of study specifics and comparisons of the 3 pivotal studies.

Table 2 Study specifics of the pivotal studies

	N01252	**N01253**	**N01358**
Number of treatment arms	4	4	3
Dosage	20 mg, 50 mg, 100 mg	5 mg, 20 mg, 50 mg	100 mg, 200 mg
Control	Placebo	Placebo	Placebo
Number of subjects	399	400	768
AEDs	1 to 2	1 to 2	1 to 2
Patient Population	Refractory	Refractory	Refractory

Use of LEV at study entry	Limited to 20% of population	Limited to 20% of population	Excluded
Age of Patient Population	16 to 70 years	16 to 70 years	16 to 80 years
Countries or Regions	Europe and India	N. America, S. America and Australia	27 countries worldwide including ~25% of the patients from North America
Study Period	Sep. 20, 2007 to Feb. 9, 2009	Sep. 7, 2007 to Jan. 2, 2009	Dec. 10 2010 to May 22, 2014
Randomization stratification	By region and use of LEV at study entry	By region and use of LEV at study entry	By country and LEV status (never used vs. prior use) and # of AEDs discontinued

Source: reviewer's summary

3.2.1.2 Efficacy Endpoints

The primary efficacy variable was the POS (Type I) frequency over the Treatment Period.

The secondary efficacy variables included:

- Responder rate (the proportion of subjects who had a ≥50% reduction in seizure frequency from Baseline) for POS (Type I) over the Treatment Period (This variable is used as the primary efficacy endpoint for European authority in Study N01358.)
- All seizure frequency (Type I+II+III) per week over the Treatment Period
- Percent reduction for POS (Type I) frequency per week from Baseline to the Treatment Period
- Categorized percentage reduction (-25% to <25%, 25% to <50%, 50% to <75%, 75% to <100%, and 100%) from Baseline in seizure frequency for POS (Type I) over the Treatment Period
- Seizure freedom rate (all seizure types) over the Treatment Period
- Time to n^{th} (n=1, 5, 10) Type I seizure during the Treatment Period

The secondary endpoint of responder rate (50% reduction in seizure frequency) was the primary endpoint for European authorities in Study N01358.

The following 3 variables were listed as secondary efficacy endpoints subject to multiplicity adjustment in Studies N01252 and N01253, but were not included as secondary efficacy endpoints in Study N01358.

- Total Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score
- Seizure Worry QOLIE-31-P score
- Daily Activities/Social Functioning QOLIE-31-P score

Patients' epileptic seizures were recorded on the daily record card (DRC), with date, number of epileptic seizures and seizure type.

3.2.2 Statistical Methodologies

Patient Population for Efficacy Analysis

Efficacy analyses were to be based on ITT patient population in all studies except for Study N01253, where modified ITT patient population was used. The ITT Population was defined as all randomized subjects who received at least 1 dose of study medication. In Study 01253, the Modified ITT (mITT) Population was defined as all subjects in the ITT population excluding all 3 randomized subjects from Site 404 as well as Subject 364/B155. Subjects from Site 404 were excluded due to serious and persistent noncompliance with applicable FDA regulation, GCP, and ICH guidelines on the part of Site 404. Subject 364/B155 was an extraordinary outlier with respect to the reported seizure frequency during the baseline and 12-week treatment period. Further concerns were found for Subject 364/B155 regarding the reported seizure type and the subject's eligibility for the study because no POS were recorded during Baseline.

3.2.2.1 Primary Efficacy Analysis

The seizure frequency was described as per week in Studies N01252 and N01253, and was described as per 28 days in Study N01358. The seizure frequency was calculated as:

$$\frac{\textit{Total number of Type I seizures over the Treatment Period}}{\textit{Total number of days with no missing seizure count in the Treatment Period}}$$

The above number was then multiplied by 7 to obtain weekly seizure frequency for Studies N01252 and N01253, or multiplied by 28 to obtain seizure frequency per 28 days for Study N01358.

The obtained seizure frequency per week or per 28 days was then transformed by logarithm ln(x+1) (where x was the seizure frequency per week or per 28 days). The log-transformed POS frequency over the Treatment Period was analyzed applying an ANCOVA model, including treatment and stratification effects as factors and the log-transformed Baseline seizure frequency per week as covariate.

The stratification variables used in the primary analysis model varied by study as follows:

- N01252 and N01253: a combined effect of region and concomitant LEV use
- N01358: effect for country and an effect for the 4 combination of levels for LEV status and number of previous AEDs (≤2 vs >2)

3.2.2.2 Handling of Missing Values

Subjects who reported a complete and non-missing seizure record for at least 1 day during the Baseline or Treatment Period were included in the analysis. If a subject had missing seizure count information for some days during the Baseline or Treatment Periods, these days were not

considered in the calculation of the seizure frequency (i.e., the seizure frequency was computed over the non-missing days of the considered period). Similarly, if a subject withdrew from the study before the end of the Treatment Period, the seizure information collected up until the time of withdrawal was used to calculate the seizure frequency over the Treatment Period.

Reviewer's Comments: *missing data appeared to be at low level in all 3 studies and generally limited to patients who discontinued prematurely.*

3.2.2.3 Sensitivity Analyses for Primary Endpoint

In studies N01252 and N01253, a sensitivity analysis was performed to investigate how the assumptions for missing seizure counts could have influenced the results. The weekly seizure count was computed by study week using the available data during that week (if the daily seizure counts were missing for all days of the week, the weekly seizure frequency was set to missing for that week). Then a Longitudinal Linear Mixed-Effects model was applied.

A non-parametric analysis applying a rank-ANCOVA model on untransformed data as a sensitivity analysis was planned for all three studies.

3.2.2.4 Multiple comparisons/multiplicity

Multiplicity Adjustment for N01252 and N01253

In Studies N01252 and N01253, the 3 doses of BRV were tested at the 5% level against placebo sequentially in the following order:

- Study N01252: 50mg/day, then the 100mg/day, and finally the 20mg/day dose.
- Study N01253: 50mg/day, then the 20mg/day, and finally the 5mg/day dose.

Thus, a next dose was compared with placebo if and only if statistical significance was reached with the current dose.

Multiplicity Adjustment for N01358

For Study 01358, statistical testing was based on the comparison of each BRV treatment group (BRV 100 and 200mg/day) to placebo with control of overall type I error rate based on the Hochberg procedure. The Hochberg procedure was applied by first testing the BRV treatment group with the larger p-value. If the larger p-value was $\leq$ 0.05, then statistical significance was achieved and both BRV treatment groups were to be declared statistically different from placebo. If the largest p-value was greater than 0.05, then the procedure was to compare the smaller p-value to 0.025. If statistical significance was achieved at this step then the BRV treatment group associated with the smaller p-value was declared statistically different from placebo. If the smaller p-value was not significant at the 0.025 level, then neither BRV treatment groups was statistically different from placebo and the study was not positive.

For the USA, 50% responder outcome was analyzed as a secondary variable with statistical testing at the nominal 0.05 level without applying a Hochberg procedure. Similarly, the USA primary analysis was a secondary analysis for Europe, with testing at a nominal 0.05 level in support of the primary responder outcome.

3.2.3 Study Results

3.2.3.1 Study Results from N01252

3.2.3.1.1 Patient Disposition - N01252

A total of 486 subjects were screened and 399 subjects were randomized in 71 study sites in Europe and India. One subject randomized to the BRV 50mg/day group was dispensed drug and died before consuming any study drug. This subject was not included in the ITT Population.

Of the 398 subjects in the ITT Population, 367 subjects (92.2%) completed the study. A total of 31 subjects (7.8%) discontinued the study. The most common reason for discontinuation was AE for all treatment groups. A summary of patient disposition is presented in Table 3.

Table 3 Disposition of patients - N01252

N (% of ITT population)	PBO	BRV		
		20 mg	50 mg	100 mg
Randomized	100	99	100	100
ITT Population	100	99	99	100
Completed study	92 (92%)	93 (93.9%)	88 (88.9%)	94 (94.0%)
Discontinued	8 (8.0%)	6 (6.1%)	11 (11.1%)	6 (6.0%)
Adverse Event	4 (4.0%)	4 (4.0%	6 (6.1%)	5 (5.0%)
Lack of Efficacy	0	0	0	0
Lost to follow-up	2 (2.0%)	0	1 (1.0%)	0
Consent withdrawn	2 (2.0%)	1 (1.0%)	1 (1.0%)	0
Other	0	1 (1.0%)	3 (3.0%)	1 (1.0%)

Source: Clinical Study Report

3.2.3.1.2 Patient Demographic and Baseline Characteristics – N01252

Patient demographics are presented in Table 4. The mean age of subjects was 37 years. A total of 227 males (57.0%) and 171 females (43.0%) enrolled in this study. The majority of subjects were Caucasian (76.6%). Except one subject with mixed race, the remaining subjects were of Asian descent.

Table 4 Patient demographics (ITT population) – N01252

	PBO N=100	BRV		
		20 mg N=99	50 mg N=99	100 mg N=100
Gender, n (%)				
Female	46 (46.0%)	38 (38.4%)	45 (45.5%)	42 (42.0%)
Male	54 (54.0%)	61 (61.6%)	54 (54.5%)	58 (58.0%)
Age, years				
Mean	36.4	35.7	38.9	38.0
Median	33.3	33.9	38.7	37.1
Race, n (%)				
Caucasian	77 (77.0%)	76 (76.8%)	76 (76.8%)	76 (76.0%)
Asian	23 (23.0%)	22 (22.2%)	23 (23.2%)	24 (24.0%)
Mixed	0	1 (1.0%)	0	0

Source: Clinical Study Report

The sponsor reported that variations in demographic characteristics were apparent between subjects in different regions (Western Europe, Eastern Europe, and India). Generally, subjects from Indian region were younger compared with subjects from other regions.

Patient baseline epileptic characteristics are presented in the following table.

Table 5 Baseline epileptic characteristics (ITT population) – N01252

	PBO N=100	BRV		
		20 mg N=99	50 mg N=99	100 mg N=100
Median epilepsy duration (years)	20.0	20.8	21.0	20.0
Median age at onset (years)	14.0	12.0	13.0	13.5
History of status epilepticus, n (%)	3 (3.0%)	8 (8.1%)	4 (4.0%)	5 (5.0%)

Source: Clinical Study Report

All subjects were taking at least 1 concomitant AED at Baseline. The most frequently used concomitant AEDs were: Carbamazepine (46.5%), Valproate (22.4%), Lamotrigine (20.9%), and Oxcarbazepine (20.4%). The majority of patients (78.9%) were taking 2 AEDs. A summary of the number of AEDs taken at baseline is presented in Table 6.

Table 6 Summary of the number of AEDs taken at baseline (ITT population) – N01252

Number of AEDs at baseline, n (%)	PBO N=100	BRV		
		20 mg N=99	50 mg N=99	100 mg N=100
1 AED	14 (14.0)	18 (18.2)	20 (20.2)	16 (16.0)
2 AEDs	83 (83.0)	77 (77.8)	77 (77.8)	77 (77.0)
3 or more AEDs	3 (3.0)	4 (4.0)	2 (2.0)	7 (7.0)

Source: Clinical Study Report

3.2.3.1.3 Efficacy Results of N01252

Analysis of the Primary Endpoint

The median POS frequency decreased in all treatment groups during the Treatment Period. The percent reductions over PBO in the POS frequency per week over the Treatment Period were 6.8%, 6.5%, and 11.7% in the BRV 20mg/day, BRV 50mg/day, and BRV 100mg/day groups, respectively. The primary outcome for study N01252 did not achieve statistical significance based on the sequential testing procedure, which required statistical significance at the 0.05 level for BRV 50mg/day versus PBO prior to the testing of BRV 100mg/day and BRV 20mg/day in sequence. The comparison of BRV 100mg/day versus PBO was nominally statistically significant with an 11.7% reduction over PBO for the primary outcome (p=0.037).

Deviations from the model assumptions in normality were noted, and a sensitivity analysis using a rank-ANCOVA model on the untransformed data was performed. The results of this sensitivity analysis achieved similar p-values as in the primary analysis. The following table presents the efficacy results from the primary analysis as well as sensitivity analyses.

Table 7 Results of efficacy analysis of seizure frequency per week – N01252

	Placebo N=100	**BRV**		
		20 mg N=99	**50 mg N=99**	**100 mg N=100**
Baseline median seizure frequency	2.07	1.93	1.80	2.02
Treatment median seizure frequency	1.75	1.34	1.49	1.26
Primary analysis LS mean % reduction (95% CI) p-value	2.21	1.99 6.8 (-4.8, 17.1) 0.239	2.00 6.5 (-5.2, 16.9) 0.261	1.84 11.7 (0.7, 21.4) 0.037
Sensitivity analysis-mixed effect LS mean % reduction (95% CI) p-value	1.77	1.57 7.4 (-3.6, 17.3) 0.178	1.66 3.9 (-7.5, 14.2) 0.484	1.52 8.9 (-1.9, 18.5) 0.104
Sensitivity analysis- ranks p-value		0.174	0.246	0.021

Source: reported in CSR and verified by the reviewer

Analysis of Secondary Endpoints

Due to the stopping rule, none of the secondary endpoints were eligible for statistical testing. The sponsor did not present the planned statistical testing for the 3 patient reported outcomes that were specified for testing with multiplicity adjustment.

The following table presents the results from analysis 50% responder rate for descriptive purpose only. The treatment effect of BRV 100 mg group compared to placebo group reached nominal significance with a p-value of 0.023.

Table 8 Fifty percent responder rate in partial seizure frequency per week

Statistics	PBO	BRV		
		20mg	50mg	100mg
	(N=100)	(N=99)	(N=99)	(N=100)
Nonresponders, n (%)	80 (80.0)	72 (72.7)	72 (72.7)	64 (64.0)
Responders, n (%)	20 (20.0)	27 (27.3)	27 (27.3)	36 (36.0)
Odds ratio (BRV vs PBO)[a]		1.39	1.36	2.13
95% Two-sided CI		0.71, 2.72	0.69, 2.66	1.11, 4.10
p-value		0.339	0.372	0.023[b]

Source: Clinical Study Report

3.2.3.2 Study Results from N01253

3.2.3.2.1 Patient Disposition in Study N01253

A total of 509 subjects were screened and 400 subjects were randomized. Four subjects were not treated. Thus, 396 subjects were included in the ITT Population.

In this study, efficacy analyses were performed on the mITT Population, defined as all subjects in the ITT Population with the exception of 4 subjects. Three subjects from Site 404 were excluded due to serious, persistent compliance issues involving the principle Investigator. One subject from Site 364 was excluded due to an extremely high seizure frequency prior to and during the study as well as due to concerns about seizure type eligibility. Thus, a total of 392 subjects were included in the mITT Population.

A total of 35 subjects (8.8%) discontinued the study. The most common reason for discontinuation was AE.

Table 9 Disposition of patients - N01253

N (%)	PBO	BRV		
		5 mg	20 mg	50 mg
Randomized	99	99	100	102
ITT Population	98	97	100	101
Modified ITT	96	96	99	101
Completed study	93 (94.9%)	82 (84.5%)	93 (93.0%)	93 (92.1%)
Discontinued	5 (5.1%)	15 (15.5%)	7 (7.0%)	8 (7.9%)
Adverse Event	2 (2.0%)	8 (8.2%	5 (5.0%)	6 (5.9%)
Lack of Efficacy	1 (1.0%)	0	0	0
Lost to follow-up	0	4 (4.1%)	0	1 (1.0%)
Consent withdrawn	0	2 (2.1%)	1 (1.0%)	1 (1.0%)
Other	2 (2.0%)	1 (1.0%)	1 (1.0%)	0

Source: Clinical Study Report

3.2.3.2.2 Patient Demographic and Baseline Characteristics - N01253

Patient demographics are presented in Table 10. The mean age of subjects was 38 years. A total of 195 males (49.2%) and 201 females (50.8%) enrolled in this study. The majority of subjects were Caucasian (72.2%).

Table 10 Patient demographics (ITT patient population) - N01253

	PBO N=98	BRV		
		5 mg N=97	20 mg N=100	50 mg N=101
Gender, n (%)				
Female	55 (56.1)	48 (49.5%)	48 (48.0%)	50 (49.5%)
Male	43 (43.9)	49 (50.5%)	52 (52.0%)	51 (50.5%)
Age, years				
Mean (SD)	37.5	38.9	37.3	38.9
Median	35.6	38.4	37.9	39.1
Race, n (%)				
Caucasian	66 (67.3)	73 (75.3)	70 (70)	77 (76.2))
Black	4 (4.1)	5 (5.2))	5 (5.0)	2 (2.0)
American India	13 (13.3)	8 (8.2)	9 (9.0)	8 (7.9)
Mixed	14 (14.3)	10 (10.3)	14 (14.0)	10 (9.9)
Other	1 (1.0)	1 (1.0)	2 (2.0)	4 (4.0)

Source: Clinical Study Report

Variations in age and race were apparent between subjects in different regions (North America/Australia, Latin America). Generally, subjects in the Latin America subgroup were younger compared with the North America/Australia subgroup. About half of the subjects in the Latin America subgroup were Caucasian (53.4%) compared with those in the North America/Australia subgroup who were mostly Caucasian (87.6%).

Demographic characteristics of subjects with concomitant LEV use at study entry were generally similar compared with subjects without concomitant LEV use at study entry.

The history of epileptic seizures and etiology of epilepsy are summarized in Table 11.

Table 11 Baseline epileptic characteristics (ITT population) – N01253

	PBO N=98	BRV		
		5 mg N=97	20 mg N=100	50 mg N=101
Median epilepsy duration (years)	23.1	19.8	21.5	26.0
Median age at onset (years)	10.0	13.0	10.6	10.0
History of status epilepticus, n (%)	11 (11.2)	5 (5.2)	13 (13.0)	10 (9.9)

Source: Clinical Study Report

All but 1 subject were taking at least 1 concomitant AED at Baseline. The most frequently used concomitant AEDs were: Carbamazepine (40.4%), Lamotrigine (27.8%), Levetiracetam (19.2%),

and Phenytoin (17.2%). A summary of the number of AEDs taken at baseline is presented in Table 12.

Table 12 Summary of the number of AEDs taken at baseline (ITT population) – N01253

Number of AEDs at baseline, n (%)	**PBO N=98**	**BRV**		
		5 mg N=97	**20 mg N=100**	**50 mg N=101**
0 AED	1 (1.0)	0	0	0
1 AED	13 (13.3)	14 (14.4)	16 (16.0)	13 (12.9)
2 AEDs	80 (81.6)	76 (78.4)	71 (71.0)	81 (81.2)
3 or more AEDs	4 (4.1)	7 (7.2)	12 (12.0)	6 (5.9)

Source: Clinical Study Report

3.2.3.2.3 Efficacy Results of N01253

The median POS frequency decreased in all treatment groups during the Treatment Period. The percent reductions over PBO in the POS frequency per week over the Treatment Period were -0.9%, 4.1%, and 12.8% in the BRV 5mg/day, BRV 20mg/day, and BRV 50mg/day groups, respectively. The primary outcome for study N01253 achieved statistical significance for BRV 50mg/day versus PBO (p=0.025). However, neither BRV 20mg/day versus PBO nor BRV 5mg/day versus PBO reached statistical significance.

Results of the primary efficacy analysis are summarized in Table 13.

Table 13 Results of efficacy analysis of seizure frequency per week – N01253

	Placebo N=96	**BRV**		
		5 mg N=96	**20 mg N=99**	**50 mg N=101**
Baseline median seizure frequency	2.63	2.32	2.23	2.85
Treatment median seizure frequency	2.15	1.80	1.96	1.70
Primary analysis LS mean % reduction (95% CI) p-value	3.13	 3.17 -0.9 (-13.9, 106) 0.885	 2.96 4.1 (-8.1, 15.0) 0.492	 2.60 12.8 (1.7, 22.6) 0.025
Sensitivity analysis-mixed effect LS mean % reduction (95% CI) p-value	2.65	 2.47 4.8 (-7.8, 16.0) 0.437	 2.36 7.9 (-4.1, 18.6) 0.189	 2.07 15.9 (4.9, 25.6) 0.006
Sensitivity analysis- ranks p-value		 0.698	 0.303	 0.003

Source: Reviewer's Analysis

As in Study N01252, marked deviation from the normal assumption was noted. Sensitivity analyses using a Linear Mixed-Effects Model and a rank-ANCOVA model on the untransformed data confirmed results from the primary analysis.

In the primary and sensitivity analyses, 4 subjects were excluded from the ITT patient population. It was found that subject 364/B155 had seizure frequency of over 1500 times of median seizure frequency of the population at both baseline and treatment period and the exclusion of this subject was justifiable. Analysis including subjects in site 404 had results similar to the ones from the primary analysis.

3.2.3.3 Study Results from N01358

3.2.3.3.1 Patient Disposition - N01358

A total of 1045 subjects were screened and 768 subjects were randomized. Among them, 375 subjects (48.8%) were enrolled from the EU region and 188 (24.5%) subjects were enrolled from the North American region.

A total of 72 subjects (9.4%) discontinued the study (Table 14). The most common reason for discontinuation was AE.

Table 14 Disposition of patients - N01358

N (%)	PBO	BRV	
		100 mg	**200 mg**
Randomized	263	254	251
Completed study	246 (93.5)	225 (88.6)	225 (89.6)
Discontinued	17 (6.5)	29 (11.4)	26 (10.4)
Adverse Event	10 (3.8)	21 (8.3)	17 (6.8)
Lack of Efficacy	1 (0.4)	1 (0.4)	0
Protocol violation	0	3 (1.2)	1 (0.4)
Lost to follow-up	0	1 (0.4)	3 (1.2)
Consent withdrawn	2 (0.8)	2 (0.8)	4 (1.6)
Other	4 (1.5)	1 (0.4)	1 (0.4)

Source: Clinical Study Report

Eight randomized subjects (4 in the placebo group, 2 in the BRV 100 mg group and 2 in the BRV 200 mg group) were excluded from the ITT Population due to discontinuation either prior to drug administration or before first on-treatment assessment. Thus, 760 subjects were included in the ITT population.

3.2.3.3.2 Patient Demographic and Baseline Characteristics - N01358

Subject demographics are presented in Table 15. The mean age of subjects was 39.5 years. Overall, there was a similar proportion of males (48.2%) compared with females (51.8%). The majority of subjects were white (72.4%).

Table 15 Patient demographics (ITT patient population) - N01358

N (%)	**PBO N=261**	**BRV**	
		100 mg N=253	**200 mg N=250**
Gender, n (%)			
Female	128 (49.0)	151 (59.7)	117 (46.8)
Male	133 (51.0)	102 (40.3)	133 (53.2)
Age, years			
Mean (SD)	39.8	39.1	39.8
Median	39.0	39.0	40.0
Race, n (%)			
Caucasian	189 (72.4)	182 (71.9)	182 (72.8)
Black	11 (4.2)	8 (3.2)	7 (2.8)
Asian	32 (12.3)	32 (12.6)	29 (11.6)
Other	26 (10.0)	29 (11.5)	29 (11.6)

Source: Clinical Study Report

The history of epileptic seizures and etiology of epilepsy are summarized in Table 16.

Table 16 Baseline epileptic characteristics (ITT population) – N01358

N (%)	**PBO N=259**	**BRV**	
		100 mg N=252	**200 mg N=249**
Median duration of epilepsy (years)	20.8	20.7	21.9
Median age at onset (years)	13.7	14.6	13.9
History of status epilepsy, n (%)	12 (4.6)	7 (2.8)	20 (8.0)

Source: Clinical Study Report

All subjects were taking at least 1 concomitant AED at Baseline. The most frequently used concomitant AEDs were: Carbamazepine (37.2%), Lamotrigine (25.9%), Valproate (21.8%), Oxcarbazepine (15.8%), Topiramate (15.0%), and Lacosamide (14.2%). A summary of the number of AEDs taken at baseline is presented in Table 17.

Table 17 Summary of the number of AEDs taken at baseline (ITT population) – N01358

Number of AEDs at baseline, n (%)	PBO N=259	BRV	
		100 mg N=252	200 mg N=249
1 AED	75 (29.0)	70 (27.8)	69 (27.7)
2 AED	181 (69.9)	182 (72.2)	179 (71.9)
$\geq$ 3 AEDs	3 (1.2)	0	1 (0.4)

Source: Clinical Study Report

3.2.3.3.3 Efficacy Results of N01358

The primary efficacy outcome for the USA was the percent reduction in POS (Type I) frequency over PBO based on an ANCOVA. A summary of percent reduction over PBO in the 28-day adjusted POS frequency is provided in Table 18.

Table 18 Results of efficacy analysis of seizure frequency per 28 days – N01358

	Placebo N=259	BRV	
		100 mg N=252	200 mg N=249
Baseline median seizure frequency	10.0	9.5	9.3
Treatment median seizure frequency	8.7	6.3	5.8
Primary analysis LS mean seizure freq per 28 days (seizure frequency per week) % reduction (95% CI) p-value	 9.2 (2.3)	 6.9 (1.7) 22.8 (13.3, 31.2) <.001	 6.8 (1.7) 23.2 (13.8, 31.6) <.001
Non-parametric rank ANCOVA p-value		 <.001	 <.001
EU primary outcome, 50% respond Responders, n (%) Odds ratio[1] p-value	 56 (21.6)	 98 (38.9) 2.39 <.001	 94 (37.8) 2.19 <.001

1. The analysis used a logistic model with effect of treatment, pooled country, and 4 combinations of stratification of previous use of AEDs and LEV status. The odds ratio represents the odds of being a responder as compared to PBO.

Source: Reported results confirmed by the reviewer

The reductions in both BRV groups were statistically significant (p<0.001). The percent reduction in the 28-day adjusted POS frequency over PBO in the BRV 100mg/day and 200mg/day groups was similar (22.8% and 23.2%, respectively) with no dose response observed.

The primary efficacy outcome for the EU was the 50% responder rate based on percent reduction in POS (Type I) frequency from Baseline to the 12-week Treatment Period. The 50% responder rates in the BRV 100mg/day and 200mg/day groups were 38.9% and 37.8%, respectively (Table 18 above), and were greater than the responder rate in the PBO group (21.6%). The odds ratios for the BRV 100mg/day and 200mg/day groups were 2.39 and 2.19, respectively; both BRV groups showed statistical significance compared with the PBO group (p<0.001).

3.3 Evaluation of Safety

Refer to Safety Review by Dr. Mary Doi and Clinical Review by Steven Dinsmore for Evaluation of Safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

As noted before, the distribution of the seizure frequency was extremely skewed. Marked deviation from the normal assumption of the model was observed, even after the log transformation. Least square (LS) mean estimates from the model could be severely influenced by the extreme values at the two ends, i.e., subjects with very low or very high seizure

frequencies, particularly in the subgroup analysis when the sample size is small. Therefore, instead of LS means, the point estimates of mean seizure frequency are presented.

Results from subgroup analysis of seizure frequency by gender, age group and race are presented by study in Table 19 for Study N01252, Table 21 for Study N01253 and Table 23 for Study N01358. Subgroup analyses of seizure frequency by region are presented in Table 20 for Study N01252, Table 22 for Study N01253, and in Table 24 for Study N01358. Large baseline differences in seizure frequency with regard to demographic characteristics and regions are noted. This is partly due to the difference in patient population in different regions. However, no substantial discrepancies in treatment difference were found in these subgroup analyses.

Note that seizure frequency per week was used in Studies N01252 and N01253, and seizure frequency per 28 days was used in Study N01358.

Table 19 Seizure frequency per week by gender, age group and race - Study N01252

Median seizure frequency per week	**PBO N=100**	**BRV**		
		20 mg N=99	**50 mg N=99**	**100 mg N=100**
Female				
N	46	38	45	42
Baseline	2.3	1.9	2.2	2.1
Treatment period	1.7	1.3	1.8	1.3
Male				
N	54	61	54	58
Baseline	2.0	2.0	1.7	2.0
Treatment period	1.8	1.4	1.3	1.3
< 37 (year)				
N	56	57	44	50
Baseline	2.0	2.0	2.1	2.3
Treatment period	1.8	1.3	1.6	2.0
≥ 37 (year				
N	44	42	55	50
Baseline	2.2	1.8	1.6	1.7
Treatment period	2.0	1.3	1.3	1.0
Caucasian				
N	77	76	76	76
Baseline	2.2	1.9	1.8	2.1
Treatment period	1.8	1.4	1.6	1.7
Other				
N	23	23	23	24
Baseline	1.5	1.7	1.9	1.6
Treatment period	1.4	0.9	1.0	0.9

Table 20 Analysis of seizure frequency by region – Study N01252

Median seizure frequency per week	**Placebo N=100**	**BRV**		
		20 mg N=99	**50 mg N=99**	**100 mg N=100**
Eastern Europe				
N	30	30	30	30
Baseline	1.8	1.8	1.7	1.5
Treatment period	1.6	1.1	1.6	1.0
Western Europe				
N	47	47	47	47
Baseline	3.4	2.2	1.9	2.4
Treatment period	3.0	1.9	1.6	2.1
Rest of the World				
N	23	22	22	23
Baseline	1.5	1.7	1.8	1.7
Treatment period	1.4	0.8	1.1	0.9

Table 21 Analysis of seizure frequency by gender, age group and race - Study N01253

Median seizure frequency per week	**PBO N=96**	**BRV**		
		5 mg N=96	**20 mg N=99**	**50 mg N=101**
Female				
N	53	47	47	50
Baseline	3.2	2.5	2.5	2.5
Treatment period	2.2	1.8	2.0	1.5
Male				
N	43	49	52	51
Baseline	2.3	2.0	2.2	3.4
Treatment period	1.8	1.9	1.8	2.0
< 37 (year)				
N	52	42	47	46
Baseline	2.9	2.4	4.4	3.5
Treatment period	2.5	1.7	3.4	2.5
≥ 37 (year				
N	44	54	52	55
Baseline	2.6	2.3	1.9	2.3
Treatment period	2.0	1.9	1.4	1.4
Caucasian				
N	66	72	70	77
Baseline	2.6	2.6	2.8	2.9
Treatment period	2.2	2.0	2.0	2.0
Other				
N	30	24	29	24
Baseline	2.8	1.6	2.0	2.0
Treatment period	2.1	1.1	1.6	1.3

Table 22 Analysis of seizure frequency by region – Study N01253

Median seizure frequency per week	**Placebo N=96**	**BRV**		
		5 mg N=96	**20 mg N=99**	**50 mg N=101**
North America / Australia				
N	53	52	55	57
Baseline	2.7	2.5	2.7	2.9
Treatment period	2.6	2.4	2.2	2.0
Latin America				
N	43	44	44	44
Baseline	2.5	2.2	2.1	2.6
Treatment period	2.0	1.7	1.6	1.5

Table 23 Analysis of seizure frequency by gender, age group and race - Study N01358

Median seizure frequency per 28 days	**Placebo N=259**	**BRV**	
		100 mg N=252	**200 mg N=249**
Female			
N	126	150	116
Baseline	10.6	10.7	10.7
Treatment period	8.7	7.4	6.7
Male			
N	133	102	133
Baseline	8.7	8.2	8.8
Treatment period	8.4	4.8	5.3
Age < 40 (years)			
N	138	136	121
Baseline	11.1	11.8	11.0
Treatment period	9.0	7.0	7.6
Age > 40 (years)			
N	121	116	128
Baseline	8.9	8.1	8.0
Treatment period	7.7	5.8	4.9
White			
N	187	182	181
Baseline	10.1	11.8	9.0
Treatment period	8.7	7.3	5.9
Asian			
N	32	32	29
Baseline	6.3	6.5	10.0
Treatment period	5.7	4.4	8.3
Other			
N	40	38	39
Baseline	12.1	8.0	11.3
Treatment period	10.1	4.3	5.3

Table 24 Analysis of seizure frequency by region – N01358

Median seizure frequency per 28 days	PBO N=259	BRV 100 mg N=252	BRV 200 mg N=249
East Europe			
N	67	66	65
Baseline	7.2	8.8	7.8
Treatment period	6.3	4.6	4.9
West Europe			
N	69	64	67
Baseline	18.2	14.0	14.0
Treatment period	11.7	9.3	9.3
North America			
N	62	64	61
Baseline	9.6	9.3	8.1
Treatment period	8.2	7.3	5.2
Asian Pacific			
N	32	31	28
Baseline	6.3	6.0	9.8
Treatment period	5.7	4.3	8.5
Latin America			
N	29	27	28
Baseline	11.5	8.4	11.9
Treatment period	8.7	5.3	4.8

4.2 Other Special/Subgroup Populations

Because the use of concomitant LEV was later determined to be a potential confounding factor in N01252 and N01253, and it was recognized that LEV and BRV had a similar mechanism of action, analyses were performed to examine the difference in efficacy in patients with or without concomitant use of LEV in Studies N01252 and N01253. The effect of prior use of LEV in Study N01358 was also evaluated.

It was reported that at least 40% of the patients in Studies N01252 and N01253 and 37% of the patients in Study N01358 used CBZ as concomitant AED. During the review process, the issue of possible confounding effect of concomitant use of Carbamazepine (CBZ) was raised, and data of CBZ use during the study were obtained from the sponsor.

A total of 322 subjects in Study N01252 and 239 subjects in N01253 had CBZ data indicating whether a subject was using CBZ as concomitant AED. All subjects in Study N01358 had CBZ data. In the analyses presented below, subjects who had missing CBZ data are assumed as they did not use CBZ. It occurred that in Study N01252, none of the subjects in the BRV 5 mg group used CBZ. No missing data occurred and no imputation was applied in Study N01358.

The data suggests that the effect of LEV is confounded with the effect of the study drug as subjects who were using LEV as concomitant AED showed less improvement or had larger increase in seizure frequency at the end of the study compared to subjects who did not use LEV

as concomitant AED. Prior use of LEV in subjects in Study N01358 does not seem to have impact on the treatment effect of BRV.

The use of CBZ does not seem to have an impact on the treatment effect of BRV. Results are presented in Table 25 for Study N01252, Table 26 for Study N01253 and Table 27 for Study N01358.

Table 25 Analyses of seizure frequency by concomitant use of LEV and CBZ – Study N01252

Median seizure frequency per week	**Placebo N=100**	**BRV**		
		20 mg N=99	**50 mg N=99**	**100 mg N=100**
No LEV as concomitant AED				
N	81	81	79	80
Baseline	2.0	1.8	1.8	2.0
Treatment period	1.7	1.2	1.4	1.1
LEV used as concomitant AED				
N	18	18	20	20
Baseline	3.5	2.8	1.8	2.1
Treatment period	1.7	2.3	1.7	2.4
No CBZ as concomitant AED				
N	62	50	55	65
Baseline	2.1	2.0	1.8	2.1
Treatment period	1.8	1.3	1.6	1.3
CBZ used as concomitant AED				
N	38	49	44	35
Baseline	2.1	1.9	1.8	1.9
Treatment period	1.6	1.4	1.2	1.1

Table 26 Analyses of seizure frequency by concomitant use of LEV and CBZ – Study N01253

Median seizure frequency per week	**Placebo N=96**	**BRV**		
		5 mg N=96	**20 mg N=99**	**50 mg N=101**
No LEV as concomitant AED				
N	77	78	80	82
Baseline	2.6	2.3	2.3	2.8
Treatment period	2.1	1.7	1.9	1.5
LEV used as concomitant AED				
N	19	18	19	19
Baseline	2.7	2.4	2.2	5.7
Treatment period	2.9	2.7	2.1	4.8
No CBZ as concomitant AED				
N	58	96	66	64
Baseline	2.6	2.3	2.2	3.0
Treatment period	2.0	1.8	2.0	1.8
CBZ used as concomitant AED				
N	38	0	33	37
Baseline	3.3		2.3	2.5
Treatment period	2.2		1.7	1.6

Table 27 Analyses of seizure frequency by prior use of LEV and concomitant use of CBZ – Study N01358

Median seizure frequency per 28 days	PBO N=259	BRV 100 mg N=252	BRV 200 mg N=249
Number AEDs ≤ 2, No prior use of LEV			
N	69	71	67
Baseline	8.2	7.3	6.5
Treatment period	7.0	4.0	3.2
Number AEDs ≤ 2, prior use of LEV			
N	13	8	9
Baseline	12.8	14.0	11.1
Treatment period	8.7	8.5	5.3
Number AEDs > 2, No prior use of LEV			
N	47	45	48
Baseline	7.5	8.1	10.4
Treatment period	8.0	4.9	6.2
Number AEDs > 2, prior use of LEV			
N	130	128	125
Baseline	11.3	12.4	11.2
Treatment period	10.8	9.2	8.2
No CBZ as concomitant AED			
N	163	157	155
Baseline	10.7	9.0	9.7
Treatment period	8.9	5.3	5.9
CBZ used as concomitant AED			
N	96	95	94
Baseline	8.1	10.9	8.9
Treatment period	7.9	7.7	5.6

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Three pivotal trials evaluated the effect of BRV at doses from 5 mg/day to 200 mg/day. The two trials conducted earlier included 20% of the subjects who were taking concomitant AED of LEV, which appeared to be a confounding factor of the study drug.

The trial N01358 was initiated after the completion of N01252 and N01253 with an improved design: it enrolled more subjects, studied higher doses of BRV, and it excluded subjects who were using LEV as concomitant AED within 90 days of study entry.

The effectiveness of BRV at daily dose of 100 mg and 200 mg found from N01358 achieved high significance level and appeared to be robust under model assumptions and consistent across demographic and baseline characteristics. The efficacy of BRV 100 mg/day found in Study N01358 was supported by results from N01252, in which the effect of BRV 100 mg/day achieved a nominal p-value-f 0.037.

The distributions of the seizure frequency at baseline and during the treatment were highly skewed and marked deviation from the model assumptions were noted in all 3 studies. Although the non-parametric rank analysis generally confirmed results from the primary analysis for the 3 studies, the least square estimate from the primary analysis may not provide a close estimate of the seizure frequency.

5.2 Conclusions and Recommendations

The 3 pivotal trials provided evidence that BRV at daily dose of 100 mg or 200 mg is effective in reducing the seizure frequency in patients with POS. The reviewer recommend that the medians (b) (4) be used in the labeling descriptions for treatment difference (b) (4) .

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/s/

XIAORONG YAN
11/09/2015

KUN JIN
11/09/2015
I concur with the review.

HSIEN MING J HUNG
11/10/2015

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

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 205-836, NDA 205-837, NDA 205-838
Drug Name:	ucb 34714
Indication(s):	104 Week Rat and Mouse Carcinogenicity Studies
Applicant:	**Sponsor:** UCB Pharma S.A. Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium **Performing Laboratory:** (b) (4)
Documents Reviewed:	**Electronic submission:** Submitted on November 22, 2014 **Electronic data:** Submitted on January 7, 2015
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -6
Statistical Reviewer:	Mohammad Atiar Rahman, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Neurology Products
Reviewing Pharmacologist:	Edward J Fisher, Ph.D.
Project Manager:	Cathleen Michaloski
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of ucb 34714 when administered orally by combination of dietary admix and twice daily gavage at appropriate drug levels for 105 weeks for both sexes of rats and male mice, and 104 weeks for female mice. Results of this review have been discussed with the reviewing pharmacologist Dr. Fisher.

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

2. Rat Study

Two separate experiments were conducted, one in male and one in female rats. In each of these two experiments there were four treated groups and one control group. Two hundred and fifty Han Wistar (Crl: WI(Han)) rats of each sex were assigned randomly to the treated and control groups in equal size of 50 rats per group. The dose levels for treated groups were 150, 230, 450 and 700 mg/kg/day. In this review these dose groups would be referred to as the low, medium, mid-hi, and high dose groups, respectively. In treated groups, the dose given by dietary admix was100 mg/kg/day and doses administered by gavage were 50, 130, 350 and 600 mg/kg/day, split into two equal daily sub doses given 6 hours apart. The test item was administered by gavage as a suspension in the vehicle, 1% w/v methylcellulose 400 cps in sterile pyrogen-free water. For dietary admix, the test item was incorporated at appropriate concentrations into a standard rodent ground diet to which rats had access *ad libitum*. Concurrent control groups received the unsupplemented diet and vehicle alone.

During the administration period all animals were routinely observed for clinical signs, treatment reactions, mortality and morbidity. A detailed clinical examination and palpation was done weekly to detect superficial masses. Body weights were recorded once during the week before the commencement of treatment, then daily for the first 13 weeks of the study and once every week thereafter. Additional measurements of body weight were performed for animals showing weight loss or deterioration in condition.

2.1. Sponsor's analyses

2.1.1. Survival analysis

The sponsor estimated the survival function by Kaplan-Meier’s method (product-limit estimator) and presented the Kaplan-Meier’s curves graphically. The sponsor statistically analyzed the mortality data using the method suggested by Peto et al. (1980), assuming death before the final sacrifice as fatal and terminal sacrifices as non-fatal. Further mortality comparisons were performed using the rank sum tests modified for censored survival data (Kruskal-Wallis test).

Sponsor's findings: The sponsor's analysis showed 15, 10, 15, 9, and 10 male rat deaths, and 10, 12, 16, 10, and 13 female rat deaths in control, low, medium, mid-hi, and high dose groups, respectively. Sponsor's analysis did not show any statistically significant differences in mortalities among dose groups in either sex of rats. The sponsor concluded that the survival was unaffected by treatment.

2.1.2. Tumor data analysis

The sponsor also analyzed the tumor data using the methods outlined in the paper of Peto et al. (1980) for dose response relationships and pairwise comparisons of the treated groups with control. Analyses of tumor data were carried out based on the time of death and whether the tumors were considered fatal or non-fatal. The study pathologist classified a tumor as fatal, probably fatal, probably non-fatal or non-fatal. In their statistical analysis the sponsor considered the tumors classified as fatal or probably fatal being fatal, and those classified as probably non-fatal or non-fatal considered being non-fatal. Tumors detected in terminally killed animals are automatically classified as nonfatal. For palpable tumors, additional analyses were performed with the tumors considered to be fatal and time of detection (rather than time of death) as the censoring time.

The analysis of fatal tumors was based on actual weeks of death (or weeks of first detection for palpable tumors). The analysis of non-fatal tumors was based on the following fixed time intervals: weeks 1-52, 53-78, 79-92 and over 92, with the terminal sacrifice treated separately. Tumor types with 10 or less number of tumor bearing animals were analyzed using the exact tests based on the discrete permutation distribution, with asymptotic tests used for tumors with higher incidence.

Analysis was conducted on all individual tumors with a minimum incidence of 3 cases. Where pathologically appropriate, analysis was also conducted on the combined incidence of related tumors.

Adjustment for multiple testing: For the evaluation of dose response relationship tests the sponsor used the levels of two-tailed 0.001, 0.01, 0.05, 0.1. For the evaluation of dose response relationship the sponsor also used the levels of one-tailed 0.005 (the test level suggested by the FDA for common tumors), and 0.025 (the test level suggested by the FDA for rare tumors). The sponsor further used the test level of one-tailed $p<0.0005$, indicating very strong evidence indeed of an effect, and one-tailed $p<0.05$, suggesting the possibility of an effect.

Reviewer's comment: *It is found from the above list of test levels, used by the sponsor, that along with a host of other test levels, the sponsor also used the multiple testing adjusted test levels for dose response relationship suggested in the FDA guidance for statistical design and analysis of carcinogenicity studies. For pairwise comparison such adjusted test levels suggested in the FDA guidance were not used by the sponsor.*

Sponsor's findings: The sponsor's analyses showed statistically significant dose response relationship across the treatment groups in the incidences of benign and combined incidences of benign or malignant thymoma in thymus in female rats. In female rats the pairwise comparisons also showed statistically significant increased incidences of this tumor type in the high dose group compared to their control. The sponsor added that based on historical control, the expected incidence of thymus/thymoma in rats over 104 weeks range is 0 – 8.7%.
The sponsor's analysis further showed statistically significant positive dose response relationship at 0.05 level in the incidence of thyroid follicular cell adenoma in male and female rats combined, and in the combined incidences of thyroid follicular cell adenoma and carcinoma in male and female rats combined.

2.2. Reviewer's analyses

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

2.2.1. Survival analysis

The survival distributions of rats in all four treatment groups were estimated using the Kaplan-Meier product limit method. The dose response relationship across treatment groups was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for male and female rats, respectively. The intercurrent mortality data are given in Tables 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 15, 10, 15, 9, and 10 male rat deaths and 10, 12, 16, 10, and 13 female rat deaths in control, low, medium, mid-hi, and high dose groups, respectively. This reviewer's analysis did not show any statistically significant differences in mortalities among dose groups in either sex of rats.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships across control and treated groups, and pairwise comparisons of each of the treated group with control. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of s_h =1. An animal that dies at week w_h without a tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}}\right)^k < 1$. The adjusted group size is then 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 that dies before the terminal sacrifice develops at least one tumor, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used, using scores 0, 200, 600, and 1833 for male rats, and 0, 200, 600, and 2000 for female rats for control, low, medium, and high dose groups, respectively. Where the score 1833 used for male rat high dose is the weighted average of 2000 mg/kg/day used for 70 weeks and 1000 mg/kg/day used for 14 weeks i.e. (2000x70+1000x14)/84).

The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male and female rats, respectively.

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

It should be noted that the FDA guidance on multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Lin and Rahman (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

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

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

			Cont	Low	Med	MidHi	High	P-Value		
Sex	Organ Name	Tumor Name	N=50	N=50	N=50	N=50	N=50	Dos Resp	C vs L	C vs M	C vs MH	C vs H
Male	SKIN & SUBCUTIS	SQUAMOUS CELL CARCIN	0	0	0	0	2	0 0375				0 2529

Female LIVER	HEPATOCELLULAR ADENO	1	3	3	6	2	0 2029	0 3002	0 2920	0 0457	0 4663
THYMUS	BENIGN THYMOMA	2	2	4	5	11	<0 001*	0 6834	0 3178	0 1908	0 0049*
	BEN+MALG THYMOMA	2	3	4	5	11	<0 001*	0 4897	0 3178	0 1908	0 0049*

Based on the criteria of adjustment for multiple testing discussed above, the incidence of benign thymoma and combined incidences of benign and malignant thymoma in thymus of female rats were considered to have statistically significant dose response relationships. Also in female rats, the pairwise comparison showed statistically significant increased incidence of benign thymoma and combined incidences of benign and malignant thymoma in thymus in high dose group compared to their control.

3. Mouse Study

Two separate experiments were conducted, one in male and one in female mice. In each of these two experiments there were three treated groups and one control group. Two hundred and forty CD-1 (Crl: CD-1(ICR)) mice of each sex were assigned randomly to the treated and control groups in equal size of 60 mice per group. The dose levels for treated groups were 400, 550 and 700 mg/kg/day. In this review these dose groups would be referred to as the low, medium, and high dose groups, respectively. In treated groups, the dose given by dietary admix was 300 mg/kg/day and doses administered by gavage were 100, 250 and 400 mg/kg/day, split into two equal daily sub doses given 6 hours apart. The test item was administered by gavage as a suspension in the vehicle, 1% w/v methylcellulose 400 cps in sterile pyrogen-free water. For dietary admix, the test item was incorporated at appropriate concentrations into a standard rodent diet to which mice had access *ad libitum*. Concurrent control group received the unsupplemented diet and vehicle alone.

During the administration period all animals were routinely observed for clinical signs, treatment reaction, mortality and morbidity. A detailed clinical examination and palpation were done weekly to detect superficial masses. Body weights were recorded once during the week before the commencement of treatment, then daily for the first 13 weeks of the study and once every week thereafter. Additional measurements of body weight were performed for animals showing weight loss or deterioration in condition.

3.1. Sponsor's analyses

3.1.1. Survival analysis

The sponsor used similar methodologies to analyze the mouse survival data as they used to analyze the rat survival data.

Sponsor’s findings: The sponsor analysis showed 28, 34, 35, and 31 male mouse deaths, 38, 40, 40, and 40 female mouse deaths in control, low, medium, and high dose groups, respectively. The sponsor’s analysis did not show any statistically significant differences in mortalities among

dose groups in either sex of mice. However, for the first year, the pairwise comparison of high dose group and control group showed statistically significant increased death in male mice ($p<0.05$) and the two sexes combined ($p<0.01$). The sponsor concluded that the survival was unaffected by treatment.

3.1.2. Tumor data analysis

The sponsor used similar methodologies to analyze the mouse tumor data as they used to analyze the rat tumor data.

Adjustment for multiple testing: The sponsor used similar methodologies for the adjustment of multiple testing as they used to analyze the rat tumor data.

Sponsor's findings: The sponsor's analyses showed statistically significant dose response relationship across treatment groups in the incidence of hepatocellular carcinomas ($p<0.001$), hepatocellular adenomas ($p<0.01$) and overall incidence of hepatocellular carcinoma or adenoma ($p<0.01$) in male mice, and ovarian benign luteomas ($p<0.05$) and ovarian benign sertoli cell tumors ($p<0.05$) in female mice. In male mice, the pairwise comparisons showed statistically significant increased incidences of hepatocellular adenoma in the medium ($p<0.05$) and high ($p<0.01$) dose groups, hepatocellular carcinoma in the high ($p<0.01$) dose group compared to their respective control.

3.2. Reviewer's analyses

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

For the analysis of both the survival data and the tumor data this reviewer used similar methodologies as he used for the analyses of the rat survival and tumor data.

3.2.1. Survival analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data of all treatment groups are given in Tables 4A and 4B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals for control, low, medium, and high dose 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 26, 34, 34,and 31 male mouse deaths, and 38, 39, 39, and 40 female mouse deaths in control, low, medium, and high dose groups, respectively. This reviewer's analysis did not show any statistically significant differences in

mortalities among dose groups in either sex of mice. The pairwise comparisons showed statistically significant decreased mortality in the female mouse low dose group compared to their control.

Reviewer's comment: *The sponsor's calculation showed 28, and 35 male mouse deaths in the control and medium dose groups, while this reviewer's calculation showed 26 and 34 male mouse deaths in these two groups, respectively. Also, the sponsor's calculation showed 40 female mouse deaths in both the low and medium dose groups, while this reviewer's calculation showed 39 deaths in each of these groups. These differences are because of the reason that there were two mice (#17,and # 18) in the male control group, one mouse (#169) in the male medium dose group, one mouse (#396) in the female low dose group, and one mouse (#457) in the female medium dose group that died naturally during their terminal sacrifice week. This reviewer classified these animals as survivors, while the sponsor counted them as dead.*

3.2.2. Tumor data analysis

The tumor rates and the p-values of the tested tumor types are given in Tables 6A and Table 6B in the appendix, for male and female mice respectively.

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

Summary Table of Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Control in Mice

			P_Value						
Sex	Organ Name	Tumor Name	Cont	Low	Med	High	Dose Resp	C vs L	C vs M	C vs H
Male	LIVER	HEPATOCELLULAR ADENOMA	7	9	16	17	<0 001*	0 3368	0 0118	0 0025*
		HEPATOCELLULAR CARCINOMA	0	2	3	9	<0 001*	0 2359	0 1083	<0 001*
		HEPATOCELLULAR ADEN+CARC	7	9	17	18	<0 001*	0 3368	0 0078*	0 0016*
Female	CERVIX	HISTIOCYTIC SARCOMA	0	1	3	3	0 0315	0 5190	0 1299	0 1249
		MALIG LYMPHOMA FOLLICLE	0	5	0	0	0 5641	0 0376*		
	KIDNEYS	HISTIOCYTIC SARCOMA	0	1	2	3	0 0391	0 5190	0 2597	0 1249
	LIVER	HISTIOCYTIC SARCOMA	1	3	8	3	0 0646	0 3466	0 0193	0 3174
	LUNGS	HISTIOCYTIC SARCOMA	0	2	6	2	0 0418	0 2661	0 0149*	0 2467
		MALIG LYMPHOMA FOLLICLE	0	5	1	0	0 4694	0 0376*	0 5000	
	MESENTERY	HISTIOCYTIC SARCOMA	0	2	6	2	0 0425	0 2661	0 0162*	0 2467
	OVARIES	BENIGN LUTEOMA	1	0	6	4	0 0268	0 5128	0 0580	0 1790
		BENIGN SERTOLI CELL TUMOU	0	0	0	3	0 0141*			0 1200
		HISTIOCYTIC SARCOMA	0	2	5	3	0 0276	0 2661	0 0312*	0 1249
	UTERUS	HISTIOCYTIC SARCOMA	0	3	6	1	0 0935	0 1348	0 0149*	0 5000
		MALIG LYMPHOMA FOLLICLE	0	5	0	0	0 5641	0 0376*		

Based on the criteria of adjustment for multiple testing discussed in the rat data analysis section, the incidence of hepatocellular adenoma, hepatocellular carcinoma and combined incidences of hepatocellular adenoma and carcinoma were considered to have statistically significant dose response relationship in male mice. In female mice the incidence of benign sertoli cell tumor in

ovaries was also considered to have statistically significant dose response relationship. All pairwise comparisons marked by the asterisks were considered to have statistically significant increased incidence in the related tumor types and dose groups compared to their respective control.

4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of ucb 34714 when administered orally by combination of dietary admix and twice daily gavage at appropriate drug levels for 105 weeks for both sexes of rats and male mice, and 104 weeks for female mice.

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

Rat study: Two separate experiments were conducted, one in male and one in female rats. In each of these two experiments there were four treated groups and one control group. Two hundred and fifty Han Wistar rats of each sex were assigned randomly to the treated and control groups in equal size of 50 rats per group. The dose levels for treated groups were 150, 230, 450 and 700 mg/kg/day. In treated groups, the dose given by dietary admix was100 mg/kg/day and doses administered by gavage were 50, 130, 350 and 600 mg/kg/day, split into two equal daily sub doses given 6 hours apart. The test item was administered by gavage as a suspension in the vehicle, 1% w/v methylcellulose 400 cps in sterile pyrogen-free water. For dietary admix, the test item was incorporated at appropriate concentrations into a standard rodent ground diet to which rats had access *ad libitum*. Concurrent control groups received the unsupplemented diet and vehicle alone.

During the administration period all animals were routinely observed for clinical signs, treatment reaction, mortality and morbidity. A detailed clinical examination and palpation were done weekly to detect superficial masses. Body weights were recorded once during the week before the commencement of treatment, then daily for the first 13 weeks of the study and once every week thereafter. Additional measurements of body weight were performed for animals showing weight loss or deterioration in condition.

The tests did not show any statistically significant differences in mortalities among dose groups in either sex of rats. The tests showed statistically significant dose response relationships in the incidence of benign thymoma and combined incidences of benign and malignant thymoma in thymus of female rats. Also in female rats, the pairwise comparison showed statistically significant increased incidence of benign thymoma and combined incidences of benign and malignant thymoma in thymus in high dose group compared to their control.

Mouse Study: Two separate experiments were conducted, one in male and one in female rats. In each of these two experiments there were three treated groups and one control group. Two hundred and forty CD-1 (Crl: CD-1(ICR)) mice of each sex were assigned randomly to the treated

and control groups in equal size of 60 rats per group. The dose levels for treated groups were 400, 550 and 700 mg/kg/day. In treated groups, the dose given by dietary admix was 300 mg/kg/day and doses administered by gavage were 100, 250 and 400 mg/kg/day, split into two equal daily sub doses given 6 hours apart. The test item was administered by gavage as a suspension in the vehicle, 1% w/v methylcellulose 400 cps in sterile pyrogen-free water. For dietary admix, the test item was incorporated at appropriate concentrations into a standard rodent diet to which mice had access *ad libitum*. Concurrent control group received the unsupplemented diet and vehicle alone.

During the administration period all animals were routinely observed for clinical signs, treatment reaction, mortality and morbidity. A detailed clinical examination and palpation were done weekly to detect superficial masses. Body weights were recorded once during the week before the commencement of treatment, then daily for the first 13 weeks of the study and once every week thereafter. Additional measurement of body weight were performed for animals showing weight loss or deterioration in condition.

The tests did not show any statistically significant differences in mortalities among dose groups in either sex of mice. The pairwise comparisons showed statistically significant decreased mortality in the female mouse low dose group compared to their control. The tests showed statistically significant dose response relationship in the incidences of hepatocellular adenoma, hepatocellular carcinoma and combined incidences of hepatocellular adenoma and carcinoma in male mice. In female mice the incidence of benign sertoli cell tumor in ovaries also showed statistically significant dose response relationship. The following pairwise comparisons showed statistically significant increased incidences in the related tumor types and dose groups compared to their respective control.

Statistically Significant Pairwise Comparisons in Mice

Sex	Organ Name	Tumor Name	Pairwise Comparison
Male	LIVER	HEPATOCELLULAR ADENOMA	C Vs H
		HEPATOCELLULAR CARCINOMA	C Vs H
		HEPATOCELLULAR_ADEN+CARC	C Vs H, and C Vs M
Female	CERVIX	MALIG LYMPHOMA FOLLICLE	C vs L
	LUNGS	HISTIOCYTIC SARCOMA	C Vs M
		MALIG LYMPHOMA FOLLICLE	C Vs L
	MESENTERY	HISTIOCYTIC SARCOMA	C Vs M
	OVARIES	HISTIOCYTIC SARCOMA	C Vs M
	UTERUS	HISTIOCYTIC SARCOMA	C Vs M
		MALIG LYMPHOMA FOLLICLE	C Vs L

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Concur: Karl Lin, Ph.D.
Team Leader, Biometrics-6

cc:
Archival NDA 205-836, NDA 205-837, NDA 205-838

Dr. Fisher
Ms. Michaloski

Dr. Tsong
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Dr. Rahman
Ms. Patrician

5. Appendix

Table 1A: Intercurrent Mortality Rate
Male Rats

	0mg|kg|day		150mg|kg|day		230mg|kg|day		450mg|kg|day		700mg|kg|day	
Week	No of Death	#Cum %	No of Death	#Cum %	No of Death	#Cum %	No of Death	#Cum %	No of Death	#Cum %
0 - 52	1	2 00	2	4 00			1	2 00	3	6 00
53 - 78	5	12 00	1	6 00	3	6 00	1	4 00	2	10 00
79 - 91	4	20 00	1	8 00	3	12 00	2	8 00	3	16 00
92 - 104	5	30 00	6	20 00	9	30 00	5	18 00	2	20 00
Ter Sac	35	70 00	40	80 00	35	70 00	41	82 00	40	80 00
Total	N=50		N=50		N=50		N=50		N=50	

Cum. %: Cumulative percentage except for Ter. Sac.

Table 1B: Intercurrent Mortality Rate
Female Rats

	0mg|kg|day		150mg|kg|day		230mg|kg|day		450mg|kg|day		700mg|kg|day	
Week	No of Death	#Cum %	No of Death	#Cum %	No of Death	#Cum %	No of Death	#Cum %	No of Death	#Cum %
0 - 52			1	2 00	1	2 00	3	6 00		
53 - 78	2	4 00	2	4 00	1	4 00	4	10 00	4	14 00
79 - 91	2	8 00	2	8 00	4	12 00	4	18 00	2	18 00
92 - 104	6	20 00	8	24 00	10	32 00	1	20 00	4	26 00
Ter Sac	40	80 00	38	76 00	34	68 00	40	80 00	37	74 00
Total	N=50		N=50		N=50		N=50		N=50	

Cum. %: Cumulative percentage except for Ter. Sac.

Table 2A: Intercurrent Mortality Comparison
Male Rats

	Test	Statistic	P-Value
Dose-Response	Likelihood Ratio	0 2376	
Homogeneity	Log-Rank	0 4351	

Table 2B: Intercurrent Mortality Comparison
Female Rats

	Test	Statistic	P-Value
Dose-Response	Likelihood Ratio	0 6075	
Homogeneity	Log-Rank	0 6477	

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Male Rats

Organ Name	Tumor Name	0 mg Cont N=50	150 mg Low N=50	230 mg Med N=50	450 mg MidHi N=50	700 mg High N=50	P_Value Dose N=50	P_Value Resp	P_Value C vs L	P_Value C vs M	P_Value C vs MH	P_Value C vs H
ABDOMINAL CAVIT	BENIGN GRANULAR CELL	0	0	1	0	0	0	4044		0	5114	
ADRENAL CORTEX	ADENOMA	0	0	0	0	1	0	1956			0	5057
ADRENAL MEDULLA	BENIGN PHAEOCHROMOCY	2	2	0	2	2	0	4260	0	3342	0	7641
	MALIGNANT LYMPHOMA	1	0	0	0	0	0	8053	0	5111	0	5056
BONE: FEMUR & S	HISTIOCYTIC SARCOMA	0	1	0	0	0	0	6018	0	5222		
	MALIGNANT LYMPHOMA	1	0	0	0	1	0	4000	0	5111	0	5056
	OSTEOSARCOMA	0	0	1	0	0	0	4027		0	5169	
BONE: VERTEBRAL	HISTIOCYTIC SARCOMA	0	1	0	0	0	0	6018	0	5222		
	OSTEOMA	1	0	0	0	0	0	8089	0	5169	0	5114
BRAIN	BENIGN GRANULAR CELL	1	6	0	3	1	0	7038	0	0662	0	5114
	HISTIOCYTIC SARCOMA	0	1	0	0	0	0	6018	0	5222		
	MALIGNANT ASTROCYTOM	0	0	0	0	1	0	1956			0	5057
	MALIGNANT EPENDYMOMA	0	1	0	1	0	0	4779	0	5222		0
	MALIGNANT LYMPHOMA	1	0	0	0	0	0	8053	0	5111	0	5056
	MALIGNANT MIXED GLIO	0	0	0	1	0	0	4044			0	5222
EPIDIDYMIDES	HISTIOCYTIC SARCOMA	0	1	0	0	0	0	6018	0	5222		
	MALIGNANT LYMPHOMA	1	0	0	0	1	0	4000	0	5111	0	5056
	MALIGNANT MESOTHELIO	0	1	0	0	1	0	3214	0	5169		
EXORBITAL LACHR	MALIGNANT LYMPHOMA	1	0	0	0	1	0	4000	0	5111	0	5056
EYES	MALIGNANT LYMPHOMA	1	0	0	0	1	0	4000	0	5111	0	5056
HARDERIAN GLAND	HISTIOCYTIC SARCOMA	0	1	0	0	0	0	6018	0	5222		
	MALIGNANT LYMPHOMA	1	0	0	0	1	0	4000	0	5111	0	5056
HEART	BENIGN SCHWANNOMA	0	1	0	0	0	0	6044	0	5169		
	HISTIOCYTIC SARCOMA	0	1	0	0	0	0	6018	0	5222		
	MALIGNANT LYMPHOMA	1	0	0	0	0	0	8053	0	5111	0	5056
KIDNEYS	HISTIOCYTIC SARCOMA	0	1	0	0	0	0	6018	0	5222		
	LIPOMA	0	0	1	0	0	0	4044		0	5114	
	MALIGNANT LYMPHOMA	1	0	0	0	1	0	4000	0	5111	0	5056
	MALIGNANT NEPHROBLAS	0	0	0	0	1	0	1991			0	5114
LARYNX	MALIGNANT LYMPHOMA	1	0	0	0	0	0	8053	0	5111	0	5056
LIVER	HEPATOCELLULAR ADENO	1	1	0	1	2	0	2103	0	2643	0	5114
	HEPATOCELLULAR CARCI	0	0	1	0	0	0	4044		0	5114	
	HISTIOCYTIC SARCOMA	0	1	0	0	0	0	6018	0	5222		
	MALIGNANT LYMPHOMA	1	0	0	0	1	0	4000	0	5111	0	5056
	MALIGNANT LYMPHOMA L	0	0	1	0	0	0	4044		0	5114	
LUNGS	BRONCHIOLO-ALVEOLAR	1	0	0	0	0	0	8089	0	5169	0	5114

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Male Rats

Organ Name	Tumor Name	0 mg Cont N=50	150 mg Low N=50	230 mg Med N=50	450 mg MidHi N=50	700 mg High N=50	P_Value Dose N=50	P_Value Resp	P_Value C vs L	P_Value C vs M	P_Value C vs MH	P_Value C vs H
LUNGS	HISTIOCYTIC SARCOMA	0	1	0	0	0	0	6018	0	5222		
	MALIGNANT LYMPHOMA	1	0	0	0	1	0	4000	0	5111	0	5056	0	5165	0	2528
LYMPH NODE: HEP	HISTIOCYTIC SARCOMA	0	1	0	0	0	0	6018	0	5222		
	MALIGNANT LYMPHOMA	1	0	0	0	0	0	8053	0	5111	0	5056	0	5165	0	5000
LYMPH NODE: LUM	MALIGNANT LYMPHOMA	1	0	0	0	0	0	8053	0	5111	0	5056	0	5165	0	5000
LYMPH NODE: MED	HAEMANGIOMA	1	0	0	0	0	0	8089	0	5169	0	5114	0	5222	0	5057
	HISTIOCYTIC SARCOMA	0	1	0	0	0	0	6018	0	5222		
	MALIGNANT LYMPHOMA	1	0	0	0	0	0	8053	0	5111	0	5056	0	5165	0	5000
LYMPH NODE: MES	HAEMANGIOMA	6	7	3	2	3	0	9489	0	5530	0	7803	0	8936	0	7696
	HAEMANGIOSARCOMA	1	0	0	2	0	0	4995	0	5169	0	5114	0	5337	0	5057
	HISTIOCYTIC SARCOMA	0	1	0	0	0	0	6018	0	5222		
	MALIGNANT LYMPHOMA	1	0	0	0	1	0	4000	0	5111	0	5056	0	5165	0	2528
LYMPH NODE: SUB	HISTIOCYTIC SARCOMA	0	1	0	0	0	0	6018	0	5222		
	MALIGNANT LYMPHOMA	1	0	0	0	1	0	4000	0	5111	0	5056	0	5165	0	2528
LYMPH NODE: UNS	MALIGNANT LYMPHOMA	1	0	0	0	0	0	8053	0	5111	0	5056	0	5165	0	5000
MAMMARY GLAND	ADENOLIPOMA	1	0	1	0	0	0	8089	0	5169	0	2586	0	5222	0	5057
	MALIGNANT LYMPHOMA	1	0	0	0	0	0	8053	0	5111	0	5056	0	5165	0	5000
NASAL CAVITY/HE	MALIGNANT SCHWANNOMA	0	1	0	0	0	0	6018	0	5222		
PANCREAS	HISTIOCYTIC SARCOMA	0	1	0	0	0	0	6018	0	5222		
	ISLET CELL ADENOMA	3	0	1	1	0	0	9446	0	8913	0	7089	0	7247	0	8836
	MALIGNANT LYMPHOMA	1	0	0	0	1	0	4000	0	5111	0	5056	0	5165	0	2528
PARATHYROID GLA	ADENOMA	4	2	3	1	1	0	9436	0	6935	0	5257	0	8461	0	8270
	MALIGNANT LYMPHOMA	1	0	0	0	0	0	8053	0	5111	0	5056	0	5165	0	5000
PEYER'S PATCHES	HISTIOCYTIC SARCOMA	0	1	0	0	0	0	6018	0	5222		
PITUITARY GLAND	MALIGNANT LYMPHOMA	1	0	0	0	0	0	8053	0	5111	0	5056	0	5165	0	5000
	MALIGNANT SCHWANNOMA	0	1	0	0	0	0	6044	0	5169		
	PARS DISTALIS ADENOM	11	10	15	13	13	0	2804	0	5230	0	3092	0	4552	0	4060
	PARS INTERMEDIA ADEN	0	1	1	0	0	0	6857	0	5169	0	5114		
PREPUTIAL GLAND	MALIGNANT LYMPHOMA	1	0	0	0	0	0	8053	0	5111	0	5056	0	5165	0	5000
PROSTATE GLAND	ADENOCARCINOMA	1	0	0	0	0	0	8053	0	5111	0	5056	0	5165	0	5000
	ADENOMA	0	0	0	0	1	0	1956			0	5057		
	MALIGNANT LYMPHOMA	1	0	0	0	0	0	8053	0	5111	0	5056	0	5165	0	5000
SALIVARY GLAND:	MALIGNANT LYMPHOMA	1	0	0	0	0	0	8053	0	5111	0	5056	0	5165	0	5000
	MALIGNANT SCHWANNOMA	0	0	0	1	0	0	4044			0	5222		

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Male Rats

Organ Name	Tumor Name	0 mg Cont N=50	150 mg Low N=50	230 mg Med N=50	450 mg MidHi N=50	700 mg High N=50	P_Value Dose	P_Value Resp	P_Value C vs L	P_Value C vs M	P_Value C vs MH	P_Value C vs H
SEMINAL VESICLE	ADENOMA	1	0	0	0	0	0 8089	0 5169	0 5114	0 5222	0 5057	
	MALIGNANT LYMPHOMA	1	0	0	0	1	0 4000	0 5111	0 5056	0 5165	0 2528	
SKELETAL MUSCLE	MALIGNANT LYMPHOMA	1	0	0	0	0	0 8053	0 5111	0 5056	0 5165	0 5000	
SKIN	BENIGN GRANULAR CELL	0	0	0	1	0	0 4044		0 5222			
	MALIGNANT LYMPHOMA	1	0	0	0	0	0 8053	0 5111	0 5056	0 5165	0 5000	
SKIN & SUBCUTIS	BASAL CELL ADENOMA	1	0	1	1	0	0 6774	0 5169	0 2586	0 2699	0 5057	
	BASAL CELL CARCINOMA	0	1	1	0	1	0 3776	0 5169	0 5169	0 5057		
	BENIGN HAIR FOLLICLE	0	0	3	0	0	0 6699	0 1293				
	BENIGN SCHWANNOMA	1	0	0	0	0	0 8089	0 5169	0 5114	0 5222	0 5057	
	FIBROMA	0	0	0	1	0	0 4044		0 5222			
	KERATOACANTHOMA	4	6	4	3	6	0 3890	0 4137	0 3956	0 5502	0 3842	
	MALIGNANT LYMPHOMA	1	0	0	0	0	0 8053	0 5111	0 5056	0 5165	0 5000	
	SEBACEOUS CELL ADENO	0	1	0	2	0	0 4049	0 5169	0 2699			
	SQUAMOUS CELL CARCIN	0	0	0	0	2	0 0375		0 2529			
	SQUAMOUS CELL PAPILL	3	0	0	2	1	0 6438	0 8913	0 8875	0 5426	0 7006	
SMALL INTESTINE	HAEMANGIOMA	0	1	0	0	0	0 6044	0 5169				
	LEIOMYOSARCOMA	0	1	0	0	0	0 6044	0 5169				
SPINAL CORD	MALIGNANT LYMPHOMA	1	0	0	0	0	0 8053	0 5111	0 5056	0 5165	0 5000	
SPLEEN	HAEMANGIOMA	1	0	0	0	1	0 3965	0 5169	0 5114	0 5222	0 2529	
	HISTIOCYTIC SARCOMA	0	1	0	0	0	0 6018	0 5222				
	MALIGNANT LYMPHOMA	1	0	0	0	1	0 4000	0 5111	0 5056	0 5165	0 2528	
	MALIGNANT LYMPHOMA L	0	0	1	0	0	0 4044	0 5114				
STERNUM INCL B	HISTIOCYTIC SARCOMA	0	1	0	0	0	0 6018	0 5222				
	MALIGNANT LYMPHOMA	1	0	0	0	1	0 4000	0 5111	0 5056	0 5165	0 2528	
STOMACH: GLANDU	HISTIOCYTIC SARCOMA	0	1	0	0	0	0 6018	0 5222				
	MALIGNANT LYMPHOMA	1	0	0	0	0	0 8053	0 5111	0 5056	0 5165	0 5000	
STOMACH: NON-GL	MALIGNANT LYMPHOMA	1	0	0	0	0	0 8053	0 5111	0 5056	0 5165	0 5000	
	SQUAMOUS CELL PAPILL	0	0	0	1	0	0 4044		0 5222			
SUB-CUTANEOUS T	BENIGN PARAGANGLIOMA	0	0	1	0	0	0 4044	0 5114				
	FIBROMA	4	1	0	1	0	0 9892	0 8400	0 9471	0 8461	0 9446	
	FIBROSARCOMA	1	3	0	0	0	0 9474	0 3253	0 5056	0 5165	0 5000	
	HAEMANGIOMA	1	0	1	0	0	0 8089	0 5169	0 2586	0 5222	0 5057	
	HISTIOCYTIC SARCOMA	0	0	0	0	1	0 1991		0 5114			
	LIPOMA	0	2	2	3	1	0 3054	0 2643	0 2586	0 1380	0 5057	
	MALIGNANT LYMPHOMA	0	0	0	0	1	0 1991		0 5114			
	MALIGNANT SCHWANNOMA	1	0	0	0	0	0 8089	0 5169	0 5114	0 5222	0 5057	
	SARCOMA, UNDIFFERENT	0	1	0	1	0	0 4804	0 5169	0 5222			
TESTES	HAEMANGIOMA	0	0	0	0	1	0 1956		0 5057			
	INTERSTITIAL CELL AD	0	2	1	0	3	0 1014	0 2643	0 5114	0 1249		

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Male Rats

Organ Name	Tumor Name	0 mg Cont N=50	150 mg Low N=50	230 mg Med N=50	450 mg MidHi N=50	700 mg High N=50	P_Value Dose Resp	P_Value C vs L	P_Value C vs M	P_Value C vs MH	P_Value C vs H
TESTES	MALIGNANT LYMPHOMA	1	0	0	0	0	0 8053	0 5111	0 5056	0 5165	0 5000
THYMUS	BENIGN THYMOMA	0	2	1	1	2	0 1937	0 2643	0 5114	0 5222	0 2529
	MALIGNANT LYMPHOMA	1	0	0	0	1	0 4000	0 5111	0 5056	0 5165	0 2528
	MALIGNANT THYMOMA	1	0	0	0	0	0 8053	0 5111	0 5056	0 5165	0 5000
THYROID GLAND	C-CELL ADENOMA	9	7	4	8	8	0 4545	0 6457	0 8937	0 5605	0 5000
	C-CELL CARCINOMA	0	1	1	1	0	0 5707	0 5169	0 5114	0 5222	
	FOLLICULAR CELL ADEN	1	0	5	4	4	0 0542	0 5169	0 1120	0 2094	0 1874
	FOLLICULAR CELL CARC	0	0	1	0	1	0 1982		0 5114		0 5057
	MALIGNANT LYMPHOMA	1	0	0	0	1	0 4000	0 5111	0 5056	0 5165	0 2528
TONGUE	BENIGN GRANULAR CELL	0	0	1	0	0	0 4044		0 5114		
	MALIGNANT LYMPHOMA	0	0	0	0	1	0 1991			0 5114	
TRACHEA	MALIGNANT LYMPHOMA	1	0	0	0	1	0 4000	0 5111	0 5056	0 5165	0 2528
URINARY BLADDER	MALIGNANT LYMPHOMA	1	0	0	0	1	0 4000	0 5111	0 5056	0 5165	0 2528

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Female Rats

Organ Name	Tumor Name	0 mg Cont N=50	150 mg Low N=50	230 mg Med N=50	450 mg MidHi N=50	700 mg High N=50	P_Value Dose N=50	P_Value Resp	P_Value C vs L	P_Value C vs M	P_Value C vs MH	P_Value C vs H
ADRENAL CORTEX	ADENOMA	2	1	0	1	0	0	8792	0 4839	0 7363	0 4670	0 7184
	MALIGNANT LYMPHOMA	0	2	0	0	0	0	7412	0 2526			
ADRENAL MEDULLA	BENIGN PHAEOCHROMOCY	0	0	1	0	0	0	3839	0 4891			
	PHAEOCHROMOCYTOMA, C	0	0	1	0	0	0	3839	0 4891			
BONE: FEMUR & S	HAEMANGIOSARCOMA	0	1	0	0	0	0	5848	0 4946			
	MALIGNANT LYMPHOMA	0	2	0	0	0	0	7412	0 2526			
BRAIN	BENIGN GRANULAR CELL	2	2	0	1	2	0	4443	0 6916	0 7418	0 4750	0 6480
	MALIGNANT ASTROCYTOM	0	1	0	0	1	0	3037	0 4946		0 4778	
	MALIGNANT EPENDYMOMA	0	0	0	0	1	0	1875			0 4719	
	MALIGNANT LYMPHOMA	0	2	0	0	0	0	7412	0 2526			
	MALIGNANT OLIGODENDR	0	0	1	0	0	0	3822	0 4946			
EXORBITAL LACHR	MALIGNANT LYMPHOMA	0	1	0	0	0	0	5822	0 5000			
EYES	MALIGNANT LYMPHOMA	0	1	0	0	0	0	5822	0 5000			
HARDERIAN GLAND	MALIGNANT LYMPHOMA	0	1	0	0	0	0	5822	0 5000			
HEART	BENIGN SCHWANNOMA	0	1	1	0	0	0	6612	0 4946	0 4891		
	MALIGNANT LYMPHOMA	0	2	0	0	0	0	7412	0 2526			
KIDNEYS	MALIGNANT LYMPHOMA	0	2	0	0	0	0	7412	0 2526			
LARGE INTESTINE	MALIGNANT LYMPHOMA	0	1	0	0	0	0	5822	0 5000			
LARYNX	MALIGNANT LYMPHOMA	0	1	0	0	0	0	5822	0 5000			
LIVER	HEPATOCELLULAR ADENO	1	3	3	6	2	0	2029	0 3002	0 2920	0 0457	0 4663
	MALIGNANT LYMPHOMA	0	2	0	0	0	0	7412	0 2526			
LUNGS	BRONCHIOLO-ALVEOLAR	0	1	0	0	1	0	2994	0 4946		0 4719	
	MALIGNANT LYMPHOMA	0	2	0	0	0	0	7412	0 2526			
LYMPH NODE: MED	MALIGNANT LYMPHOMA	0	1	0	0	0	0	5822	0 5000			
LYMPH NODE: MES	HAEMANGIOMA	0	0	3	1	2	0	1052	0 1130	0 4891	0 2255	
	MALIGNANT LYMPHOMA	0	2	0	0	0	0	7412	0 2526			
LYMPH NODE: SUB	MALIGNANT LYMPHOMA	0	2	0	0	0	0	7412	0 2526			
MAMMARY GLAND	ADENOCARCINOMA	4	1	0	0	0	0	9978	0 8126	0 9362	0 9333	0 9269
	ADENOCARCINOMA IN FI	1	0	0	0	1	0	3784	0 4946	0 4891	0 4835	0 7240
	ADENOMA	0	3	0	0	0	0	8251	0 1170			
	FIBROADENOMA	13	9	7	6	3	0	9964	0 7673	0 8760	0 9257	0 9903
	FIBROADENOMA WITH AT	4	0	3	0	0	0	9903	0 9389	0 4754	0 9333	0 9269
	MALIGNANT LYMPHOMA	0	2	0	0	0	0	7412	0 2526			

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Female Rats

Organ Name	Tumor Name	0 mg Cont N=50	150 mg Low N=50	230 mg Med N=50	450 mg MidHi N=50	700 mg High N=50	P_Value Dose	P_Value Resp	P_Value C vs L	P_Value C vs M	P_Value C vs MH	P_Value C vs H
MEDIASTINUM	FIBROSARCOMA	1	0	0	0	0	0 7902	0 4946	0 4891	0 4835	0 4719	
	MALIGNANT SCHWANNOMA	0	0	1	0	0	0 3839		0 4891			
MESENTERY	MALIGNANT PARAGANGLI	0	1	0	0	0	0 5848	0 4946				
NASAL CAVITY/HE	SQUAMOUS CELL CARCIN	0	0	1	0	0	0 3839		0 4891			
OVARIES	BENIGN GRANULOSA CEL	0	0	1	0	1	0 1841		0 4891		0 4719	
	BENIGN THECOMA	0	0	1	0	0	0 3839		0 4891			
	MALIGNANT LYMPHOMA	0	1	0	0	0	0 5822	0 5000				
	PAPILLARY CSYTADENOM	0	0	1	0	1	0 1841		0 4891		0 4719	
	SERTOLIFORM ADENOMA	1	1	0	0	0	0 8702	0 7473	0 4891	0 4835	0 4719	
	TUBULOSTROMAL ADENOM	3	1	1	2	3	0 2848	0 6753	0 6668	0 4584	0 5957	
OVIDUCTS	MALIGNANT LYMPHOMA	0	1	0	0	0	0 5822	0 5000				
PANCREAS	ISLET CELL ADENOMA	0	0	0	0	1	0 1875				0 4719	
	MALIGNANT LYMPHOMA	0	1	0	0	0	0 5822	0 5000				
PARATHYROID GLA	ADENOMA	0	0	1	0	0	0 3839		0 4891			
	MALIGNANT LYMPHOMA	0	1	0	0	0	0 5822	0 5000				
PEYER'S PATCHES	MALIGNANT LYMPHOMA	0	1	0	0	0	0 5822	0 5000				
PITUITARY GLAND	MALIGNANT LYMPHOMA	0	2	0	0	0	0 7412	0 2526				
	PARS DISTALIS ADENOM	35	24	35	34	19	0 9713	0 9655	0 4621	0 4396	0 9923	
PREPUTIAL GLAND	MALIGNANT LYMPHOMA	0	2	0	0	0	0 7412	0 2526				
SALIVARY GLAND:	ADENOCARCINOMA	1	0	0	0	0	0 7902	0 4946	0 4891	0 4835	0 4719	
	ADENOMA	1	0	0	1	0	0 5784	0 4946	0 4891	0 7360	0 4719	
	MALIGNANT LYMPHOMA	0	1	0	0	0	0 5822	0 5000				
SKIN & SUBCUTIS	KERATOACANTHOMA	1	0	1	1	0	0 6501	0 4946	0 7418	0 7418	0 4719	
	MALIGNANT LYMPHOMA	0	1	0	0	0	0 5822	0 5000				
	SQUAMOUS CELL CARCIN	1	0	0	0	0	0 7902	0 4946	0 4891	0 4835	0 4719	
	SQUAMOUS CELL PAPILL	1	1	0	0	0	0 8702	0 7473	0 4891	0 4835	0 4719	
SPINAL CORD	MALIGNANT LYMPHOMA	0	2	0	0	0	0 7412	0 2526				
	MALIGNANT LYMPHOMA L	1	0	0	0	0	0 7867	0 4894	0 4839	0 4783	0 4667	
SPLEEN	MALIGNANT LYMPHOMA	0	2	0	0	0	0 7412	0 2526				
STERNUM INCL B	MALIGNANT LYMPHOMA	0	2	0	0	0	0 7412	0 2526				
STOMACH: GLANDU	MALIGNANT LYMPHOMA	0	1	0	0	0	0 5822	0 5000				
STOMACH: NON-GL	MALIGNANT LYMPHOMA	0	1	0	0	0	0 5822	0 5000				
SUB-CUTANEOUS T	FIBROMA	1	0	0	0	0	0 7902	0 4946	0 4891	0 4835	0 4719	

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Female Rats

Organ Name	Tumor Name	0 mg Cont N=50	150 mg Low N=50	230 mg Med N=50	450 mg MidHi N=50	700 mg High N=50	P_Value Dose Resp	P_Value C vs L	P_Value C vs M	P_Value C vs MH	P_Value C vs H
THORACIC CAVITY	HIBERNOMA	0	0	0	1	0	0 3839		0 4835		
THYMUS	BENIGN THYMOMA	2	2	4	5	11	<0 001*	0 6834	0 3178	0 1908	0 0049*
	MALIGNANT LYMPHOMA	0	2	0	0	0	0 7412	0 2526			
	MALIGNANT THYMOMA	0	1	0	0	0	0 5848	0 4946			
	BEN+MALG THYMOMA	2	3	4	5	11	<0 001*	0 4897	0 3178	0 1908	0 0049*
THYROID GLAND	C-CELL ADENOMA	5	5	3	8	1	0 7563	0 6301	0 6182	0 2336	0 8707
	C-CELL CARCINOMA	2	0	1	0	0	0 9380	0 7473	0 4835	0 7360	0 7240
	FOLLICULAR CELL ADEN	0	2	1	3	2	0 0978	0 2419	0 4891	0 1090	0 2199
	FOLLICULAR CELL CARC	0	0	1	0	0	0 3839		0 4891		
	MALIGNANT LYMPHOMA	0	1	0	0	0	0 5822	0 5000			
TRACHEA	MALIGNANT LYMPHOMA	0	1	0	0	0	0 5822	0 5000			
URINARY BLADDER	MALIGNANT LYMPHOMA	0	1	0	0	0	0 5822	0 5000			
UTERUS	ENDOMETRIAL ADENOCAR	0	0	0	0	1	0 1875		0 4719		
		6	8	6	1	2	0 9865	0 3865	0 5894	0 9339	0 8272
	ENDOMETRIAL ADENOMA	2	3	1	0	1	0 8549	0 4897	0 4835	0 7360	0 4574
	ENDOMETRIAL STROMAL	9	4	2	8	4	0 6927	0 8761	0 9702	0 4601	0 8478
	LEIOMYOSARCOMA	0	0	0	1	0	0 3839		0 4835		
	YOLK SAC CARCINOMA	0	0	1	0	0	0 3839		0 4891		
ZYMBAL'S GLAND	CARCINOMA	0	0	0	0	1	0 1911		0 4778		

Table 4A: Intercurrent Mortality Rate in Male Mice

	0 mg|kg|day		400 mg|kg|day		550 mg|kg|day		700 mg|kg|day	
Week	No of Death	#Cum %	No of Death	#Cum %	No of Death	#Cum %	No of Death	#Cum %
0 - 52	7	11 67	7	11 67	11	18 33	19	31 67
53 - 78	4	18 33	7	23 33	7	30 00	2	35 00
79 - 83	2	21 67	2	26 67	2	33 33	1	36 67
84 - 91	7	33 33	7	38 33	1	35 00	2	40 00
92 - 104	6	43 33	11	56 67	13	56 67	7	51 67
Ter Sac	34	56 67	26	43 33	26	43 33	29	48 33
Total	N=60		N=60		N=60		N=60	

#Cum. %: Cumulative percentage except for Ter. Sac.

Table 4B: Intercurrent Mortality Rate Female Mice

	0 mg|kg|day		400 mg|kg|day		550 mg|kg|day		700 mg|kg|day	
Week	No of Death	#Cum %	No of Death	#Cum %	No of Death	#Cum %	No of Death	#Cum %
0 - 52	6	10 00	5	8 33	8	13 33	11	18 33
53 - 78	14	33 33	13	30 00	11	31 67	9	33 33
79 - 83	1	35 00	2	33 33	4	38 33	2	36 67
84 - 91	7	46 67	7	45 00	6	48 33	8	50 00
92 - 103	10	63 33	12	65 00	10	65 00	10	66 67
Ter Sac	22	36 67	21	35 00	21	35 00	20	33 33
Total	N=60		N=60		N=60		N=60	

 # Cum. %: Cumulative percentage except for Ter. Sac.

Table 5A: Intercurrent Mortality Comparison Male Mice

Test	Statistic	P-Value
Dose-Response	Likelihood Ratio	0 2229
Homogeneity	Log-Rank	0 6305

Table 5B: Intercurrent Mortality Comparison Female Mice

Test	Statistic	P-Value
Dose-Response	Likelihood Ratio	0 7392
Homogeneity	Log-Rank	0 9824

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Com C N=60	400 mg Low N=60	550 mg Med N=60	700 mg High N=60	P_Value Dose Resp	P_Value L vs Com C	P_Value M vs Com C	P_Value H vs Com C
ABDOMINAL CAVIT	MALIG LYMPHOMA FOLLICLE	0	1	0	0	0 7321	0 4886		
	MALIGNANT MESOTHELIOMA	1	0	0	0	0 7278	0 4831	0 4773	0 4524
ADRENAL CORTEX	ADENOMA (TYPE A)	1	0	0	0	0 7278	0 4831	0 4773	0 4524
	ADENOMA (TYPE B)	3	2	2	0	0 8842	0 4782	0 4669	0 8456
	MALIG LYMPHOMA FOLLICLE	3	0	0	0	0 9798	0 8620	0 8572	0 8358
	MALIG LYMPHOMA LYMPHOBLA	0	0	1	0	0 4793		0 4886	
AORTIC ARCH	MALIG LYMPHOMA LYMPHOBLA	0	0	1	0	0 4793		0 4886	
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793		0 4886	
BONE & MARROW:	HAEMANGIOMA	1	0	0	0	0 7321	0 4886	0 4828	0 4578
	HISTIOCYTIC SARCOMA	1	0	0	0	0 7321	0 4886	0 4828	0 4578
	MALIG LYMPHOMA FOLLICLE	5	1	1	0	0 9917	0 8711	0 8648	0 9508
	MALIG LYMPHOMA LYMPHOBLA	0	0	2	1	0 1306		0 2359	0 4578
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793		0 4886	
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7321	0 4886	0 4828	0 4578
	MALIGNANT MASTOCYTOMA	1	0	0	0	0 7278	0 4831	0 4773	0 4524
BONE: EXTRA SEC	OSTEOSARCOMA	0	0	2	0	0 3433		0 2359	
BONE: FEMUR & S	HAEMANGIOSARCOMA	1	0	0	0	0 7321	0 4886	0 4828	0 4578
	HISTIOCYTIC SARCOMA	1	0	0	0	0 7321	0 4886	0 4828	0 4578
	MALIG LYMPHOMA FOLLICLE	2	1	1	1	0 6691	0 4663	0 4574	0 4199
	MALIG LYMPHOMA LYMPHOBLA	0	0	2	1	0 1306		0 2359	0 4578
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793		0 4886	
	MALIGNANT MASTOCYTOMA	1	0	0	0	0 7278	0 4831	0 4773	0 4524
BONE: VERTEBRAL	HAEMANGIOMA	1	0	0	0	0 7321	0 4886	0 4828	0 4578
	MALIG LYMPHOMA FOLLICLE	0	1	0	1	0 3417	0 4886		0 4578
	OSTEOSARCOMA	0	0	1	0	0 4793		0 4886	
BRAIN	MALIG LYMPHOMA FOLLICLE	2	1	0	0	0 9245	0 4744	0 7296	0 7031
	MALIG LYMPHOMA LYMPHOBLA	0	0	1	1	0 1646		0 4886	0 4578
	MALIGNANT MENINGIOMA	1	0	0	0	0 7278	0 4831	0 4773	0 4524
DIAPHRAGM	HISTIOCYTIC SARCOMA	1	0	0	0	0 7278	0 4831	0 4773	0 4524
EPIDIDYMIDES	HISTIOCYTIC SARCOMA	0	0	0	1	0 2262			0 4578
	INTERSTITIAL CELL ADENOMA	0	0	1	1	0 1639		0 4828	0 4578
	MALIG LYMPHOMA FOLLICLE	2	1	0	0	0 9221	0 4663	0 7240	0 6972
	MALIG LYMPHOMA LYMPHOBLA	0	0	2	1	0 1306		0 2359	0 4578
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793		0 4886	
EXORBITAL LACHR	MALIG LYMPHOMA FOLLICLE	2	1	0	0	0 9221	0 4663	0 7240	0 6972
	MALIG LYMPHOMA LYMPHOBLA	0	0	2	1	0 1306		0 2359	0 4578
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793		0 4886	
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7321	0 4886	0 4828	0 4578
EYES	MALIG LYMPHOMA FOLLICLE	1	1	0	0	0 7878	0 7357	0 4773	0 4524

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Com C N=60	400 mg Low N=60	550 mg Med N=60	700 mg High N=60	P_Value Dose Resp	P_Value L vs Com C	P_Value M vs Com C	P_Value H vs Com C
EYES	MALIG LYMPHOMA LYMPHOBLA	0	0	1	1	0 1646	0 4886	0 4578	
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793	0 4886		
GALL BLADDER	MALIG LYMPHOMA FOLLICLE	3	1	0	0	0 9739	0 6573	0 8572	0 8358
	MALIG LYMPHOMA LYMPHOBLA	0	0	0	1	0 2262	0 4578		
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7321	0 4886	0 4828	0 4578
	PAPILLARY CYSTADENOMA	1	1	0	0	0 7878	0 7357	0 4773	0 4524
HARDERIAN GLAND	ADENOMA	7	2	10	4	0 5042	0 9046	0 2439	0 6180
	MALIG LYMPHOMA FOLLICLE	3	1	0	0	0 9727	0 6489	0 8528	0 8310
	MALIG LYMPHOMA LYMPHOBLA	0	0	1	1	0 1646	0 4886	0 4578	
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793	0 4886		
HEART	MALIG LYMPHOMA FOLLICLE	1	1	0	0	0 7878	0 7357	0 4773	0 4524
	MALIG LYMPHOMA LYMPHOBLA	0	0	1	1	0 1646	0 4886	0 4578	
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793	0 4886		
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7321	0 4886	0 4828	0 4578
KIDNEYS	HAEMANGIOMA	1	0	0	0	0 7321	0 4886	0 4828	0 4578
	HISTIOCYTIC SARCOMA	1	0	0	0	0 7321	0 4886	0 4828	0 4578
	MALIG LYMPHOMA FOLLICLE	5	3	0	1	0 9745	0 5793	0 9610	0 8355
	MALIG LYMPHOMA LYMPHOBLA	0	0	2	1	0 1306	0 2359	0 4578	
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793	0 4886		
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7321	0 4886	0 4828	0 4578
	TUBULAR CELL ADENOMA	2	0	0	0	0 9271	0 7357	0 7296	0 7031
LARGE INTESTINE	MALIG LYMPHOMA FOLLICLE	1	1	0	0	0 7878	0 7357	0 4773	0 4524
		3	1	0	0	0 9727	0 6489	0 8528	0 8310
	MALIG LYMPHOMA LYMPHOBLA	0	0	0	1	0 2262	0 4578		
		1	1	0 1646	0 4886	0 4578			
LARYNX	MALIG LYMPHOMA FOLLICLE	1	1	0	0	0 7878	0 7357	0 4773	0 4524
	MALIG LYMPHOMA LYMPHOBLA	0	0	1	1	0 1646	0 4886	0 4578	
LIVER	HAEMANGIOMA	1	1	0	0	0 7915	0 7414	0 4828	0 4578
	HEPATOCELLULAR ADENOMA	7	9	16	17	<0 001*	0 3368	0 0118	0 0025*
	HEPATOCELLULAR CARCINOMA	0	2	3	9	<0 001*	0 2359	0 1083	<0 001*
	HEPATOCELLULAR_ADEN+CARC	7	9	17	18	<0 001*	0 3368	0 0078*	0 0016*
	MALIG LYMPHOMA FOLLICLE	4	3	0	1	0 9400	0 4380	0 9238	0 7385
	MALIG LYMPHOMA LYMPHOBLA	0	0	2	1	0 1306	0 2359	0 4578	
	MALIG LYMPHOMA LYMPHOCYT	0	0	1	0	0 4762	0 4828		
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793	0 4886		
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7321	0 4886	0 4828	0 4578
LUNGS	BRONCHIOLO-ALVEOLAR ADENO	8	10	9	10	0 2169	0 3548	0 4365	0 2708
	BRONCHIOLO-ALVEOLAR CARCI	8	10	8	4	0 6837	0 3373	0 5306	0 7031
	HISTIOCYTIC SARCOMA	1	0	0	0	0 7278	0 4831	0 4773	0 4524
	MALIG LYMPHOMA FOLLICLE	3	2	0	0	0 9641	0 4474	0 8528	0 8310
	MALIG LYMPHOMA LYMPHOBLA	0	0	2	1	0 1306	0 2359	0 4578	
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793	0 4886		
	MALIGNANT MASTOCYTOMA	1	0	0	0	0 7278	0 4831	0 4773	0 4524

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Com C N=60	400 mg Low N=60	550 mg Med N=60	700 mg High N=60	P_Value Dose Resp	P_Value L vs Com C	P_Value M vs Com C	P_Value H vs Com C
LYMPH NODE: AXI	MALIG LYMPHOMA FOLLICLE	2	0	0	0	0 9271	0 7357	0 7296	0 7031
	MALIG LYMPHOMA LYMPHOBLA	0	0	2	0	0 3433		0 2359	
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793		0 4886	
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7321	0 4886	0 4828	0 4578
LYMPH NODE: BRO	MALIG LYMPHOMA FOLLICLE	3	2	0	1	0 8855	0 4574	0 8572	0 6076
	MALIG LYMPHOMA LYMPHOBLA	0	0	0	1	0 2262			0 4578
LYMPH NODE: HEP	HISTIOCYTIC SARCOMA	1	0	0	0	0 7321	0 4886	0 4828	0 4578
	MALIG LYMPHOMA FOLLICLE	2	2	0	2	0 5786	0 6658	0 7296	0 6165
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793		0 4886	
LYMPH NODE: ILI	MALIG LYMPHOMA FOLLICLE	2	1	0	0	0 9245	0 4744	0 7296	0 7031
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7321	0 4886	0 4828	0 4578
LYMPH NODE: ING	MALIG LYMPHOMA LYMPHOBLA	0	0	1	0	0 4793		0 4886	
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793		0 4886	
LYMPH NODE: LUM	MALIG LYMPHOMA FOLLICLE	3	2	0	0	0 9658	0 4574	0 8572	0 8358
	MALIG LYMPHOMA LYMPHOBLA	0	0	2	1	0 1306		0 2359	0 4578
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793		0 4886	
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7321	0 4886	0 4828	0 4578
LYMPH NODE: MED	MALIG LYMPHOMA FOLLICLE	0	2	0	0	0 5349	0 2359		
	MALIG LYMPHOMA LYMPHOBLA	0	0	2	0	0 3433		0 2359	
LYMPH NODE: MES	HISTIOCYTIC SARCOMA	1	0	0	0	0 7321	0 4886	0 4828	0 4578
	MALIG LYMPHOMA FOLLICLE	4	4	1	2	0 7964	0 5793	0 7751	0 5446
	MALIG LYMPHOMA LYMPHOBLA	0	0	2	1	0 1306		0 2359	0 4578
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793		0 4886	
	MALIG LYMPHOMA PLEOMORPH	1	1	0	0	0 7915	0 7414	0 4828	0 4578
LYMPH NODE: PAN	MALIG LYMPHOMA FOLLICLE	0	0	0	1	0 2262			0 4578
LYMPH NODE: REN	MALIG LYMPHOMA FOLLICLE	3	3	1	2	0 6727	0 6181	0 6480	0 3991
LYMPH NODE: SUB	MALIG LYMPHOMA FOLLICLE	5	2	0	0	0 9958	0 7347	0 9610	0 9508
	MALIG LYMPHOMA LYMPHOBLA	0	0	2	1	0 1306		0 2359	0 4578
	MALIG LYMPHOMA LYMPHOCYT	0	0	0	1	0 2262			0 4578
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793		0 4886	
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7321	0 4886	0 4828	0 4578
LYMPH NODE: UNS	MALIG LYMPHOMA LYMPHOBLA	0	0	2	0	0 3433		0 2359	
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7321	0 4886	0 4828	0 4578
MESENTERY	MALIG LYMPHOMA FOLLICLE	1	0	0	0	0 7278	0 4831	0 4773	0 4524
	MALIG LYMPHOMA LYMPHOBLA	0	0	1	0	0 4793		0 4886	
NASAL CAVITY/HE	MALIG LYMPHOMA FOLLICLE	5	1	0	0	0 9973	0 8711	0 9610	0 9508
	MALIG LYMPHOMA LYMPHOBLA	0	0	2	1	0 1306		0 2359	0 4578

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Com C N=60	400 mg Low N=60	550 mg Med N=60	700 mg High N=60	P_Value Dose Resp	P_Value L vs Com C	P_Value M vs Com C	P_Value H vs Com C
NASAL CAVITY/HE	MALIG LYMPHOMA NOS	0	0	1	0	0 4793		0 4886	
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7321	0 4886	0 4828	0 4578
	MALIGNANT MASTOCYTOMA	1	0	0	0	0 7278	0 4831	0 4773	0 4524
OESOPHAGUS	MALIG LYMPHOMA LYMPHOBLA	0	0	1	1	0 1646		0 4886	0 4578
OPTIC NERVES	HISTIOCYTIC SARCOMA	0	1	0	0	0 7337	0 4944		
	MALIG LYMPHOMA LYMPHOBLA	0	0	0	1	0 2262			0 4578
PANCREAS	ISLET CELL ADENOMA	0	1	0	2	0 1300	0 4886		0 2066
	MALIG LYMPHOMA FOLLICLE	4	1	0	0	0 9912	0 7833	0 9238	0 9084
	MALIG LYMPHOMA LYMPHOBLA	0	0	2	1	0 1306		0 2359	0 4578
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793		0 4886	
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7321	0 4886	0 4828	0 4578
PEYER'S PATCHES	MALIG LYMPHOMA FOLLICLE	4	1	0	0	0 9912	0 7833	0 9238	0 9084
	MALIG LYMPHOMA LYMPHOBLA	0	0	2	1	0 1306		0 2359	0 4578
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793		0 4886	
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7321	0 4886	0 4828	0 4578
PITUITARY GLAND	MALIG LYMPHOMA FOLLICLE	2	1	0	0	0 9245	0 4744	0 7296	0 7031
	MALIG LYMPHOMA LYMPHOBLA	0	0	1	1	0 1646		0 4886	0 4578
	PARS DISTALIS ADENOMA	0	2	1	0	0 4147	0 2359	0 4828	
	PARS INTERMEDIA ADENOMA	1	0	0	1	0 5285	0 4831	0 4773	0 7031
PREPUTIAL/CLITO	MALIG LYMPHOMA FOLLICLE	2	0	0	0	0 9247	0 7301	0 7240	0 6972
	MALIG LYMPHOMA LYMPHOBLA	0	0	1	1	0 1646		0 4886	0 4578
PROSTATE GLAND	MALIG LYMPHOMA FOLLICLE	3	1	0	0	0 9739	0 6573	0 8572	0 8358
	MALIG LYMPHOMA LYMPHOBLA	0	0	2	1	0 1306		0 2359	0 4578
SALIVARY GLAND:	HISTIOCYTIC SARCOMA	1	0	0	0	0 7321	0 4886	0 4828	0 4578
	MALIG LYMPHOMA FOLLICLE	1	0	0	0	0 7278	0 4831	0 4773	0 4524
		3	1	0	0	0 9727	0 6489	0 8528	0 8310
	MALIG LYMPHOMA LYMPHOBLA	0	0	1	1	0 1646		0 4886	0 4578
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7321	0 4886	0 4828	0 4578
SCIATIC NERVE	MALIG LYMPHOMA FOLLICLE	1	0	0	0	0 7278	0 4831	0 4773	0 4524
SEMINAL VESICLE	MALIG LYMPHOMA FOLLICLE	3	1	0	0	0 9727	0 6489	0 8528	0 8310
	MALIG LYMPHOMA LYMPHOBLA	0	0	1	1	0 1646		0 4886	0 4578
SKELETAL MUSCLE	MALIG LYMPHOMA FOLLICLE	1	1	0	0	0 7878	0 7357	0 4773	0 4524
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7321	0 4886	0 4828	0 4578
SKIN	MALIG LYMPHOMA FOLLICLE	2	1	0	0	0 9221	0 4663	0 7240	0 6972
SKIN & SUBCUTIS	MALIG LYMPHOMA FOLLICLE	1	0	0	0	0 7278	0 4831	0 4773	0 4524
	MALIG LYMPHOMA LYMPHOBLA	0	0	0	1	0 2262			0 4578

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Com C N=60	400 mg Low N=60	550 mg Med N=60	700 mg High N=60	P_Value Dose Resp	P_Value L vs Com C	P_Value M vs Com C	P_Value H vs Com C
SMALL INTESTINE	MALIG LYMPHOMA FOLLICLE	1	1	0	0	0 7878	0 7357	0 4773	0 4524
		2	1	0	0	0 9221	0 4663	0 7240	0 6972
		3	1	0	0	0 9727	0 6489	0 8528	0 8310
	MALIG LYMPHOMA LYMPHOBLA	0	0	0	1	0 2262			0 4578
			1	1	0 1646		0 4886	0 4578	
SPINAL CORD	HISTIOCYTIC SARCOMA	0	1	0	0	0 7337	0 4944		
	MALIG LYMPHOMA FOLLICLE	3	1	0	0	0 9739	0 6573	0 8572	0 8358
	MALIG LYMPHOMA LYMPHOBLA	0	0	2	1	0 1306		0 2359	0 4578
SPLEEN	HAEMANGIOMA	0	1	1	0	0 4705	0 4886	0 4828	
	HISTIOCYTIC SARCOMA	1	0	0	0	0 7321	0 4886	0 4828	0 4578
	MALIG LYMPHOMA FOLLICLE	5	4	1	1	0 9479	0 4295	0 8648	0 8355
	MALIG LYMPHOMA LYMPHOBLA	0	0	2	1	0 1306		0 2359	0 4578
	MALIG LYMPHOMA LYMPHOCYT	0	0	1	0	0 4762		0 4828	
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793		0 4886	
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7321	0 4886	0 4828	0 4578
STOMACH: GLANDU	MALIG LYMPHOMA FOLLICLE	2	1	0	0	0 9221	0 4663	0 7240	0 6972
	MALIG LYMPHOMA LYMPHOBLA	0	0	0	1	0 2262			0 4578
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793		0 4886	
STOMACH: NON-GL	MALIG LYMPHOMA FOLLICLE	1	1	0	0	0 7878	0 7357	0 4773	0 4524
	MALIG LYMPHOMA LYMPHOBLA	0	0	0	1	0 2262			0 4578
	SQUAMOUS CELL CARCINOMA	0	0	1	0	0 4762		0 4828	
SUB-CUTANEOUS T	FIBROSARCOMA	1	2	0	0	0 7675	0 4831	0 4773	0 4524
	HAEMANGIOSARCOMA	1	0	0	0	0 7321	0 4886	0 4828	0 4578
	UNDIFFERENTIATED SARCOMA	2	0	0	0	0 9271	0 7357	0 7296	0 7031
TESTES	HAEMANGIOMA	0	1	0	0	0 7321	0 4886		
	HAEMANGIOSARCOMA	0	0	1	0	0 4762		0 4828	
	INTERSTITIAL CELL ADENOMA	3	5	6	4	0 2020	0 3441	0 2084	0 4049
	MALIG LYMPHOMA FOLLICLE	1	0	0	0	0 7278	0 4831	0 4773	0 4524
	MALIG LYMPHOMA LYMPHOBLA	0	0	1	0	0 4793		0 4886	
	RETE TESTIS PAPILLARY	0	1	0	0	0 7321	0 4886		
THYMUS	BENIGN THYMOMA	0	0	0	1	0 2262			0 4578
	HISTIOCYTIC SARCOMA	1	0	0	0	0 7321	0 4886	0 4828	0 4578
	MALIG LYMPHOMA FOLLICLE	4	2	0	0	0 9875	0 6075	0 9238	0 9084
	MALIG LYMPHOMA LYMPHOBLA	0	0	2	1	0 1306		0 2359	0 4578
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793		0 4886	
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7321	0 4886	0 4828	0 4578
TONGUE	MALIG LYMPHOMA FOLLICLE	1	0	0	0	0 7278	0 4831	0 4773	0 4524
	MALIG LYMPHOMA LYMPHOBLA	0	0	1	0	0 4793		0 4886	
TRACHEA	MALIG LYMPHOMA FOLLICLE	1	0	0	0	0 7278	0 4831	0 4773	0 4524
	MALIG LYMPHOMA LYMPHOBLA	0	0	0	1	0 2262			0 4578
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793		0 4886	

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Com C N=60	400 mg Low N=60	550 mg Med N=60	700 mg High N=60	P_Value Dose Resp	P_Value L vs Com C	P_Value M vs Com C	P_Value H vs Com C
URETER	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7321	0 4886	0 4828	0 4578
URINARY BLADDER	HISTIOCYTIC SARCOMA	1	0	0	0	0 7321	0 4886	0 4828	0 4578
	MALIG LYMPHOMA FOLLICLE	3	1	0	0	0 9727	0 6489	0 8528	0 8310
	MALIG LYMPHOMA LYMPHOBLA	0	0	2	0	0 3433		0 2359	
	MALIG LYMPHOMA NOS	0	0	1	0	0 4793		0 4886	
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7321	0 4886	0 4828	0 4578

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Com C N=60	400 mg Low N=60	550 mg Med N=60	700 mg High N=60	P_Value Dose Resp	P_Value L vs Com C	P_Value M vs Com C	P_Value H vs Com C
ABDOMINAL CAVIT	HISTIOCYTIC SARCOMA	0	0	1	0	0 4902		0 5000	
	UNDIFFERENTIATED SARCOMA	0	0	1	0	0 4902		0 5000	
ADIPOSE TISSUE, MALIG	LYMPHOMA PLEOMORPH	1	0	0	0	0 7516	0 5128	0 5000	0 4933
ADRENAL CORTEX	ADENOMA (TYPE A)	0	1	0	0	0 4902	0 5128		
	HISTIOCYTIC SARCOMA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA FOLLICLE	1	3	0	0	0 7920	0 3466	0 5000	0 4933
	MALIG LYMPHOMA LYMPHOBLA	3	1	3	1	0 7322	0 6922	0 6504	0 6630
	MALIG LYMPHOMA PLEOMORPH	1	1	0	0	0 8047	0 2532	0 4935	0 4868
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
ADRENAL MEDULLA	BENIGN PHAEOCHROMOCYTOMA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA FOLLICLE	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	1	0	1	0	0 6798	0 5063	0 7532	0 4868
	MYELOID LEUKAEMIA GRANULO	0	1	0	0	0 4870	0 5190		
AORTIC ARCH	MALIG LYMPHOMA PLEOMORPH	0	1	1	0	0 5000	0 5128	0 5065	
BONE & MARROW:	HISTIOCYTIC SARCOMA	0	0	2	1	0 1520		0 2597	0 5000
	MALIG LYMPHOMA FOLLICLE	2	5	0	0	0 9028	0 2705	0 7533	0 7467
	MALIG LYMPHOMA IMMUNOBLA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	4	2	2	2	0 8167	0 6737	0 6504	0 6381
	MALIG LYMPHOMA LYMPHOCYT	0	0	0	1	0 2468		0 5000	
	MALIG LYMPHOMA PLEOMORPH	4	1	2	1	0 9093	0 8206	0 6502	0 7956
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
BONE: EXTRA SEC	OSTEOMA	0	1	0	0	0 4870	0 5190		
	OSTEOSARCOMA	1	0	0	0	0 7468	0 5063	0 4935	0 4868
BONE: FEMUR & S	HAEMANGIOMA	0	1	0	0	0 4902	0 5128		
	HAEMANGIOSARCOMA	1	1	0	0	0 8088	0 2597	0 5000	0 4933
	HISTIOCYTIC SARCOMA	0	0	2	2	0 0546		0 2597	0 2467
	MALIG LYMPHOMA FOLLICLE	1	5	0	0	0 7810	0 1315	0 5000	0 4933
	MALIG LYMPHOMA LYMPHOBLA	3	2	2	1	0 7931	0 5116	0 4881	0 6630
	MALIG LYMPHOMA LYMPHOCYT	0	0	0	1	0 2468		0 5000	
	MALIG LYMPHOMA PLEOMORPH	3	1	2	1	0 8034	0 7016	0 4878	0 6623
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
BONE: VERTEBRAL	HISTIOCYTIC SARCOMA	0	0	2	1	0 1520		0 2597	0 5000
	MALIG LYMPHOMA FOLLICLE	0	3	0	0	0 5379	0 1397		
	MALIG LYMPHOMA LYMPHOBLA	2	2	2	1	0 6244	0 3265	0 6827	0 4805
	MALIG LYMPHOMA PLEOMORPH	0	0	2	1	0 1471		0 2532	0 4933
BRAIN	HISTIOCYTIC SARCOMA	0	0	1	0	0 4935		0 5065	
	MALIG LYMPHOMA FOLLICLE	0	2	0	0	0 4964	0 2725		
	MALIG LYMPHOMA LYMPHOBLA	2	2	0	2	0 6271	0 3265	0 7403	0 6827
	MALIG LYMPHOMA PLEOMORPH	2	2	1	0	0 8646	0 3269	0 5000	0 7400
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Com C N=60	400 mg Low N=60	550 mg Med N=60	700 mg High N=60	P_Value Dose Resp	P_Value L vs Com C	P_Value M vs Com C	P_Value H vs Com C
CERVIX	HAEMANGIOSARCOMA	1	0	0	0	0 7468	0 5063	0 4935	0 4868
	HISTIOCYTIC SARCOMA	0	1	3	3	0 0315	0 5190	0 1299	0 1249
	LEIOMYOMA	1	0	0	0	0 7516	0 5128	0 5000	0 4933
	MALIG LYMPHOMA FOLLICLE	0	5	0	0	0 5641	0 0376*		
	MALIG LYMPHOMA LYMPHOBLA	3	1	3	2	0 5989	0 6922	0 6504	0 4760
	MALIG LYMPHOMA LYMPHOCYT	0	0	0	1	0 2418			0 4933
	MALIG LYMPHOMA PLEOMORPH	1	1	1	0	0 7003	0 2597	0 2532	0 4933
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
EAR	MYELOID LEUKAEMIA GRANULO	0	1	0	0	0 4870	0 5190		
EXORBITAL LACHR	MALIG LYMPHOMA FOLLICLE	2	3	0	0	0 9184	0 5480	0 7533	0 7467
	MALIG LYMPHOMA LYMPHOBLA	4	1	3	1	0 8562	0 8126	0 4723	0 7877
	MALIG LYMPHOMA PLEOMORPH	2	1	0	1	0 8023	0 5096	0 7468	0 4800
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
EYES	MALIG LYMPHOMA FOLLICLE	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA PLEOMORPH	0	1	0	0	0 4902	0 5128		
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
GALL BLADDER	HISTIOCYTIC SARCOMA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA FOLLICLE	0	2	1	0	0 4492	0 2661	0 5000	
	MALIG LYMPHOMA LYMPHOBLA	3	1	1	0	0 9527	0 7016	0 6827	0 8649
	MALIG LYMPHOMA PLEOMORPH	2	1	0	0	0 9350	0 5096	0 7468	0 7400
	PAPILLARY CYSTADENOMA	0	1	0	0	0 4902	0 5128		
HARDERIAN GLAND	ADENOCARCINOMA	0	1	1	0	0 4999	0 5190	0 5065	
	ADENOMA	1	3	5	4	0 0607	0 3364	0 1061	0 1711
	MALIG LYMPHOMA FOLLICLE	0	3	0	0	0 5379	0 1397		
	MALIG LYMPHOMA LYMPHOBLA	4	2	3	2	0 7488	0 6621	0 4723	0 6260
	MALIG LYMPHOMA LYMPHOCYT	0	0	0	1	0 2468			0 5000
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7516	0 5128	0 5000	0 4933
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
HEART	HISTIOCYTIC SARCOMA	0	2	1	1	0 2723	0 2661	0 5065	0 5000
	MALIG LYMPHOMA FOLLICLE	1	3	0	0	0 7920	0 3466	0 5000	0 4933
	MALIG LYMPHOMA LYMPHOBLA	2	1	2	2	0 5361	0 5190	0 3173	0 6925
	MALIG LYMPHOMA LYMPHOCYT	0	0	0	2	0 0597			0 2467
	MALIG LYMPHOMA PLEOMORPH	2	2	2	1	0 6278	0 3173	0 6925	0 4800
	MYELOID LEUKAEMIA GRANULO	0	1	0	0	0 4870	0 5190		
KIDNEYS	HISTIOCYTIC SARCOMA	0	1	2	3	0 0391	0 5190	0 2597	0 1249
	MALIG LYMPHOMA FOLLICLE	2	5	1	0	0 8490	0 2705	0 5000	0 7467
	MALIG LYMPHOMA IMMUNOBLA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	5	2	3	2	0 8625	0 7837	0 6158	0 7521
	MALIG LYMPHOMA LYMPHOCYT	0	0	0	2	0 0597			0 2467
	MALIG LYMPHOMA PLEOMORPH	3	4	3	0	0 8493	0 5284	0 6626	0 8700
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
LARGE INTESTINE	HISTIOCYTIC SARCOMA	0	0	0	1	0 2468			0 5000

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Com C N=60	400 mg Low N=60	550 mg Med N=60	700 mg High N=60	P_Value Dose Resp	P_Value L vs Com C	P_Value M vs Com C	P_Value H vs Com C
LARGE INTESTINE	HISTIOCYTIC SARCOMA	0	0	1	0	0 4935		0 5065	
	MALIG LYMPHOMA FOLLICLE	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	1	1	0	0	0 8039	0 2595	0 4935	0 4868
		2	1	1	0	0 8713	0 5094	0 4904	0 7334
		3	0	0	0	0 9828	0 8751	0 8652	0 8599
	MALIG LYMPHOMA PLEOMORPH	1	1	1	0	0 6936	0 2595	0 7532	0 4868
			2	0		0 5699	0 2595	0 5000	0 4868
		2	1	0	0	0 9351	0 5190	0 7468	0 7400
	MYELOID LEUKAEMIA GRANULO	1	0	0	0	0 7468	0 5063	0 4935	0 4868
LARYNX	MALIG LYMPHOMA FOLLICLE	0	2	0	0	0 4966	0 2661		
	MALIG LYMPHOMA LYMPHOBLA	3	1	2	1	0 7999	0 6922	0 4760	0 6630
	MALIG LYMPHOMA PLEOMORPH	1	2	1	0	0 6980	0 5195	0 2532	0 4933
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
LIVER	HAEMANGIOMA	1	1	1	0	0 6917	0 2532	0 7468	0 4868
	HEPATOCELLULAR ADENOMA	2	2	0	1	0 7980	0 3273	0 7533	0 4899
	HISTIOCYTIC SARCOMA	1	3	8	3	0 0646	0 3466	0 0193	0 3174
	MALIG LYMPHOMA FOLLICLE	2	6	1	0	0 8384	0 1851	0 5000	0 7467
	MALIG LYMPHOMA IMMUNOBLA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	5	2	3	2	0 8625	0 7837	0 6158	0 7521
	MALIG LYMPHOMA LYMPHOCYT	0	0	0	2	0 0597		0 2467	
	MALIG LYMPHOMA PLEOMORPH	4	2	2	1	0 8990	0 6624	0 6502	0 7956
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
LUNGS	BRONCHIOLO-ALVEOLAR ADENO	7	7	4	9	0 4365	0 4243	0 7262	0 3684
	BRONCHIOLO-ALVEOLAR CARCI	3	2	4	4	0 3374	0 5240	0 5144	0 5000
	HISTIOCYTIC SARCOMA	0	2	6	2	0 0418	0 2661	0 0149*	0 2467
	MALIG LYMPHOMA FOLLICLE	0	5	1	0	0 4694	0 0376*	0 5000	
	MALIG LYMPHOMA IMMUNOBLA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	5	2	3	2	0 8625	0 7837	0 6158	0 7521
	MALIG LYMPHOMA LYMPHOCYT	0	0	1	1	0 1782		0 5000	0 4933
	MALIG LYMPHOMA PLEOMORPH	5	3	1	1	0 9675	0 6298	0 8878	0 8745
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
LYMPH NODE: AXI	MALIG LYMPHOMA FOLLICLE	1	4	0	0	0 7926	0 2206	0 5000	0 4933
	MALIG LYMPHOMA IMMUNOBLA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	2	2	1	1	0 7084	0 3265	0 4904	0 4805
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7468	0 5063	0 4935	0 4868
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
LYMPH NODE: BRO	HISTIOCYTIC SARCOMA	0	1	1	0	0 4966	0 5190	0 5000	
	MALIG LYMPHOMA FOLLICLE	0	0	1	0	0 4902		0 5000	
	MALIG LYMPHOMA LYMPHOBLA	0	0	0	1	0 2468		0 5000	
	MALIG LYMPHOMA LYMPHOCYT	0	1	1	0	0 4966	0 5128	0 5000	
	MALIG LYMPHOMA PLEOMORPH	3	1	0	0	0 9801	0 7020	0 8751	0 8700
LYMPH NODE: CER	MALIG LYMPHOMA PLEOMORPH	1	1	0	0	0 8047	0 2532	0 4935	0 4868
LYMPH NODE: HEP	HISTIOCYTIC SARCOMA	0	1	2	1	0 1918	0 5190	0 2532	0 5000

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Com C N=60	400 mg Low N=60	550 mg Med N=60	700 mg High N=60	P_Value Dose Resp	P_Value L vs Com C	P_Value M vs Com C	P_Value H vs Com C
LYMPH NODE: HEP	MALIG LYMPHOMA FOLLICLE	1	4	0	0	0 7926	0 2206	0 5000	0 4933
	MALIG LYMPHOMA IMMUNOBLA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	3	1	2	1	0 8028	0 6922	0 4881	0 6630
	MALIG LYMPHOMA PLEOMORPH	2	1	2	0	0 7934	0 5096	0 6925	0 7400
	MYELOID LEUKAEMIA GRANULO	0	1	0	0	0 4870	0 5190		
LYMPH NODE: ILI	HISTIOCYTIC SARCOMA	0	0	3	0	0 2570	0 1200		
	MALIG LYMPHOMA FOLLICLE	0	1	0	0	0 4902	0 5128		
	MALIG LYMPHOMA LYMPHOCYT	0	0	1	0	0 4902	0 5000		
	MALIG LYMPHOMA PLEOMORPH	0	1	2	1	0 1875	0 5190	0 2532	0 4933
LYMPH NODE: ING	MALIG LYMPHOMA FOLLICLE	2	3	0	0	0 9184	0 5480	0 7533	0 7467
	MALIG LYMPHOMA IMMUNOBLA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	1	0	1	0	0 6798	0 5063	0 7532	0 4868
	MALIG LYMPHOMA PLEOMORPH	4	0	2	0	0 9726	0 9422	0 6502	0 9325
	MYELOID LEUKAEMIA GRANULO	1	0	0	0	0 7468	0 5063	0 4935	0 4868
LYMPH NODE: LUM	HISTIOCYTIC SARCOMA	0	1	3	2	0 0691	0 5190	0 1299	0 2467
	MALIG LYMPHOMA FOLLICLE	1	5	0	0	0 7814	0 1380	0 5000	0 4933
	MALIG LYMPHOMA IMMUNOBLA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	5	2	3	1	0 9248	0 7837	0 6158	0 8750
	MALIG LYMPHOMA PLEOMORPH	3	0	1	0	0 9633	0 8797	0 6827	0 8649
	MYELOID LEUKAEMIA GRANULO	0	1	0	0	0 4870	0 5190		
LYMPH NODE: MED	HISTIOCYTIC SARCOMA	0	0	2	0	0 3659	0 2467		
	MALIG LYMPHOMA FOLLICLE	1	0	0	0	0 7516	0 5128	0 5000	0 4933
	MALIG LYMPHOMA PLEOMORPH	1	0	1	1	0 5353	0 5063	0 7532	0 7400
LYMPH NODE: MES	HISTIOCYTIC SARCOMA	0	2	2	1	0 2106	0 2661	0 2597	0 5000
	MALIG LYMPHOMA FOLLICLE	2	6	1	0	0 8384	0 1851	0 5000	0 7467
	MALIG LYMPHOMA IMMUNOBLA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	5	2	3	2	0 8625	0 7837	0 6158	0 7521
	MALIG LYMPHOMA LYMPHOCYT	0	0	1	2	0 0589	0 5000	0 2467	
	MALIG LYMPHOMA PLEOMORPH	6	3	4	2	0 8977	0 7465	0 6153	0 8424
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
LYMPH NODE: PAN	HISTIOCYTIC SARCOMA	0	0	1	0	0 4902	0 5000		
	MALIG LYMPHOMA FOLLICLE	1	0	0	0	0 7516	0 5128	0 5000	0 4933
	MALIG LYMPHOMA PLEOMORPH	0	1	0	0	0 4870	0 5190		
LYMPH NODE: REN	HISTIOCYTIC SARCOMA	0	1	2	1	0 1918	0 5190	0 2532	0 5000
	MALIG LYMPHOMA FOLLICLE	1	2	1	0	0 6955	0 5380	0 7533	0 4933
	MALIG LYMPHOMA LYMPHOBLA	2	1	2	0	0 7964	0 5190	0 3173	0 7400
	MALIG LYMPHOMA PLEOMORPH	2	1	3	0	0 7110	0 5096	0 5000	0 7400
	MYELOID LEUKAEMIA GRANULO	1	0	0	0	0 7468	0 5063	0 4935	0 4868
LYMPH NODE: SPL	MALIG LYMPHOMA PLEOMORPH	0	0	0	1	0 2468	0 5000		
LYMPH NODE: SUB	HISTIOCYTIC SARCOMA	0	0	1	0	0 4935	0 5065		
	MALIG LYMPHOMA FOLLICLE	2	6	1	0	0 8384	0 1851	0 5000	0 7467

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Com C N=60	400 mg Low N=60	550 mg Med N=60	700 mg High N=60	P_Value Dose Resp	P_Value L vs Com C	P_Value M vs Com C	P_Value H vs Com C
LYMPH NODE: SUB	MALIG LYMPHOMA IMMUNOBLA	0	1	0	0		0 4870	0 5190	
	MALIG LYMPHOMA LYMPHOBLA	5	2	3	2		0 8625	0 7837	0 6158	0 7521
	MALIG LYMPHOMA LYMPHOCYT	0	1	1	0		0 4966	0 5128	0 5000	
	MALIG LYMPHOMA PLEOMORPH	5	2	2	1		0 9516	0 7737	0 7629	0 8745
	MYELOID LEUKAEMIA GRANULO	1	1	0	0		0 8039	0 2595	0 4935	0 4868
LYMPH NODE: UNS	MALIG LYMPHOMA FOLLICLE	0	4	0	0		0 5688	0 0742		
	MALIG LYMPHOMA IMMUNOBLA	0	1	0	0		0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	5	2	2	1		0 9509	0 7837	0 7521	0 8750
	MALIG LYMPHOMA PLEOMORPH	2	1	1	0		0 8760	0 5190	0 5000	0 7400
	MYELOID LEUKAEMIA GRANULO	1	1	0	0		0 8039	0 2595	0 4935	0 4868
LYMPH NODE:POPL	MALIG LYMPHOMA PLEOMORPH	1	0	0	0		0 7516	0 5128	0 5000	0 4933
MAMMARY GLAND	ADENOCARCINOMA	1	0	2	0		0 5515	0 5063	0 5000	0 4868
	ADENOMA	1	1	0	1		0 5564	0 2597	0 5000	0 7467
	HISTIOCYTIC SARCOMA	0	0	0	1		0 2468		0 5000	
	MALIG LYMPHOMA FOLLICLE	0	2	0	0		0 4964	0 2725		
	MALIG LYMPHOMA LYMPHOBLA	4	1	3	2		0 7682	0 8204	0 4860	0 6381
	MALIG LYMPHOMA LYMPHOCYT	0	0	1	1		0 1782		0 5000	0 4933
	MALIG LYMPHOMA PLEOMORPH	2	2	1	0		0 8642	0 3173	0 5000	0 7400
	MYELOID LEUKAEMIA GRANULO	1	1	0	0		0 8039	0 2595	0 4935	0 4868
MEDIASTINUM	HISTIOCYTIC SARCOMA	0	0	1	1		0 1831		0 5065	0 5000
	MALIG LYMPHOMA FOLLICLE	0	2	0	0		0 4964	0 2725		
	MALIG LYMPHOMA LYMPHOBLA	0	2	1	2		0 1474	0 2725	0 5065	0 2532
	MALIG LYMPHOMA PLEOMORPH	0	0	0	1		0 2418		0 4933	
MESENTERY	HISTIOCYTIC SARCOMA	0	2	6	2		0 0425	0 2661	0 0162*	0 2467
	MALIG LYMPHOMA FOLLICLE	0	2	0	0		0 4966	0 2661		
	MALIG LYMPHOMA LYMPHOBLA	2	2	1	1		0 7084	0 3265	0 4904	0 4805
	MALIG LYMPHOMA LYMPHOCYT	0	0	1	1		0 1782		0 5000	0 4933
	MALIG LYMPHOMA PLEOMORPH	5	1	2	1		0 9590	0 8938	0 7629	0 8745
	MYELOID LEUKAEMIA GRANULO	1	1	0	0		0 8039	0 2595	0 4935	0 4868
NASAL CAVITY/HE	HISTIOCYTIC SARCOMA	1	0	2	1		0 4461	0 5063	0 5096	0 7468
	MALIG LYMPHOMA FOLLICLE	1	4	0	0		0 7926	0 2123	0 5000	0 4933
	MALIG LYMPHOMA LYMPHOBLA	4	2	3	2		0 7488	0 6621	0 4723	0 6260
	MALIG LYMPHOMA PLEOMORPH	3	2	2	0		0 9051	0 5122	0 5000	0 8700
	MYELOID LEUKAEMIA GRANULO	1	1	0	0		0 8039	0 2595	0 4935	0 4868
OESOPHAGUS	MALIG LYMPHOMA LYMPHOBLA	1	0	0	0		0 7468	0 5063	0 4935	0 4868
	MALIG LYMPHOMA PLEOMORPH	1	1	0	0		0 8088	0 2597	0 5000	0 4933
	MYELOID LEUKAEMIA GRANULO	1	0	0	0		0 7468	0 5063	0 4935	0 4868
OPTIC NERVES	MALIG LYMPHOMA LYMPHOBLA	0	0	1	2		0 0613		0 5065	0 2532
	MALIG LYMPHOMA PLEOMORPH	0	1	0	0		0 4902	0 5128		
OVARIES	BENIGN GRANULOSA CELL TUM	0	1	1	1		0 2591	0 5128	0 5065	0 4933
	BENIGN LUTEOMA	1	0	6	4		0 0268	0 5128	0 0580	0 1790

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Com C N=60	400 mg Low N=60	550 mg Med N=60	700 mg High N=60	P_Value Dose Resp	P_Value L vs Com C	P_Value M vs Com C	P_Value H vs Com C
OVARIES	BENIGN SERTOLI CELL TUMOU	0	0	0	3	0 0141*			0 1200
	HISTIOCYTIC SARCOMA	0	2	5	3	0 0276	0 2661	0 0312*	0 1249
	MALIG LYMPHOMA FOLLICLE	2	5	0	0	0 9028	0 2705	0 7533	0 7467
	MALIG LYMPHOMA IMMUNOBLA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	5	2	2	2	0 9023	0 7837	0 7632	0 7521
	MALIG LYMPHOMA LYMPHOCYT	0	0	0	2	0 0597			0 2467
	MALIG LYMPHOMA PLEOMORPH	3	2	2	1	0 7923	0 5000	0 4878	0 6623
	MALIGNANT TERATOMA	0	1	0	0	0 4870	0 5190		
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
	PAPILLARY CYSTADENOMA	0	1	0	1	0 3643	0 5190		0 4933
	TUBULOSTROMAL ADENOMA	2	1	4	3	0 2463	0 5096	0 3249	0 4875
OVIDUCTS	CARCINOMA	0	0	1	0	0 4902			0 5000
	HISTIOCYTIC SARCOMA	0	1	1	0	0 4966	0 5190		0 5000
	MALIG LYMPHOMA FOLLICLE	0	4	0	0	0 5688			0 0742
	MALIG LYMPHOMA IMMUNOBLA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	4	1	3	2	0 7578	0 8126	0 4723	0 6260
	MALIG LYMPHOMA LYMPHOCYT	0	0	0	1	0 2418			0 4933
	MALIG LYMPHOMA PLEOMORPH	2	0	1	0	0 8888	0 7595	0 5000	0 7400
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
PANCREAS	HISTIOCYTIC SARCOMA	0	1	1	0	0 4966	0 5190	0 5000	
	ISLET CELL ADENOMA	2	0	1	0	0 8928	0 7659	0 5099	0 7467
	MALIG LYMPHOMA FOLLICLE	1	5	0	0	0 7810	0 1315	0 5000	0 4933
	MALIG LYMPHOMA IMMUNOBLA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	3	2	3	1	0 7263	0 5116	0 6504	0 6630
	MALIG LYMPHOMA LYMPHOCYT	0	0	0	2	0 0597			0 2467
	MALIG LYMPHOMA PLEOMORPH	4	1	4	1	0 8135	0 8206	0 6441	0 7956
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
PARATHYROID GLA	MALIG LYMPHOMA LYMPHOBLA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA PLEOMORPH	2	0	0	0	0 9371	0 7595	0 7468	0 7400
PEYER'S PATCHES	HISTIOCYTIC SARCOMA	0	0	0	1	0 2468			0 5000
	MALIG LYMPHOMA FOLLICLE	2	4	0	0	0 9123	0 3869	0 7533	0 7467
	MALIG LYMPHOMA IMMUNOBLA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	3	2	1	1	0 8531	0 5116	0 6731	0 6630
	MALIG LYMPHOMA PLEOMORPH	3	2	1	0	0 9438	0 5119	0 6827	0 8649
	MYELOID LEUKAEMIA GRANULO	1	0	0	0	0 7468	0 5063	0 4935	0 4868
PITUITARY GLAND	MALIG LYMPHOMA FOLLICLE	0	3	0	0	0 5379	0 1397		
	MALIG LYMPHOMA LYMPHOBLA	1	2	1	1	0 4797	0 5281	0 7532	0 7468
	MALIG LYMPHOMA PLEOMORPH	0	0	2	0	0 3675		0 2532	
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
	PARS DISTALIS ADENOMA	3	0	0	1	0 9524	0 8891	0 8800	0 6825
PREPUTIAL/CLITO	MALIG LYMPHOMA FOLLICLE	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	1	1	1	1	0 5714	0 2595	0 7532	0 7468
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7516	0 5128	0 5000	0 4933
	MYELOID LEUKAEMIA GRANULO	1	0	0	0	0 7468	0 5063	0 4935	0 4868

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Com C N=60	400 mg Low N=60	550 mg Med N=60	700 mg High N=60	P_Value Dose Resp	P_Value L vs Com C	P_Value M vs Com C	P_Value H vs Com C
SALIVARY GLAND:	MALIG LYMPHOMA FOLLICLE	0	1	0	0	0 4870	0 5190		
		1	2	0	0	0 7970	0 5288	0 5000	0 4933
	MALIG LYMPHOMA LYMPHOBLA	0	1	1	1	0 2622	0 5190	0 5065	0 5000
		2	1	2	1	0 6337	0 5190	0 6925	0 4901
		5	1	2	1	0 9591	0 8937	0 7632	0 8750
	MALIG LYMPHOMA LYMPHOCYT	0	1	0	0	0 4902	0 5128		
	MALIG LYMPHOMA PLEOMORPH	0	1	0	0	0 4902	0 5128		
		2	2	0	0	0 9241	0 3173	0 7468	0 7400
	MYELOID LEUKAEMIA GRANULO	1	0	0	0	0 7468	0 5063	0 4935	0 4868
SCIATIC NERVE	MALIG LYMPHOMA LYMPHOBLA	0	0	0	1	0 2468			0 5000
	MALIG LYMPHOMA PLEOMORPH	0	1	0	0	0 4902	0 5128		
SKELETAL MUSCLE	MALIG LYMPHOMA FOLLICLE	0	2	0	0	0 4964	0 2725		
	MALIG LYMPHOMA LYMPHOBLA	0	0	1	1	0 1831		0 5065	0 5000
	MALIG LYMPHOMA PLEOMORPH	0	1	0	0	0 4870	0 5190		
		2	2	0	0	0 9241	0 3173	0 7468	0 7400
	MYELOID LEUKAEMIA GRANULO	1	0	0	0	0 7468	0 5063	0 4935	0 4868
	RHABDOMYOSARCOMA	1	0	0	0	0 7468	0 5063	0 4935	0 4868
SKIN	MALIG LYMPHOMA FOLLICLE	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	1	0	1	1	0 5405	0 5063	0 7532	0 7468
	MALIG LYMPHOMA PLEOMORPH	0	0	0	1	0 2418			0 4933
	MYELOID LEUKAEMIA GRANULO	1	0	0	0	0 7468	0 5063	0 4935	0 4868
SKIN & SUBCUTIS	BASAL CELL CARCINOMA	1	0	0	0	0 7516	0 5128	0 5000	0 4933
	MALIG LYMPHOMA FOLLICLE	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	1	0	1	1	0 5405	0 5063	0 7532	0 7468
	SQUAMOUS CELL CARCINOMA	1	0	0	0	0 7468	0 5063	0 4935	0 4868
	SQUAMOUS CELL PAPILLOMA	0	1	0	0	0 4870	0 5190		
SMALL INTESTINE	HISTIOCYTIC SARCOMA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA FOLLICLE	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	2	1	1	0	0 8713	0 5094	0 4904	0 7334
			2	0		0 7893	0 5094	0 6923	0 7334
	MALIG LYMPHOMA PLEOMORPH	1	1	1	0	0 6936	0 2595	0 7532	0 4868
		2	2	1	0	0 8646	0 3269	0 5000	0 7400
	MYELOID LEUKAEMIA GRANULO	1	0	0	0	0 7468	0 5063	0 4935	0 4868
SPINAL CORD	MALIG LYMPHOMA FOLLICLE	0	2	0	0	0 4964	0 2725		
	MALIG LYMPHOMA LYMPHOBLA	4	1	1	2	0 8722	0 8126	0 7964	0 6260
	MALIG LYMPHOMA PLEOMORPH	2	3	2	0	0 7894	0 5240	0 6925	0 7400
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
	SQUAMOUS CELL CARCINOMA	1	0	0	0	0 7516	0 5128	0 5000	0 4933
SPLEEN	HAEMANGIOMA	1	0	0	0	0 7468	0 5063	0 4935	0 4868
	HISTIOCYTIC SARCOMA	0	2	1	1	0 2723	0 2661	0 5065	0 5000
	MALIG LYMPHOMA FOLLICLE	2	5	1	0	0 8490	0 2705	0 5000	0 7467
	MALIG LYMPHOMA IMMUNOBLA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	5	1	3	2	0 8715	0 8937	0 6158	0 7521

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Com C N=60	400 mg Low N=60	550 mg Med N=60	700 mg High N=60	P_Value Dose Resp	P_Value L vs Com C	P_Value M vs Com C	P_Value H vs Com C
SPLEEN	MALIG LYMPHOMA LYMPHOCYT	0	1	1	1	0 2570	0 5128	0 5000	0 4933
	MALIG LYMPHOMA PLEOMORPH	5	4	3	2	0 8508	0 5000	0 6153	0 7516
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
STOMACH: GLANDU ADENOMA		0	0	1	0	0 4935		0 5065	
	HISTIOCYTIC SARCOMA	0	1	1	1	0 2622	0 5190	0 5065	0 5000
	MALIG LYMPHOMA FOLLICLE	0	3	0	0	0 5379	0 1397		
	MALIG LYMPHOMA LYMPHOBLA	5	1	2	1	0 9591	0 8937	0 7632	0 8750
	MALIG LYMPHOMA PLEOMORPH	3	1	1	0	0 9549	0 7020	0 6925	0 8700
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
STOMACH: NON-GL HISTIOCYTIC SARCOMA		0	1	1	0	0 4999	0 5190	0 5065	
	MALIG LYMPHOMA FOLLICLE	0	2	0	0	0 4966	0 2661		
	MALIG LYMPHOMA LYMPHOBLA	3	1	3	1	0 7421	0 7016	0 6624	0 6727
	MALIG LYMPHOMA PLEOMORPH	2	0	0	0	0 9371	0 7595	0 7468	0 7400
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
SUB-CUTANEOUS T FIBROSARCOMA		1	1	1	1	0 5623	0 2595	0 7468	0 7400
	HISTIOCYTIC SARCOMA	0	0	1	0	0 4902		0 5000	
	MALIG LYMPHOMA LYMPHOCYT	0	0	0	1	0 2468		0 5000	
	MALIG LYMPHOMA PLEOMORPH	1	1	0	1	0 5490	0 2532	0 4935	0 7400
	RHABDOMYOSARCOMA	1	0	0	0	0 7468	0 5063	0 4935	0 4868
	UNDIFFERENTIATED SARCOMA	1	3	5	3	0 1108	0 3466	0 1060	0 3074
THORACIC CAVITY MALIG LYMPHOMA PLEOMORPH		1	0	0	0	0 7468	0 5063	0 4935	0 4868
THYMUS	BENIGN THYMOMA	1	1	0	1	0 5564	0 2597	0 5000	0 7467
	HISTIOCYTIC SARCOMA	0	3	2	1	0 2284	0 1348	0 2532	0 5000
	MALIG LYMPHOMA FOLLICLE	2	6	1	0	0 8384	0 1851	0 5000	0 7467
	MALIG LYMPHOMA IMMUNOBLA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	5	1	3	2	0 8715	0 8937	0 6158	0 7521
	MALIG LYMPHOMA LYMPHOCYT	0	1	1	2	0 1161	0 5128	0 5000	0 2467
	MALIG LYMPHOMA PLEOMORPH	4	4	2	1	0 8891	0 3702	0 6502	0 7956
	MALIGNANT THYMOMA	1	0	0	0	0 7516	0 5128	0 5000	0 4933
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
THYROID GLAND MALIG LYMPHOMA FOLLICLE		1	2	0	0	0 7970	0 5288	0 5000	0 4933
	MALIG LYMPHOMA LYMPHOBLA	0	1	1	1	0 2622	0 5190	0 5065	0 5000
	MALIG LYMPHOMA PLEOMORPH	2	0	0	0	0 9371	0 7595	0 7468	0 7400
TONGUE	MALIG LYMPHOMA FOLLICLE	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	2	1	1	2	0 5479	0 5094	0 4904	0 6827
	MALIG LYMPHOMA LYMPHOCYT	0	0	0	1	0 2418		0 4933	
	MALIG LYMPHOMA PLEOMORPH	1	2	0	0	0 7968	0 5195	0 5000	0 4933
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
TRACHEA	MALIG LYMPHOMA FOLLICLE	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	1	1	1	0	0 6936	0 2595	0 7532	0 4868
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Com C N=60	400 mg Low N=60	550 mg Med N=60	700 mg High N=60	P_Value Dose Resp	P_Value L vs Com C	P_Value M vs Com C	P_Value H vs Com C
URETER	MALIG LYMPHOMA IMMUNOBLA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA PLEOMORPH	1	0	0	0	0 7468	0 5063	0 4935	0 4868
URINARY BLADDER	HISTIOCYTIC SARCOMA	0	0	1	1	0 1831	0 5065	0 5000	
	MALIG LYMPHOMA FOLLICLE	1	5	0	0	0 7810	0 1315	0 5000	0 4933
	MALIG LYMPHOMA IMMUNOBLA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	5	2	3	2	0 8625	0 7837	0 6158	0 7521
	MALIG LYMPHOMA PLEOMORPH	3	4	1	1	0 8524	0 5284	0 6925	0 6723
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
UTERUS	BENIGN GRANULAR CELL TUMO	0	1	0	0	0 4902	0 5128		
	ENDOMETRIAL ADENOCARCINOM	2	2	1	0	0 8682	0 3370	0 5000	0 7467
	ENDOMETRIAL STROMAL POLYP	5	3	6	0	0 8967	0 6721	0 5000	0 9688
	ENDOMETRIAL STROMAL SARCO	1	0	1	0	0 6846	0 5128	0 7533	0 4933
	HAEMANGIOMA	0	0	0	2	0 0597		0 2467	
	HAEMANGIOSARCOMA	1	1	0	0	0 8088	0 2597	0 5000	0 4933
	HISTIOCYTIC SARCOMA	0	3	6	1	0 0935	0 1348	0 0149*	0 5000
	LEIOMYOMA	6	3	4	2	0 8987	0 7714	0 6150	0 8421
	LEIOMYOSARCOMA	0	1	0	0	0 4902	0 5128		
	MALIG LYMPHOMA FOLLICLE	0	5	0	0	0 5641	0 0376*		
	MALIG LYMPHOMA IMMUNOBLA	0	1	0	0	0 4870	0 5190		
	MALIG LYMPHOMA LYMPHOBLA	5	2	3	2	0 8625	0 7837	0 6158	0 7521
	MALIG LYMPHOMA LYMPHOCYT	0	0	0	1	0 2418		0 4933	
	MALIG LYMPHOMA PLEOMORPH	3	1	2	0	0 9083	0 6923	0 4878	0 8649
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868
VAGINA	HISTIOCYTIC SARCOMA	0	0	1	1	0 1831	0 5065	0 5000	
	LEIOMYOMA	0	0	0	1	0 2468		0 5000	
	MALIG LYMPHOMA FOLLICLE	0	2	0	0	0 4966	0 2661		
	MALIG LYMPHOMA LYMPHOBLA	3	1	3	2	0 5989	0 6922	0 6504	0 4760
	MALIG LYMPHOMA LYMPHOCYT	0	0	0	1	0 2468		0 5000	
	MALIG LYMPHOMA PLEOMORPH	1	0	1	0	0 6855	0 5128	0 2532	0 4933
	MYELOID LEUKAEMIA GRANULO	1	1	0	0	0 8039	0 2595	0 4935	0 4868

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

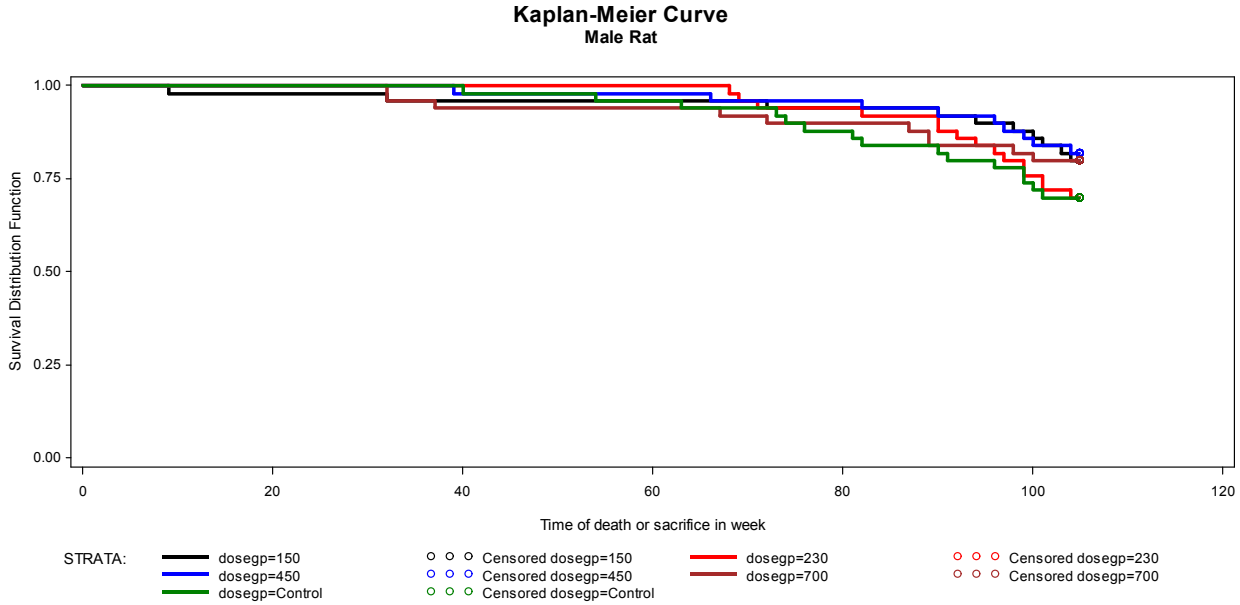


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

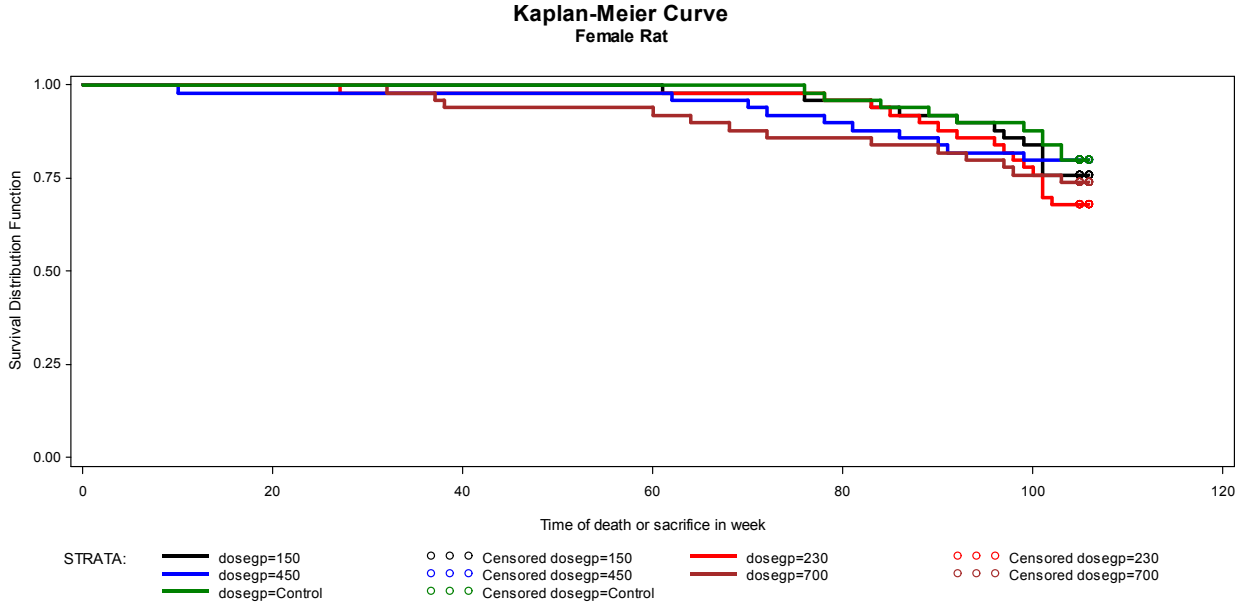


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

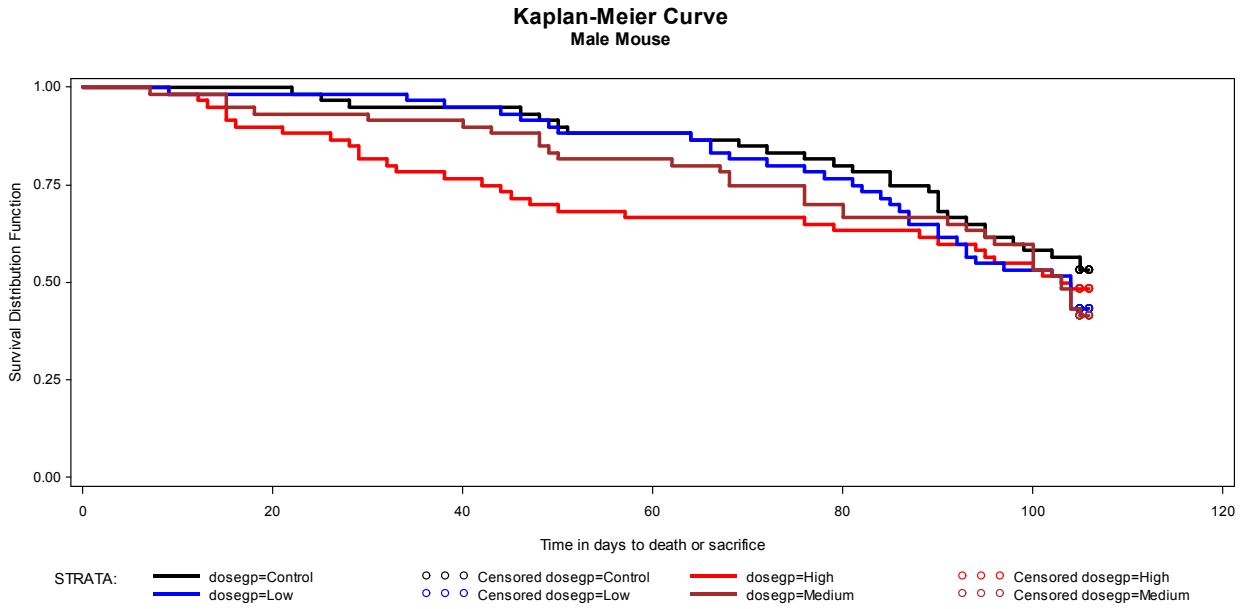
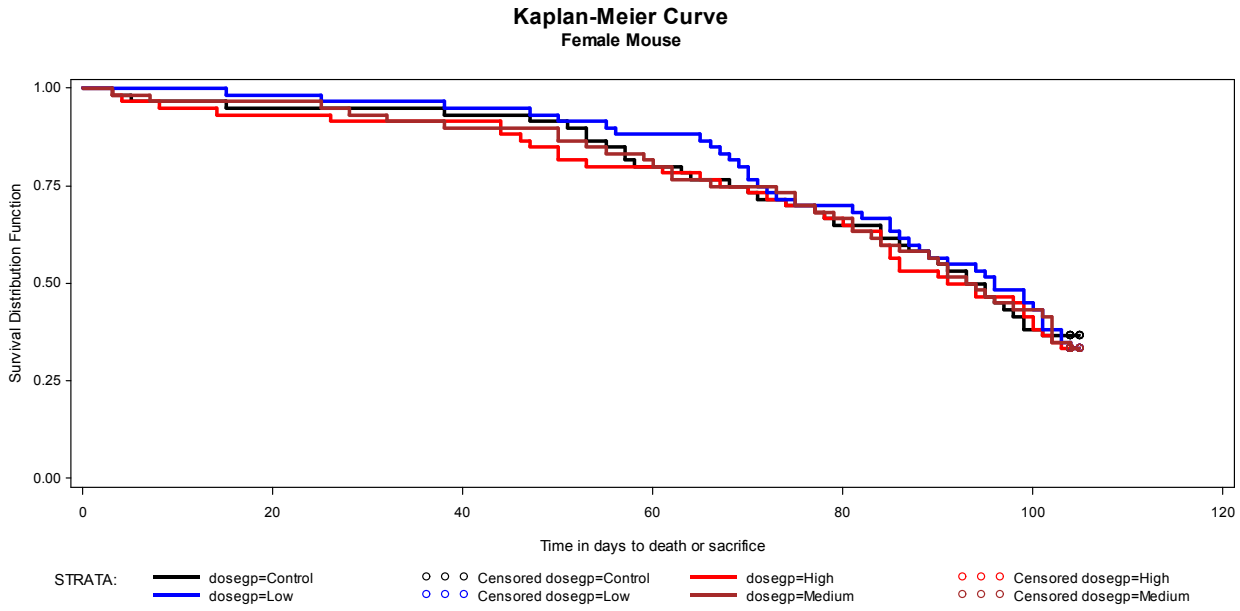


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



6. References

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/s/

MOHAMMAD A RAHMAN
09/16/2015

KARL K LIN
09/17/2015
Concur with review

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

sNDA/BLA Serial Number:	205,836/SN150
Drug Name:	Brivaracetam
Indication(s):	Partial Onset Seizures
Applicant:	UCB Inc.
Date(s):	Date of Submission: November 22, 2014 PDUFA Due Date: November 20, 2015
Review Priority:	Standard Review
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Sharon Yan, Ph.D.
Concurring Reviewers:	Kun Jin, Ph.D., Team Leader James Hung, Ph.D., Director
Medical Division:	Neurology
Clinical Team:	Steven Dinsmore, M.D., Clinical Reviewer Norman Hershkowitz, M.D., Team Leader Eric Bastings, M.D., Deputy Director Billy Dunn, M.D., Acting Director
Project Manager:	Cathleen Michaloski, BSN, MPH, RAC

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1 EXECUTIVE SUMMARY

Three pivotal, fixed-dose, randomized, double-blind, placebo-controlled studies were conducted to establish the efficacy of Brivaracetam in patients with (b) (4) partial onset seizures (b) (4)

The three trials N01252, N01253, and N01358 evaluated Brivaracetam (BRV) at daily doses from 5 mg to 200 mg against placebo. Although none of the tested BRV doses had duplicated positive efficacy in 2 or more of the trials, the data strongly suggested that BRV 100 mg/day and 200 mg/day were effective. The effectiveness of BRV 50 mg/day could not be conclusively determined as statistical significance was reached in Study N01253, but not in N01252. BRV at doses below 50 mg daily did not show effectiveness.

Concomitant use of levetiracetam (LEV) appeared to be a confounding factor as patients who took LEV as concomitant antiepileptic drug (AED) (occurred in 20% of patients in N01252 and N01253) did not seem to have reduction in seizure frequency as seen in patients who were not using LEV as concomitant AED.

In trial N01252, BRV at doses 20 mg, 50 mg, and 100 mg were tested against placebo. The primary outcome did not achieve statistical significance based on the sequential testing procedure, which required statistical significance at the 0.05 level for BRV 50mg versus placebo prior to the testing of BRV 100mg and BRV 20mg in sequence. The comparison of BRV 100mg/day versus PBO was nominally statistically significant with an 11.7% reduction of seizure frequency over PBO (p=0.037).

In trial N01253, BRV at doses 5 mg, 20 mg, and 50 mg were tested against placebo. The effect of BRV 50 mg achieved statistical significance (p=0.025).

Trial N01358 was initiated after the completion of N01252 and N01253. Patients using LEV as concomitant AED were excluded from the trial after the findings in N01252 and N01253 that LEV was a potential confounding factor. Both of the tested doses Brivaracetam 100 mg and 200 mg achieved statistical significance in efficacy as compared to placebo ($p < .001$for both doses).

2 INTRODUCTION

2.1 Overview

The clinical development of BRV with oral formulations in subjects 16 years of age and older with POS is composed of 2 dose-ranging studies, 3 pivotal Phase 3 studies and 1 safety study. The evidence for efficacy of BRV for treatment of POS are supported by 3 pivotal phase-3 studies N01252, N01253, and N01358, which are included in this review. The three pivotal studies were randomized, double-blind, placebo-controlled, fixed-dose, multicenter studies in adults (≥16 years) with refractory POS with or without secondary generalization. The 3 studies

were designed to evaluate the efficacy and safety of twice-daily oral administration of BRV 5mg/day to 200mg/day.

Study N01252, conducted in Europe and India, evaluated the efficacy and safety of twice-daily oral administration of BRV tablets at doses of 20mg/day, 50mg/day, and 100mg/day. Because both BRV and LEV were known to bind to the same SV2A binding site, the number of subjects using LEV as concomitant AED was limited to 20% of the total study population. Subjects completed an 8-week prospective Baseline Period followed by a 12-week Treatment Period during which they received randomized study drug without up-titration.

N01253 was a global study, with design similar to N01252. The study evaluated BRV tablets at doses of 5mg/day, 20mg/day, and 50mg/day. Like N01252, the number of subjects taking LEV at the time of study entry was limited to 20% of randomized subjects.

N01358, conducted after the completion of N01252 and N01253, was a global study with design similar to Studies N01252 and N01253, and evaluated BRV tablets at doses of 100mg/day and 200mg/day. Subjects who were receiving LEV within 90 days prior to study entry were excluded from this study.

A summary of the phase-3 pivotal studies are presented in Table 1.

Table 1 List of studies included in this review

Study	Phase and Design	Duration of treatment	Dosage	Comparator	# of Subjects randomized	Study Population
Protocol N01252	Phase 3, randomized, double-blind, PBO-controlled in Europe and India	12 weeks	20 mg/day, 50 mg/day, 100 mg/day	Exit rate estimated from historical data	399	Patients with POS; < 20% LEV user
Protocol N01253	Phase 3, randomized, double-blind, PBO-controlled conducted globally	12 weeks	5 mg/day, 20 mg/day, 50 mg/day	Exit rate estimated from historical data	400	Patients with POS; < 20% LEV user
Protocol N01358	Phase 3, randomized, double-blind, PBO-controlled conducted globally	12 weeks	100 mg/day, 200 mg/day		768	Patients with POS; excludes patients using LEV at entry

2.2 Data Sources

All documents reviewed for this NDA submission are in electronic form with eCTD format. The electronic files are compatible with eCTD viewer software Global Summit. Both raw and derived datasets are included in the submission. The SAS programs for primary and secondary analyses are also included. The path to CDER Electronic Document Room for documents of this NDA is listed below:

\\cdsesub1\evsprod\NDA205836

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

No data issues were identified.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

The three studies, N01252, N01253 and N01358, were similarly designed with the same primary objective but studied different dosage of BRV.

The primary objective of the three studies were to evaluate the efficacy of BRV as compared to placebo in reducing seizure frequency in subjects with partial onset seizures not fully controlled despite optimal treatment with 1 to 2 concomitant AEDs.

The three pivotal studies were randomized, double-blind, parallel-group, placebo-controlled studies to determine efficacy and safety of BRV in subjects of at least 16 years old with partial onset seizures (POS). Eligible subjects were enrolled and entered an 8-week Baseline Period. Subjects who had at least 8 POS whether or not secondarily generalized during the 8-Week Baseline Period were randomized in equal numbers to one of the dose groups or placebo for each studies described in Table 2. Subjects received full dose of the randomized treatment without titration. The Treatment Period lasted 12 weeks. At the end of the Treatment Period, the subject either entered a long term follow-up (LTFU) study, or entered a Down-Titration Period of 1 to 4 weeks depending on the study, followed by a 2-week Study Drug-Free Period.

The use of concomitant LEV was limited to 20% of the subjects in N01252 and N01253. Because the use of concomitant LEV was later determined to be a potential confounding factor in N01252 and N01253, and it was recognized that LEV and BRV had a similar mechanism of action, patients receiving concomitant LEV within 90 days prior to study entry were excluded from N01358. The following table presents a summary of study specifics and comparisons of the 3 pivotal studies.

Table 2 Study specifics of the pivotal studies

	N01252	**N01253**	**N01358**
Number of treatment arms	4	4	3
Dosage	20 mg, 50 mg, 100 mg	5 mg, 20 mg, 50 mg	100 mg, 200 mg
Control	Placebo	Placebo	Placebo
Number of subjects	399	400	768
AEDs	1 to 2	1 to 2	1 to 2
Patient Population	Refractory	Refractory	Refractory

Use of LEV at study entry	Limited to 20% of population	Limited to 20% of population	Excluded
Age of Patient Population	16 to 70 years	16 to 70 years	16 to 80 years
Countries or Regions	Europe and India	N. America, S. America and Australia	27 countries worldwide including ~25% of the patients from North America
Study Period	Sep. 20, 2007 to Feb. 9, 2009	Sep. 7, 2007 to Jan. 2, 2009	Dec. 10 2010 to May 22, 2014
Randomization stratification	By region and use of LEV at study entry	By region and use of LEV at study entry	By country and LEV status (never used vs. prior use) and # of AEDs discontinued

Source: reviewer's summary

3.2.1.2 Efficacy Endpoints

The primary efficacy variable was the POS (Type I) frequency over the Treatment Period.

The secondary efficacy variables included:

- Responder rate (the proportion of subjects who had a ≥50% reduction in seizure frequency from Baseline) for POS (Type I) over the Treatment Period (This variable is used as the primary efficacy endpoint for European authority in Study N01358.)
- All seizure frequency (Type I+II+III) per week over the Treatment Period
- Percent reduction for POS (Type I) frequency per week from Baseline to the Treatment Period
- Categorized percentage reduction (-25% to <25%, 25% to <50%, 50% to <75%, 75% to <100%, and 100%) from Baseline in seizure frequency for POS (Type I) over the Treatment Period
- Seizure freedom rate (all seizure types) over the Treatment Period
- Time to n^{th} (n=1, 5, 10) Type I seizure during the Treatment Period

The secondary endpoint of responder rate (50% reduction in seizure frequency) was the primary endpoint for European authorities in Study N01358.

The following 3 variables were listed as secondary efficacy endpoints subject to multiplicity adjustment in Studies N01252 and N01253, but were not included as secondary efficacy endpoints in Study N01358.

- Total Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score
- Seizure Worry QOLIE-31-P score
- Daily Activities/Social Functioning QOLIE-31-P score

Patients' epileptic seizures were recorded on the daily record card (DRC), with date, number of epileptic seizures and seizure type.

3.2.2 Statistical Methodologies

Patient Population for Efficacy Analysis

Efficacy analyses were to be based on ITT patient population in all studies except for Study N01253, where modified ITT patient population was used. The ITT Population was defined as all randomized subjects who received at least 1 dose of study medication. In Study 01253, the Modified ITT (mITT) Population was defined as all subjects in the ITT population excluding all 3 randomized subjects from Site 404 as well as Subject 364/B155. Subjects from Site 404 were excluded due to serious and persistent noncompliance with applicable FDA regulation, GCP, and ICH guidelines on the part of Site 404. Subject 364/B155 was an extraordinary outlier with respect to the reported seizure frequency during the baseline and 12-week treatment period. Further concerns were found for Subject 364/B155 regarding the reported seizure type and the subject's eligibility for the study because no POS were recorded during Baseline.

3.2.2.1 Primary Efficacy Analysis

The seizure frequency was described as per week in Studies N01252 and N01253, and was described as per 28 days in Study N01358. The seizure frequency was calculated as:

$$\frac{\textit{Total number of Type I seizures over the Treatment Period}}{\textit{Total number of days with no missing seizure count in the Treatment Period}}$$

The above number was then multiplied by 7 to obtain weekly seizure frequency for Studies N01252 and N01253, or multiplied by 28 to obtain seizure frequency per 28 days for Study N01358.

The obtained seizure frequency per week or per 28 days was then transformed by logarithm ln(x+1) (where x was the seizure frequency per week or per 28 days). The log-transformed POS frequency over the Treatment Period was analyzed applying an ANCOVA model, including treatment and stratification effects as factors and the log-transformed Baseline seizure frequency per week as covariate.

The stratification variables used in the primary analysis model varied by study as follows:

- N01252 and N01253: a combined effect of region and concomitant LEV use
- N01358: effect for country and an effect for the 4 combination of levels for LEV status and number of previous AEDs (≤2 vs >2)

3.2.2.2 Handling of Missing Values

Subjects who reported a complete and non-missing seizure record for at least 1 day during the Baseline or Treatment Period were included in the analysis. If a subject had missing seizure count information for some days during the Baseline or Treatment Periods, these days were not

considered in the calculation of the seizure frequency (i.e., the seizure frequency was computed over the non-missing days of the considered period). Similarly, if a subject withdrew from the study before the end of the Treatment Period, the seizure information collected up until the time of withdrawal was used to calculate the seizure frequency over the Treatment Period.

Reviewer's Comments: *missing data appeared to be at low level in all 3 studies and generally limited to patients who discontinued prematurely.*

3.2.2.3 Sensitivity Analyses for Primary Endpoint

In studies N01252 and N01253, a sensitivity analysis was performed to investigate how the assumptions for missing seizure counts could have influenced the results. The weekly seizure count was computed by study week using the available data during that week (if the daily seizure counts were missing for all days of the week, the weekly seizure frequency was set to missing for that week). Then a Longitudinal Linear Mixed-Effects model was applied.

A non-parametric analysis applying a rank-ANCOVA model on untransformed data as a sensitivity analysis was planned for all three studies.

3.2.2.4 Multiple comparisons/multiplicity

Multiplicity Adjustment for N01252 and N01253

In Studies N01252 and N01253, the 3 doses of BRV were tested at the 5% level against placebo sequentially in the following order:

- Study N01252: 50mg/day, then the 100mg/day, and finally the 20mg/day dose.
- Study N01253: 50mg/day, then the 20mg/day, and finally the 5mg/day dose.

Thus, a next dose was compared with placebo if and only if statistical significance was reached with the current dose.

Multiplicity Adjustment for N01358

For Study 01358, statistical testing was based on the comparison of each BRV treatment group (BRV 100 and 200mg/day) to placebo with control of overall type I error rate based on the Hochberg procedure. The Hochberg procedure was applied by first testing the BRV treatment group with the larger p-value. If the larger p-value was $\leq$ 0.05, then statistical significance was achieved and both BRV treatment groups were to be declared statistically different from placebo. If the largest p-value was greater than 0.05, then the procedure was to compare the smaller p-value to 0.025. If statistical significance was achieved at this step then the BRV treatment group associated with the smaller p-value was declared statistically different from placebo. If the smaller p-value was not significant at the 0.025 level, then neither BRV treatment groups was statistically different from placebo and the study was not positive.

For the USA, 50% responder outcome was analyzed as a secondary variable with statistical testing at the nominal 0.05 level without applying a Hochberg procedure. Similarly, the USA primary analysis was a secondary analysis for Europe, with testing at a nominal 0.05 level in support of the primary responder outcome.

3.2.3 Study Results

3.2.3.1 Study Results from N01252

3.2.3.1.1 Patient Disposition - N01252

A total of 486 subjects were screened and 399 subjects were randomized in 71 study sites in Europe and India. One subject randomized to the BRV 50mg/day group was dispensed drug and died before consuming any study drug. This subject was not included in the ITT Population.

Of the 398 subjects in the ITT Population, 367 subjects (92.2%) completed the study. A total of 31 subjects (7.8%) discontinued the study. The most common reason for discontinuation was AE for all treatment groups. A summary of patient disposition is presented in Table 3.

Table 3 Disposition of patients - N01252

N (% of ITT population)	PBO	BRV		
		20 mg	50 mg	100 mg
Randomized	100	99	100	100
ITT Population	100	99	99	100
Completed study	92 (92%)	93 (93.9%)	88 (88.9%)	94 (94.0%)
Discontinued	8 (8.0%)	6 (6.1%)	11 (11.1%)	6 (6.0%)
Adverse Event	4 (4.0%)	4 (4.0%	6 (6.1%)	5 (5.0%)
Lack of Efficacy	0	0	0	0
Lost to follow-up	2 (2.0%)	0	1 (1.0%)	0
Consent withdrawn	2 (2.0%)	1 (1.0%)	1 (1.0%)	0
Other	0	1 (1.0%)	3 (3.0%)	1 (1.0%)

Source: Clinical Study Report

3.2.3.1.2 Patient Demographic and Baseline Characteristics – N01252

Patient demographics are presented in Table 4. The mean age of subjects was 37 years. A total of 227 males (57.0%) and 171 females (43.0%) enrolled in this study. The majority of subjects were Caucasian (76.6%). Except one subject with mixed race, the remaining subjects were of Asian descent.

Table 4 Patient demographics (ITT population) – N01252

	PBO N=100	BRV		
		20 mg N=99	50 mg N=99	100 mg N=100
Gender, n (%)				
Female	46 (46.0%)	38 (38.4%)	45 (45.5%)	42 (42.0%)
Male	54 (54.0%)	61 (61.6%)	54 (54.5%)	58 (58.0%)
Age, years				
Mean	36.4	35.7	38.9	38.0
Median	33.3	33.9	38.7	37.1
Race, n (%)				
Caucasian	77 (77.0%)	76 (76.8%)	76 (76.8%)	76 (76.0%)
Asian	23 (23.0%)	22 (22.2%)	23 (23.2%)	24 (24.0%)
Mixed	0	1 (1.0%)	0	0

Source: Clinical Study Report

The sponsor reported that variations in demographic characteristics were apparent between subjects in different regions (Western Europe, Eastern Europe, and India). Generally, subjects from Indian region were younger compared with subjects from other regions.

Patient baseline epileptic characteristics are presented in the following table.

Table 5 Baseline epileptic characteristics (ITT population) – N01252

	PBO N=100	BRV		
		20 mg N=99	50 mg N=99	100 mg N=100
Median epilepsy duration (years)	20.0	20.8	21.0	20.0
Median age at onset (years)	14.0	12.0	13.0	13.5
History of status epilepticus, n (%)	3 (3.0%)	8 (8.1%)	4 (4.0%)	5 (5.0%)

Source: Clinical Study Report

All subjects were taking at least 1 concomitant AED at Baseline. The most frequently used concomitant AEDs were: Carbamazepine (46.5%), Valproate (22.4%), Lamotrigine (20.9%), and Oxcarbazepine (20.4%). The majority of patients (78.9%) were taking 2 AEDs. A summary of the number of AEDs taken at baseline is presented in Table 6.

Table 6 Summary of the number of AEDs taken at baseline (ITT population) – N01252

Number of AEDs at baseline, n (%)	PBO N=100	BRV		
		20 mg N=99	50 mg N=99	100 mg N=100
1 AED	14 (14.0)	18 (18.2)	20 (20.2)	16 (16.0)
2 AEDs	83 (83.0)	77 (77.8)	77 (77.8)	77 (77.0)
3 or more AEDs	3 (3.0)	4 (4.0)	2 (2.0)	7 (7.0)

Source: Clinical Study Report

3.2.3.1.3 Efficacy Results of N01252

Analysis of the Primary Endpoint

The median POS frequency decreased in all treatment groups during the Treatment Period. The percent reductions over PBO in the POS frequency per week over the Treatment Period were 6.8%, 6.5%, and 11.7% in the BRV 20mg/day, BRV 50mg/day, and BRV 100mg/day groups, respectively. The primary outcome for study N01252 did not achieve statistical significance based on the sequential testing procedure, which required statistical significance at the 0.05 level for BRV 50mg/day versus PBO prior to the testing of BRV 100mg/day and BRV 20mg/day in sequence. The comparison of BRV 100mg/day versus PBO was nominally statistically significant with an 11.7% reduction over PBO for the primary outcome (p=0.037).

Deviations from the model assumptions in normality were noted, and a sensitivity analysis using a rank-ANCOVA model on the untransformed data was performed. The results of this sensitivity analysis achieved similar p-values as in the primary analysis. The following table presents the efficacy results from the primary analysis as well as sensitivity analyses.

Table 7 Results of efficacy analysis of seizure frequency per week – N01252

	Placebo N=100	**BRV**		
		20 mg N=99	**50 mg N=99**	**100 mg N=100**
Baseline median seizure frequency	2.07	1.93	1.80	2.02
Treatment median seizure frequency	1.75	1.34	1.49	1.26
Primary analysis LS mean % reduction (95% CI) p-value	2.21	1.99 6.8 (-4.8, 17.1) 0.239	2.00 6.5 (-5.2, 16.9) 0.261	1.84 11.7 (0.7, 21.4) 0.037
Sensitivity analysis-mixed effect LS mean % reduction (95% CI) p-value	1.77	1.57 7.4 (-3.6, 17.3) 0.178	1.66 3.9 (-7.5, 14.2) 0.484	1.52 8.9 (-1.9, 18.5) 0.104
Sensitivity analysis- ranks p-value		0.174	0.246	0.021

Source: reported in CSR and verified by the reviewer

Analysis of Secondary Endpoints

Due to the stopping rule, none of the secondary endpoints were eligible for statistical testing. The sponsor did not present the planned statistical testing for the 3 patient reported outcomes that were specified for testing with multiplicity adjustment.

The following table presents the results from analysis 50% responder rate for descriptive purpose only. The treatment effect of BRV 100 mg group compared to placebo group reached nominal significance with a p-value of 0.023.

Table 8 Fifty percent responder rate in partial seizure frequency per week

Statistics	PBO	BRV		
		20mg	50mg	100mg
	(N=100)	(N=99)	(N=99)	(N=100)
Nonresponders, n (%)	80 (80.0)	72 (72.7)	72 (72.7)	64 (64.0)
Responders, n (%)	20 (20.0)	27 (27.3)	27 (27.3)	36 (36.0)
Odds ratio (BRV vs PBO)[a]		1.39	1.36	2.13
95% Two-sided CI		0.71, 2.72	0.69, 2.66	1.11, 4.10
p-value		0.339	0.372	0.023[b]

Source: Clinical Study Report

3.2.3.2 Study Results from N01253

3.2.3.2.1 Patient Disposition in Study N01253

A total of 509 subjects were screened and 400 subjects were randomized. Four subjects were not treated. Thus, 396 subjects were included in the ITT Population.

In this study, efficacy analyses were performed on the mITT Population, defined as all subjects in the ITT Population with the exception of 4 subjects. Three subjects from Site 404 were excluded due to serious, persistent compliance issues involving the principle Investigator. One subject from Site 364 was excluded due to an extremely high seizure frequency prior to and during the study as well as due to concerns about seizure type eligibility. Thus, a total of 392 subjects were included in the mITT Population.

A total of 35 subjects (8.8%) discontinued the study. The most common reason for discontinuation was AE.

Table 9 Disposition of patients - N01253

N (%)	PBO	BRV		
		5 mg	20 mg	50 mg
Randomized	99	99	100	102
ITT Population	98	97	100	101
Modified ITT	96	96	99	101
Completed study	93 (94.9%)	82 (84.5%)	93 (93.0%)	93 (92.1%)
Discontinued	5 (5.1%)	15 (15.5%)	7 (7.0%)	8 (7.9%)
Adverse Event	2 (2.0%)	8 (8.2%	5 (5.0%)	6 (5.9%)
Lack of Efficacy	1 (1.0%)	0	0	0
Lost to follow-up	0	4 (4.1%)	0	1 (1.0%)
Consent withdrawn	0	2 (2.1%)	1 (1.0%)	1 (1.0%)
Other	2 (2.0%)	1 (1.0%)	1 (1.0%)	0

Source: Clinical Study Report

3.2.3.2.2 Patient Demographic and Baseline Characteristics - N01253

Patient demographics are presented in Table 10. The mean age of subjects was 38 years. A total of 195 males (49.2%) and 201 females (50.8%) enrolled in this study. The majority of subjects were Caucasian (72.2%).

Table 10 Patient demographics (ITT patient population) - N01253

	PBO N=98	**BRV**		
		5 mg N=97	**20 mg N=100**	**50 mg N=101**
Gender, n (%)				
Female	55 (56.1)	48 (49.5%)	48 (48.0%)	50 (49.5%)
Male	43 (43.9)	49 (50.5%)	52 (52.0%)	51 (50.5%)
Age, years				
Mean (SD)	37.5	38.9	37.3	38.9
Median	35.6	38.4	37.9	39.1
Race, n (%)				
Caucasian	66 (67.3)	73 (75.3)	70 (70)	77 (76.2))
Black	4 (4.1)	5 (5.2))	5 (5.0)	2 (2.0)
American India	13 (13.3)	8 (8.2)	9 (9.0)	8 (7.9)
Mixed	14 (14.3)	10 (10.3)	14 (14.0)	10 (9.9)
Other	1 (1.0)	1 (1.0)	2 (2.0)	4 (4.0)

Source: Clinical Study Report

Variations in age and race were apparent between subjects in different regions (North America/Australia, Latin America). Generally, subjects in the Latin America subgroup were younger compared with the North America/Australia subgroup. About half of the subjects in the Latin America subgroup were Caucasian (53.4%) compared with those in the North America/Australia subgroup who were mostly Caucasian (87.6%).

Demographic characteristics of subjects with concomitant LEV use at study entry were generally similar compared with subjects without concomitant LEV use at study entry.

The history of epileptic seizures and etiology of epilepsy are summarized in Table 11.

Table 11 Baseline epileptic characteristics (ITT population) – N01253

	PBO N=98	**BRV**		
		5 mg N=97	**20 mg N=100**	**50 mg N=101**
Median epilepsy duration (years)	23.1	19.8	21.5	26.0
Median age at onset (years)	10.0	13.0	10.6	10.0
History of status epilepticus, n (%)	11 (11.2)	5 (5.2)	13 (13.0)	10 (9.9)

Source: Clinical Study Report

All but 1 subject were taking at least 1 concomitant AED at Baseline. The most frequently used concomitant AEDs were: Carbamazepine (40.4%), Lamotrigine (27.8%), Levetiracetam (19.2%),

and Phenytoin (17.2%). A summary of the number of AEDs taken at baseline is presented in Table 12.

Table 12 Summary of the number of AEDs taken at baseline (ITT population) – N01253

Number of AEDs at baseline, n (%)	**PBO N=98**	**BRV**		
		5 mg N=97	**20 mg N=100**	**50 mg N=101**
0 AED	1 (1.0)	0	0	0
1 AED	13 (13.3)	14 (14.4)	16 (16.0)	13 (12.9)
2 AEDs	80 (81.6)	76 (78.4)	71 (71.0)	81 (81.2)
3 or more AEDs	4 (4.1)	7 (7.2)	12 (12.0)	6 (5.9)

Source: Clinical Study Report

3.2.3.2.3 Efficacy Results of N01253

The median POS frequency decreased in all treatment groups during the Treatment Period. The percent reductions over PBO in the POS frequency per week over the Treatment Period were -0.9%, 4.1%, and 12.8% in the BRV 5mg/day, BRV 20mg/day, and BRV 50mg/day groups, respectively. The primary outcome for study N01253 achieved statistical significance for BRV 50mg/day versus PBO (p=0.025). However, neither BRV 20mg/day versus PBO nor BRV 5mg/day versus PBO reached statistical significance.

Results of the primary efficacy analysis are summarized in Table 13.

Table 13 Results of efficacy analysis of seizure frequency per week – N01253

	Placebo N=96	**BRV**		
		5 mg N=96	**20 mg N=99**	**50 mg N=101**
Baseline median seizure frequency	2.63	2.32	2.23	2.85
Treatment median seizure frequency	2.15	1.80	1.96	1.70
Primary analysis LS mean % reduction (95% CI) p-value	3.13	 3.17 -0.9 (-13.9, 106) 0.885	 2.96 4.1 (-8.1, 15.0) 0.492	 2.60 12.8 (1.7, 22.6) 0.025
Sensitivity analysis-mixed effect LS mean % reduction (95% CI) p-value	2.65	 2.47 4.8 (-7.8, 16.0) 0.437	 2.36 7.9 (-4.1, 18.6) 0.189	 2.07 15.9 (4.9, 25.6) 0.006
Sensitivity analysis- ranks p-value		 0.698	 0.303	 0.003

Source: Reviewer's Analysis

As in Study N01252, marked deviation from the normal assumption was noted. Sensitivity analyses using a Linear Mixed-Effects Model and a rank-ANCOVA model on the untransformed data confirmed results from the primary analysis.

In the primary and sensitivity analyses, 4 subjects were excluded from the ITT patient population. It was found that subject 364/B155 had seizure frequency of over 1500 times of median seizure frequency of the population at both baseline and treatment period and the exclusion of this subject was justifiable. Analysis including subjects in site 404 had results similar to the ones from the primary analysis.

3.2.3.3 Study Results from N01358

3.2.3.3.1 Patient Disposition - N01358

A total of 1045 subjects were screened and 768 subjects were randomized. Among them, 375 subjects (48.8%) were enrolled from the EU region and 188 (24.5%) subjects were enrolled from the North American region.

A total of 72 subjects (9.4%) discontinued the study (Table 14). The most common reason for discontinuation was AE.

Table 14 Disposition of patients - N01358

N (%)	PBO	BRV	
		100 mg	**200 mg**
Randomized	263	254	251
Completed study	246 (93.5)	225 (88.6)	225 (89.6)
Discontinued	17 (6.5)	29 (11.4)	26 (10.4)
Adverse Event	10 (3.8)	21 (8.3)	17 (6.8)
Lack of Efficacy	1 (0.4)	1 (0.4)	0
Protocol violation	0	3 (1.2)	1 (0.4)
Lost to follow-up	0	1 (0.4)	3 (1.2)
Consent withdrawn	2 (0.8)	2 (0.8)	4 (1.6)
Other	4 (1.5)	1 (0.4)	1 (0.4)

Source: Clinical Study Report

Eight randomized subjects (4 in the placebo group, 2 in the BRV 100 mg group and 2 in the BRV 200 mg group) were excluded from the ITT Population due to discontinuation either prior to drug administration or before first on-treatment assessment. Thus, 760 subjects were included in the ITT population.

3.2.3.3.2 Patient Demographic and Baseline Characteristics - N01358

Subject demographics are presented in Table 15. The mean age of subjects was 39.5 years. Overall, there was a similar proportion of males (48.2%) compared with females (51.8%). The majority of subjects were white (72.4%).

Table 15 Patient demographics (ITT patient population) - N01358

N (%)	**PBO N=261**	**BRV**	
		100 mg N=253	**200 mg N=250**
Gender, n (%)			
Female	128 (49.0)	151 (59.7)	117 (46.8)
Male	133 (51.0)	102 (40.3)	133 (53.2)
Age, years			
Mean (SD)	39.8	39.1	39.8
Median	39.0	39.0	40.0
Race, n (%)			
Caucasian	189 (72.4)	182 (71.9)	182 (72.8)
Black	11 (4.2)	8 (3.2)	7 (2.8)
Asian	32 (12.3)	32 (12.6)	29 (11.6)
Other	26 (10.0)	29 (11.5)	29 (11.6)

Source: Clinical Study Report

The history of epileptic seizures and etiology of epilepsy are summarized in Table 16.

Table 16 Baseline epileptic characteristics (ITT population) – N01358

N (%)	**PBO N=259**	**BRV**	
		100 mg N=252	**200 mg N=249**
Median duration of epilepsy (years)	20.8	20.7	21.9
Median age at onset (years)	13.7	14.6	13.9
History of status epilepsy, n (%)	12 (4.6)	7 (2.8)	20 (8.0)

Source: Clinical Study Report

All subjects were taking at least 1 concomitant AED at Baseline. The most frequently used concomitant AEDs were: Carbamazepine (37.2%), Lamotrigine (25.9%), Valproate (21.8%), Oxcarbazepine (15.8%), Topiramate (15.0%), and Lacosamide (14.2%). A summary of the number of AEDs taken at baseline is presented in Table 17.

Table 17 Summary of the number of AEDs taken at baseline (ITT population) – N01358

Number of AEDs at baseline, n (%)	PBO N=259	BRV	
		100 mg N=252	200 mg N=249
1 AED	75 (29.0)	70 (27.8)	69 (27.7)
2 AED	181 (69.9)	182 (72.2)	179 (71.9)
$\geq$ 3 AEDs	3 (1.2)	0	1 (0.4)

Source: Clinical Study Report

3.2.3.3.3 Efficacy Results of N01358

The primary efficacy outcome for the USA was the percent reduction in POS (Type I) frequency over PBO based on an ANCOVA. A summary of percent reduction over PBO in the 28-day adjusted POS frequency is provided in Table 18.

Table 18 Results of efficacy analysis of seizure frequency per 28 days – N01358

	Placebo N=259	BRV	
		100 mg N=252	200 mg N=249
Baseline median seizure frequency	10.0	9.5	9.3
Treatment median seizure frequency	8.7	6.3	5.8
Primary analysis LS mean seizure freq per 28 days (seizure frequency per week) % reduction (95% CI) p-value	 9.2 (2.3)	 6.9 (1.7) 22.8 (13.3, 31.2) <.001	 6.8 (1.7) 23.2 (13.8, 31.6) <.001
Non-parametric rank ANCOVA p-value		 <.001	 <.001
EU primary outcome, 50% respond Responders, n (%) Odds ratio[1] p-value	 56 (21.6)	 98 (38.9) 2.39 <.001	 94 (37.8) 2.19 <.001

1. The analysis used a logistic model with effect of treatment, pooled country, and 4 combinations of stratification of previous use of AEDs and LEV status. The odds ratio represents the odds of being a responder as compared to PBO.

Source: Reported results confirmed by the reviewer

The reductions in both BRV groups were statistically significant (p<0.001). The percent reduction in the 28-day adjusted POS frequency over PBO in the BRV 100mg/day and 200mg/day groups was similar (22.8% and 23.2%, respectively) with no dose response observed.

The primary efficacy outcome for the EU was the 50% responder rate based on percent reduction in POS (Type I) frequency from Baseline to the 12-week Treatment Period. The 50% responder rates in the BRV 100mg/day and 200mg/day groups were 38.9% and 37.8%, respectively (Table 18 above), and were greater than the responder rate in the PBO group (21.6%). The odds ratios for the BRV 100mg/day and 200mg/day groups were 2.39 and 2.19, respectively; both BRV groups showed statistical significance compared with the PBO group (p<0.001).

3.3 Evaluation of Safety

Refer to Safety Review by Dr. Mary Doi and Clinical Review by Steven Dinsmore for Evaluation of Safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

As noted before, the distribution of the seizure frequency was extremely skewed. Marked deviation from the normal assumption of the model was observed, even after the log transformation. Least square (LS) mean estimates from the model could be severely influenced by the extreme values at the two ends, i.e., subjects with very low or very high seizure

frequencies, particularly in the subgroup analysis when the sample size is small. Therefore, instead of LS means, the point estimates of mean seizure frequency are presented.

Results from subgroup analysis of seizure frequency by gender, age group and race are presented by study in Table 19 for Study N01252, Table 21 for Study N01253 and Table 23 for Study N01358. Subgroup analyses of seizure frequency by region are presented in Table 20 for Study N01252, Table 22 for Study N01253, and in Table 24 for Study N01358. Large baseline differences in seizure frequency with regard to demographic characteristics and regions are noted. This is partly due to the difference in patient population in different regions. However, no substantial discrepancies in treatment difference were found in these subgroup analyses.

Note that seizure frequency per week was used in Studies N01252 and N01253, and seizure frequency per 28 days was used in Study N01358.

Table 19 Seizure frequency per week by gender, age group and race - Study N01252

Median seizure frequency per week	**PBO N=100**	**BRV**		
		20 mg N=99	**50 mg N=99**	**100 mg N=100**
Female				
N	46	38	45	42
Baseline	2.3	1.9	2.2	2.1
Treatment period	1.7	1.3	1.8	1.3
Male				
N	54	61	54	58
Baseline	2.0	2.0	1.7	2.0
Treatment period	1.8	1.4	1.3	1.3
< 37 (year)				
N	56	57	44	50
Baseline	2.0	2.0	2.1	2.3
Treatment period	1.8	1.3	1.6	2.0
≥ 37 (year				
N	44	42	55	50
Baseline	2.2	1.8	1.6	1.7
Treatment period	2.0	1.3	1.3	1.0
Caucasian				
N	77	76	76	76
Baseline	2.2	1.9	1.8	2.1
Treatment period	1.8	1.4	1.6	1.7
Other				
N	23	23	23	24
Baseline	1.5	1.7	1.9	1.6
Treatment period	1.4	0.9	1.0	0.9

Table 20 Analysis of seizure frequency by region – Study N01252

Median seizure frequency per week	**Placebo N=100**	**BRV**		
		20 mg N=99	**50 mg N=99**	**100 mg N=100**
Eastern Europe				
N	30	30	30	30
Baseline	1.8	1.8	1.7	1.5
Treatment period	1.6	1.1	1.6	1.0
Western Europe				
N	47	47	47	47
Baseline	3.4	2.2	1.9	2.4
Treatment period	3.0	1.9	1.6	2.1
Rest of the World				
N	23	22	22	23
Baseline	1.5	1.7	1.8	1.7
Treatment period	1.4	0.8	1.1	0.9

Table 21 Analysis of seizure frequency by gender, age group and race - Study N01253

Median seizure frequency per week	**PBO N=96**	**BRV**		
		5 mg N=96	**20 mg N=99**	**50 mg N=101**
Female				
N	53	47	47	50
Baseline	3.2	2.5	2.5	2.5
Treatment period	2.2	1.8	2.0	1.5
Male				
N	43	49	52	51
Baseline	2.3	2.0	2.2	3.4
Treatment period	1.8	1.9	1.8	2.0
< 37 (year)				
N	52	42	47	46
Baseline	2.9	2.4	4.4	3.5
Treatment period	2.5	1.7	3.4	2.5
≥ 37 (year				
N	44	54	52	55
Baseline	2.6	2.3	1.9	2.3
Treatment period	2.0	1.9	1.4	1.4
Caucasian				
N	66	72	70	77
Baseline	2.6	2.6	2.8	2.9
Treatment period	2.2	2.0	2.0	2.0
Other				
N	30	24	29	24
Baseline	2.8	1.6	2.0	2.0
Treatment period	2.1	1.1	1.6	1.3

Table 22 Analysis of seizure frequency by region – Study N01253

Median seizure frequency per week	**Placebo N=96**	**BRV**		
		5 mg N=96	**20 mg N=99**	**50 mg N=101**
North America / Australia				
N	53	52	55	57
Baseline	2.7	2.5	2.7	2.9
Treatment period	2.6	2.4	2.2	2.0
Latin America				
N	43	44	44	44
Baseline	2.5	2.2	2.1	2.6
Treatment period	2.0	1.7	1.6	1.5

Table 23 Analysis of seizure frequency by gender, age group and race - Study N01358

Median seizure frequency per 28 days	**Placebo N=259**	**BRV**	
		100 mg N=252	**200 mg N=249**
Female			
N	126	150	116
Baseline	10.6	10.7	10.7
Treatment period	8.7	7.4	6.7
Male			
N	133	102	133
Baseline	8.7	8.2	8.8
Treatment period	8.4	4.8	5.3
Age < 40 (years)			
N	138	136	121
Baseline	11.1	11.8	11.0
Treatment period	9.0	7.0	7.6
Age > 40 (years)			
N	121	116	128
Baseline	8.9	8.1	8.0
Treatment period	7.7	5.8	4.9
White			
N	187	182	181
Baseline	10.1	11.8	9.0
Treatment period	8.7	7.3	5.9
Asian			
N	32	32	29
Baseline	6.3	6.5	10.0
Treatment period	5.7	4.4	8.3
Other			
N	40	38	39
Baseline	12.1	8.0	11.3
Treatment period	10.1	4.3	5.3

Table 24 Analysis of seizure frequency by region – N01358

Median seizure frequency per 28 days	PBO N=259	BRV 100 mg N=252	BRV 200 mg N=249
East Europe			
N	67	66	65
Baseline	7.2	8.8	7.8
Treatment period	6.3	4.6	4.9
West Europe			
N	69	64	67
Baseline	18.2	14.0	14.0
Treatment period	11.7	9.3	9.3
North America			
N	62	64	61
Baseline	9.6	9.3	8.1
Treatment period	8.2	7.3	5.2
Asian Pacific			
N	32	31	28
Baseline	6.3	6.0	9.8
Treatment period	5.7	4.3	8.5
Latin America			
N	29	27	28
Baseline	11.5	8.4	11.9
Treatment period	8.7	5.3	4.8

4.2 Other Special/Subgroup Populations

Because the use of concomitant LEV was later determined to be a potential confounding factor in N01252 and N01253, and it was recognized that LEV and BRV had a similar mechanism of action, analyses were performed to examine the difference in efficacy in patients with or without concomitant use of LEV in Studies N01252 and N01253. The effect of prior use of LEV in Study N01358 was also evaluated.

It was reported that at least 40% of the patients in Studies N01252 and N01253 and 37% of the patients in Study N01358 used CBZ as concomitant AED. During the review process, the issue of possible confounding effect of concomitant use of Carbamazepine (CBZ) was raised, and data of CBZ use during the study were obtained from the sponsor.

A total of 322 subjects in Study N01252 and 239 subjects in N01253 had CBZ data indicating whether a subject was using CBZ as concomitant AED. All subjects in Study N01358 had CBZ data. In the analyses presented below, subjects who had missing CBZ data are assumed as they did not use CBZ. It occurred that in Study N01252, none of the subjects in the BRV 5 mg group used CBZ. No missing data occurred and no imputation was applied in Study N01358.

The data suggests that the effect of LEV is confounded with the effect of the study drug as subjects who were using LEV as concomitant AED showed less improvement or had larger increase in seizure frequency at the end of the study compared to subjects who did not use LEV

as concomitant AED. Prior use of LEV in subjects in Study N01358 does not seem to have impact on the treatment effect of BRV.

The use of CBZ does not seem to have an impact on the treatment effect of BRV. Results are presented in Table 25 for Study N01252, Table 26 for Study N01253 and Table 27 for Study N01358.

Table 25 Analyses of seizure frequency by concomitant use of LEV and CBZ – Study N01252

Median seizure frequency per week	**Placebo N=100**	**BRV**		
		20 mg N=99	**50 mg N=99**	**100 mg N=100**
No LEV as concomitant AED				
N	81	81	79	80
Baseline	2.0	1.8	1.8	2.0
Treatment period	1.7	1.2	1.4	1.1
LEV used as concomitant AED				
N	18	18	20	20
Baseline	3.5	2.8	1.8	2.1
Treatment period	1.7	2.3	1.7	2.4
No CBZ as concomitant AED				
N	62	50	55	65
Baseline	2.1	2.0	1.8	2.1
Treatment period	1.8	1.3	1.6	1.3
CBZ used as concomitant AED				
N	38	49	44	35
Baseline	2.1	1.9	1.8	1.9
Treatment period	1.6	1.4	1.2	1.1

Table 26 Analyses of seizure frequency by concomitant use of LEV and CBZ – Study N01253

Median seizure frequency per week	**Placebo N=96**	**BRV**		
		5 mg N=96	**20 mg N=99**	**50 mg N=101**
No LEV as concomitant AED				
N	77	78	80	82
Baseline	2.6	2.3	2.3	2.8
Treatment period	2.1	1.7	1.9	1.5
LEV used as concomitant AED				
N	19	18	19	19
Baseline	2.7	2.4	2.2	5.7
Treatment period	2.9	2.7	2.1	4.8
No CBZ as concomitant AED				
N	58	96	66	64
Baseline	2.6	2.3	2.2	3.0
Treatment period	2.0	1.8	2.0	1.8
CBZ used as concomitant AED				
N	38	0	33	37
Baseline	3.3		2.3	2.5
Treatment period	2.2		1.7	1.6

Table 27 Analyses of seizure frequency by prior use of LEV and concomitant use of CBZ – Study N01358

Median seizure frequency per 28 days	PBO N=259	BRV 100 mg N=252	BRV 200 mg N=249
Number AEDs ≤ 2, No prior use of LEV			
N	69	71	67
Baseline median seizure frequency	8.2	7.3	6.5
Treatment	7.0	4.0	3.2
Number AEDs ≤ 2, prior use of LEV			
N	13	8	9
Baseline median seizure frequency	12.8	14.0	11.1
% reduction (nominal p-value)	8.7	8.5	5.3
Number AEDs > 2, No prior use of LEV			
N	47	45	48
Baseline median seizure frequency	7.5	8.1	10.4
% reduction (nominal p-value)	8.0	4.9	6.2
Number AEDs > 2, prior use of LEV			
N	130	128	125
Baseline median seizure frequency	11.3	12.4	11.2
% reduction (nominal p-value)	10.8	9.2	8.2
No CBZ as concomitant AED			
N	163	157	155
Baseline	10.7	9.0	9.7
Treatment period	8.9	5.3	5.9
CBZ used as concomitant AED			
N	96	95	94
Baseline	8.1	10.9	8.9
Treatment period	7.9	7.7	5.6

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Three pivotal trials evaluated the effect of BRV at doses from 5 mg/day to 200 mg/day. The two trials conducted earlier included 20% of the subjects who were taking concomitant AED of LEV, which appeared to be a confounding factor of the study drug.

The trial N01358 was initiated after the completion of N01252 and N01253 with an improved design: it enrolled more subjects, studied higher doses of BRV, and it excluded subjects who were using LEV as concomitant AED within 90 days of study entry.

The effectiveness of BRV at daily dose of 100 mg and 200 mg found from N01358 achieved high significance level and appeared to be robust under model assumptions and consistent across demographic and baseline characteristics. The efficacy of BRV 100 mg/day found in Study N01358 was supported by results from N01252, in which the effect of BRV 100 mg/day achieved a nominal p-value-f 0.037.

The distributions of the seizure frequency at baseline and during the treatment were highly skewed and marked deviation from the model assumptions were noted in all 3 studies. Although the non-parametric rank analysis generally confirmed results from the primary analysis for the 3 studies, the least square estimate from the primary analysis may not provide a close estimate of the seizure frequency.

5.2 Conclusions and Recommendations

The 3 pivotal trials provided evidence that BRV at daily dose of 100 mg or 200 mg is effective in reducing the seizure frequency in patients with POS. The reviewer recommend that the medians (b) (4) be used in the labeling descriptions for treatment (b) (4)

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/s/

XIAORONG YAN
08/26/2015

KUN JIN
08/26/2015
I concur with the review.

HSIEN MING J HUNG
08/26/2015

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

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	NDA 205-836/0000
Drug Name:	Briviact (brivaracetam)
Indication(s):	Not applicable
Applicant:	UCB Pharma
Date(s):	Date of Document received: 11/24/2014 Date of Stat Consult from CSS received: 1/8/2015 DESIRED COMPLETION date: 2/9/2015
Review Priority:	30 days
Biometrics Division:	Division of Biometrics VI/Office of Biostatistics (DBVI)
Statistical Reviewer:	Wei Liu, Ph.D., Mathematical Statistician, QT-CSS/DBVI/OB/OTS
Concurring Reviewers:	Qianyu Dang, Ph.D., Team Leader, DBVI/OB/OTS Yi Tsong, Ph.D., Division Director, DBVI/OB/OTS
Medical Division:	Controlled Substance Staff
The CSS Team:	Martin Rusinowitz, M.D., OD/CSS Michael Klein, Ph.D., Director, OD/CSS
Project Manager:	Sandra Saltz, OD/CSS
Keywords: NDA review, clinical studies, Crossover design; drug abuse potential; Self-reported endpoint; Multiple endpoints	

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EXECUTIVE SUMMARY

Confirmation of abuse-potential:
The data of Study N01295, a phase 1 study of a mono-center, randomized, double-blind, triple dummy placebo, unscheduled and scheduled comparators controlled, single-dose crossover trial to evaluate the abuse potential of brivaracetam in subjects with a history of recreational CNS depressant use, submitted by UCB Pharma was evaluated

The numbers of completers were 36 (82%) with a total of 44 subjects randomized to the treatment phase. The number of completers assured the analysis power greater than 80% for detecting a significant difference between placebo and each dose of the positive control (alprazolam) on the Drug Liking (at the moment) VAS.

This reviewer confirmed that:

All brivaracetam doses (50, 200, and 1000 mg) were significantly greater than placebo on all four primary variables: Drug Liking (at the moment) VAS, Overall Drug Liking VAS (at 12- and 24-hour), Subjective Effects VAS: High, and ARCI: PCAG scale.

In general, brivaracetam at the selected doses was not significantly different from alprazolam (at doses 1.5 mg and 3.0 mg, respectively) and levetiracetam at 4000 mg based on primary analysis.

The assay sensitivity showed significant difference from placebo at both doses 1.5 mg and 3.0 mg of alprazolam, although the mean difference at the lower dose is numerically larger than that at the high dose as observed for drug-liking (at the moment) VAS scores (but not for other primary endpoints) as shown in Table 1.

The results from all primary and key secondary endpoints demonstrate abuse potential of brivaracetam.

The results of the primary analysis (paired-test) on completers set by this reviewer are summarized in Table 1.

Table 1. Summary of Paired-data Analysis for Primary Endpoints VAS Emax –Completers population (N=36)

Difference	ALP 1.5 mg	ALP 3.0 mg	BRV 50 mg	BRV 200 mg	BRV 10000 mg	LEV 4000 mg
Drug-Liking VAS[1]						
drug-PLB (stderr) 95% CI p-value	28.4 (4.8) (18.6,38.3) <.0001	24.3 (4.9) (14.3, 34.4) <.0001	19.3 (5.1) (8.9, 29.8) 0.0007	24.7 (5.2) (14.2, 35.3) <.0001	29.8 (4.8) (19.9, 39.7) <.0001	19.1 (5.6) (7.7, 30.5) 0.0015
drug-A1.5 (stderr) 95% CI p-value			-8.4 (2.6) (-13.7,-3.0) 0.0031	-3.2 (2.7) (-8.7, 2.3) 0.2461	1.7 (2.2) (-2.9, 6.3) 0.4635	-8.7 (3.6) (-16.0, -1.4) 0.0204
drug-A3 (stderr) 95% CI p-value			-5.2 (3.0) (-11.1,0.8) 0.0898	0.0 (3.1) (-6.3, 6.4) 0.9909	4.9 (2.4) (-0.2, 10.0) 0.0588	-5.5 (3.9) (-13.3, 2.3) 0.1631
drug-LEV (stderr) 95% CI p-value			0.7 (3.9) (-7.4, 8.7) 0.864	5.8 (3.9) (-2.3, 13.8) 0.1515	10.6 (3.9) (2.7, 18.5) 0.0103	
Overall Drug-Liking VAS[1]						
drug-PLB (stderr) 95% CI p-value	22.5 (5.0) (12.2,32.7) 0.0001	25.1 (5.5) (14.0, 36.2) <.0001	22.2 (5.6) (10.9,33.5) 0.0003	23.7 (5.5) (12.6, 34.8) 0.0001	30.1 (5.5) (19.0, 41.2) <.0001	20.2 (6.1) (7.9, 32.5) 0.0018
drug-A1.5 (stderr) 95% CI p-value			-0.2 (4.3) (-9.0,8.6) 0.956	1.1 (4.6) (-8.3, 10.5) 0.8201	7.2 (4.0) (-1.0, 15.5) 0.0827	-2.4 (5.7) (-14.0, 9.3) 0.6808
drug-A3 (stderr) 95% CI p-value			-2.5 (5.2) (-13.1,8.1) 0.6362	-1.2 (5.4) (-12.2, 9.8) 0.8271	5.0 (4.9) (-5.1,15.1) 0.3184	-4.6 (6.4) (-17.6, 8.4) 0.4753
drug-LEV (stderr) 95% CI p-value			1.7 (5.7) (-10.1,13.4) 0.7745	3.0 (5.9) (-9.2, 15.1) 0.6208	9.2 (5.3) (-1.9, 20.2) 0.0994	
High VSA[1]						
drug-PLB (stderr) 95% CI p-value	54.7 (5.6) (43.2,66.2) .0001	55.7 (5.3) (447, 66.6) .0001	41.9 (6.1) (29.5,54.3) .0001	48.7 (5.8) (36.9, 60.5) .0001	53.5 (6.0) (41.3, 65.7) .0001	43.6 (6.3) (30.8, 56.3) .0001
drug-A1.5 (stderr) 95% CI p-value			-12.3 (4.0) (-20.3,-4.2) 0.0037	-5.7 (3.7) (-13.1,1.7) 0.1266	-1.1 (3.6) (-8.4, 6.2) 0.761	-10.8 (4.4) (-19.6,-1.9) 0.0192
drug-A3 (stderr) 95% CI p-value			-13.3 (3.4) (-20.2,-6.3) 0.0005	-6.7 (2.8) (-12.4, -1.0) 0.0234	-2.1 (3.0) (-8.2, 4.1) 0.5015	-11.7 (3.7) (-19.4,-4.0) 0.0043
drug-LEV (stderr) 95% CI p-value			-1.1 (4.8) (-10.9, 8.7) 0.8222	5.5 (4.4) (-3.6, 14.6) 0.2288	10.0 (4.8) (0.2, 19.9) 0.0453	
ARCI PCAG[1]						
drug-PLB (stderr) 95% CI p-value	6.4 (0.8) (4.9, 8.0) .0001	7.6 (0.7) (6.1, 9.1) .0001	3.4 (0.7) (1.9, 4.9) .0001	4.2 (0.7) (2.8, 5.6) .0001	4.1 (0.7) (2.7, 5.6) .0001	3.9 (0.7) (2.4, 5.3) .0001
drug-A1.5 (stderr) 95% CI p-value			-3.1 (0.7) (-4.4, -1.7) .0001	-2.3 (0.7) (-3.6, -0.9) 0.0015	-2.4 (0.7) (-3.7, -1.0) 0.0011	-2.6 (0.6) (-3.9, -1.3) 0.0003
drug-A3 (stderr) 95% CI p-value			-4.1 (0.6) (-5.4, -2.9) .0001	-3.3 (0.6) (-4.6, -2.1) .0001	-3.4 (0.6) (-4.7, -2.1) .0001	-3.7 (0.6) (-4.9, -2.5) .0001
drug-LEV (stderr) 95% CI p-value			-0.4 (0.4) (-1.3, 0.4) 0.3059	0.3 (0.3) (-0.4, 1.1) 0.3296	0.3 (0.5) (-0.8, 1.3) 0.5799	

Note: PLB=placebo; A1.5= ALP 1.5 mg= alprazolam 1.5 mg; A3= ALP 3.0 mg= alprazolam 3.0 mg; LEV= LEV 4000 mg = levetiracetam, BRV= brivaracetam

Considerations that may limit the effect:

- The missing rate of subjects from the study was 18%. The sponsor did not replace the 8 non-completers, leading to an unbalanced Williams square design in estimation of mean differences.
- Although the difference between positive control and placebo was observed greater than 24 VAS points of drug-liking (at the moment) in this study, a margin should be pre-defined for subjects' qualification.
- The sponsor's analyses were based on per protocol set using apparently not a paired test. The primary analysis should be a paired test on completers population.
- The assay sensitivity showed significant difference from placebo at both doses 1.5 mg and 3.0 mg of alprazolam, although the mean difference at the lower dose is numerically larger than that at the high dose as observed for drug-liking (at the moment) VAS scores (but not for other primary endpoints).
- The null hypothesis should be: there is drug abuse potential and the alternative hypothesis should be: there is no drug abuse potential.

Recommendations:
Recommendations for the proposed label are included in the subsection 2.2.2.2.

1. INTRODUCTION

1.1 Overview

1.1.1 Background Information

On 11/24/2014, the Agency received the submission of NDA205836 from UCB Pharma (the sponsor). The study N01295 (Reference was made to INDs 70205 (b) (4) for the solid oral dosage (b) (4) of brivaracetam; to IND 103908 for the development of brivaracetam as an intravenous formulation; and to IND 110606 for the development of brivaracetam oral solution.) included in this NDA submission needed a statistical review for drug abuse potential as requested by CSS on 1/8/2015. This was a Phase I, randomized, double-blind, triple-dummy, placebo, unscheduled and scheduled comparators-controlled study to assess the drug abuse potential of brivaracetam (BRV). This submission seeks for the approval to market brivaracetam tablets (10mg, 25mg, 50mg, 75mg, and 100mg) as adjunctive therapy in the treatment of partial onset seizures in patients 16 years of age and older with epilepsy.

We did not locate the data for primary and secondary analyses (all PD data), so we sent an Information Request on 1/26/2015 to the Sponsor. We received the PD data and SAS codes as requested from the sponsor on 1/30/2015.

Brivaracetam (BRV) is a 2-pyrrolidinone derivative, interacting with a brain-specific binding site SV2A (Synaptic Vesicle protein 2A). The abuse potential of BRV had not yet been assessed in humans. This clinical study was performed to evaluate the abuse potential of BRV. Because BRV does not belong to any established pharmacologic class associated with abuse, and Alprazolam (ALP) has sedative and anticonvulsant properties and a pharmacokinetic profile similar to BRV, ALP was selected as the positive control. ALP is a Schedule IV benzodiazepine

with demonstrated abuse potential in laboratory and epidemiological studies. Levetiracetam has been used as an unscheduled drug in the assessment of the addiction potential of BRV.

In addition, LEV produced positive signals on a number of measures of abuse potential, but differed from BRV on some of the primary measures. Therefore, because LEV is in the same pharmacologic class as BRV and has a similar mechanism of action and adverse event profile, but is not subject to abuse, it was included as an unscheduled comparator to determine the clinical relevance of the results obtained with BRV.

1.1.2 Specific Studies Reviewed

The study N01295 is reviewed. The design properties are summarized in Table 2. Throughout this review, BRV is referred to brivaracetam (testing drug), ALP to Alprazolam (positive control), and LEV to Levetiracetam (negative control).

Table 2. List of Studies Included in this Review

Study ID (Period)	Location	Design	Primary Endpoints	Treatments	Number of Subjects
N01295 (11/17/2008 – 3/3/2009)	1 site in Toronto, Canada	R, DB, AC, PC, MD, seven-arms crossover to evaluate the abuse potential of single dose intact oral BRV	VAS Emax for Drug Liking, Overall Drug Liking, High, and ARCI PCAG scale	ALP 1.5 mg ALP 3.0 mg BRV 50 mg BRV 200 mg BRV 1000 mg LEV 4000 mg Placebo	44 randomized and 36 subjects completed all treatment periods

Abbreviations: DB = double blind; PC = placebo-controlled; AC = active-controlled; R = randomized; MD=multi-dose; ARCI PCAG scale= Addiction Research
Center Inventory (ARCI) Pentobarbital Chlorpromazine Alcohol Group (PCAG) scale

1.2 Data Sources

The sponsor submitted this NDA including the study data to the FDA CDER Electronic Document Room (EDR). The submission is recorded in the EDR with the link shown below. The data were submitted in SAS Xport transport format.

Application:	NDA205836
Company	UCB Pharma
Drug	Briviact (brivaracetam)
CDER EDR link	\\Cdsesub1\evsprod\NDA205836\0000
Letter date	November 20, 2014

2. STATISTICAL EVALUATION

2.1 Data and Analysis Quality

Relevant issues about the quality and integrity of the submitted data include:

We did not locate the data for primary and secondary analyses (all PD data), so we sent an Information Request on 1/26/2015 to the Sponsor. We received the PD data and SAS codes as requested from the sponsor on 1/30/2015. In the 1/30/2015 submission, the data and analysis quality are acceptable.

2.2 Human Abuse Potential Study

2.2.1 Overview

2.2.1.1 Objectives of the Study

The primary objective of this study was to assess the abuse potential of single oral doses of brivaracetam (BRV) compared to alprazolam (ALP) and placebo. The secondary objectives of this study were to assess the abuse potential of single oral doses of BRV compared to levetiracetam (LEV), to investigate the pharmacokinetics of BRV, and to further evaluate the safety and tolerability of BRV.

2.2.1.2 Study Design and Endpoints

This HAP Study N01295 was entitled: "A mono-center, randomized, double-blind, triple dummy placebo, unscheduled and scheduled comparators controlled, single-dose crossover trial to evaluate the abuse potential of brivaracetam in subjects with a history of recreational CNS depressant use."

The study was conducted in Canada and consisted of an initial prestudy Qualification Phase (QP) and a main Treatment Phase. Each subject completed a Screening Visit within 3 weeks (21 days) prior to the QP. During the 4-day, in-house QP, subjects received placebo and 2 mg ALP (positive control) in a randomized, double-blind crossover design. Only subjects who could distinguish between placebo and 2 mg ALP were qualified for the Treatment Phase.

The Treatment Phase commenced within 14 days of the QP and lasted up to 9 weeks for each subject. Randomization of the treatment sequences for the Treatment Phase was performed according to a Williams design. The Williams square was design with two 7 × 7 Latin squares for randomization (ie, 14 different treatment sequences and 7 Treatment Periods). During the Treatment Phase, subjects received single doses of each treatment:

Treatment A (1): placebo

Treatment B (2): 50mg BRV

Treatment C (3): 200mg BRV

Treatment D (4): 1000mg BRV

Treatment E (5): 1.5mg ALP (positive control)

Treatment F (6): 3mg ALP (positive control)

Treatment G (7): 4000mg LEV (negative control)

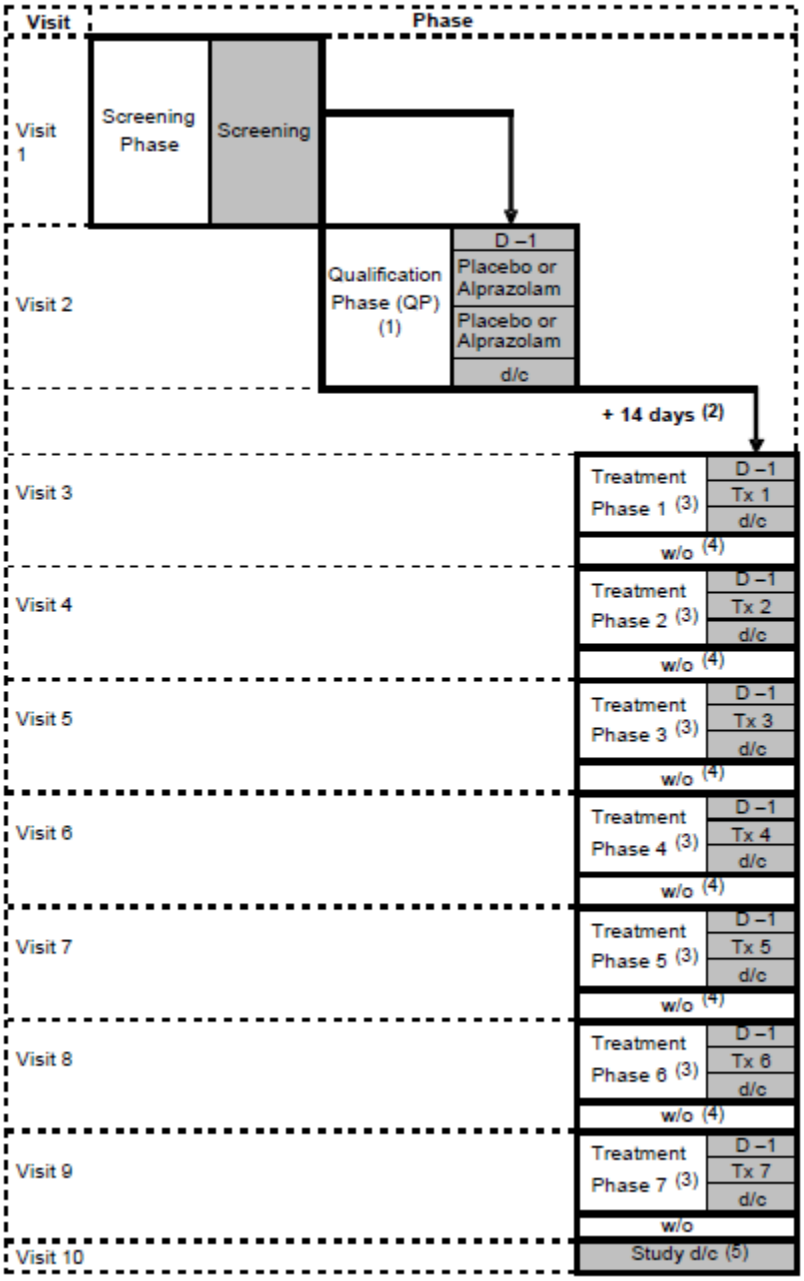
These treatments were administered orally in a randomized, double-blind, triple-dummy manner (1 per Treatment Period for a total of 7 periods). A Wash-Out Period of approximately 7 to 10 days separated each treatment administration. Each Treatment Period included a 42- to 44-hour confinement period. Subjects reported to the clinical site 1 day before dosing at each Treatment Period and were discharged from the clinic approximately 24 hours after administration of study drug.

The study ended with a Discharge Visit examination approximately 7 days after the last administration of study medication. The total duration of the study for each subject was approximately 15 weeks.

A total of 44 subjects (100.0%) were randomized to the Treatment Phase, took at least 1 dose of study medication and were included in the intent-to-treat (ITT) and perprotocol populations. Fifteen subjects who had protocol deviations affecting the pharmacodynamic variables were partially excluded from the per-protocol population (only the missing or affected period(s) were excluded from the analysis).

The sponsor's design diagram is shown in Figure 1.

Figure 1. Study Schematic



Source: sponsor's n01295-csr.pdf Section 3.7Schematic diagram.

2.2.1.3 Abuse Potential Measures

The pharmacodynamics endpoints for this study were shown in Table 3:

Table 3. Overview of the pharmacodynamics endpoints

Variable[c]	E_{max}	E_{min}	AUE[e]	Mean	te_{max}
Primary Variables					
Drug Liking VAS[d]	x[a]	x[b]	x		X
Overall Drug Liking VAS[d]	x[a]	x[b]		x	
Subjective Effects VAS: High	x		x		x
ARCI PCAG scale	x		x		x
Secondary variables					
Take Drug Again VAS	x			x	
ARCI: MBG Scale	x		x		x
ARCI: LSD Scale	x		x		x
Subjective Effects VAS: Any Drug Effects	x		x		x
Subjective Effects VAS: Good Drug Effects	x		x		x
Subjective Effects VAS: Bad Drug Effects	x		x		x
Take Drug Again VAS	x		x		x
Other variables					
ARCI: Amphetamine Scale	x		x		x
ARCI: BG Scale	x	x	x		x
Subjective Effects VAS: Dizziness	x		x		x

ARCI=Addiction Research Centre Inventory; AUE=area under the time effect curve; BG=Benzedrine Group; Emax=maximum effect; Emin=minimum effect; LSD=Lysergic Acid Diethylamide; MBG=Morphine Benzedrine Group; PCAG=Pentobarbital Chlorpromazine Alcohol Group; temax=time to maximum effect; VAS=visual analog scale
a. Provided information on maximum liking.
b. Provided information on maximum disliking.
c. Detailed information about the scale description, interpretation, and question texts are described in the protocol.
d. Bipolar scale ranging from 0 (= strong disliking) to 100 (= strong liking).
e. AUE(0-12) and AUE(0-24) were calculated.
Source: sponsor's n01295-csr.pdf Section 3.7 Schematic diagram.

2.2.1.4 Analysis Population and Sample Size

The sponsor defined the following analysis population:

The intent-to-treat (ITT) population consisted of all randomized subjects who took at least 1 dose of study medication during the Treatment Phase of the study.

The per-protocol population was defined as a subset of the ITT population, consisting of subjects who had no major protocol deviations affecting the primary pharmacodynamics variables, as confirmed during the study's pre-analysis review prior to database lock.

Subjects who had protocol deviations affecting the pharmacodynamic variables during a particular period or who did not have evaluable data for a period were partially excluded from

the per-protocol population (only the missing or affected period(s) were deleted from the evaluable analysis).

Dropout subjects who did not complete a particular Treatment Period were partially excluded from the per-protocol population for the period(s) they did not complete.

Determination of Sample Size

In order to allow for a balanced design, 3 subjects were allocated to each of the 14 treatment sequences (i.e., n=42), with the intent to have at least 35 completers (at least 1 subject per sequence). In the event of dropouts, subjects were replaced after consultation with the clinical study statistician at UCB.

A sample size of 35 subjects would have greater than 80% power to detect a significant difference between placebo and each dose of ALP on the Drug Liking VAS, assuming that the standard deviation was approximately 2.05 times larger than the difference in means (estimated from the sponsor's study SP903 from a 100-point VAS scale, assuming a minimally clinically relevant change of 10-units and a standard deviation of the within subject treatment difference of 20.5), using a paired t-test with a 0.05 two-sided significance level. The Drug Liking VAS was expected to show the lowest effect size compared to the other parameters assessed for the validity of the study. Therefore, it could be assumed that the validity test (3 out of 6 variables have to show an effect for ALP against placebo) has also at least 80% power. In order to take into account a dropout rate (estimated from the study SP903), 7 additional subjects were enrolled.

2.2.1.5 Statistical Methodologies used in the Sponsor's Analyses

Hypothesis testing:

For each of the parameters, the null hypothesis was: there is no treatment effect, and the alternative hypothesis was: there is a treatment effect.

For each of the contrasts or pairwise comparisons, the null hypothesis was: there is no treatment effect difference between the tested pair, and the alternative hypothesis was: there is a treatment effect difference between the tested pair. A 5% Type I error rate with a P value less than 0.05 was considered as statistically significant for all individual hypothesis tests. All statistical tests were performed using two-tailed significance criteria.

E_{max} values of the primary, secondary, and supportive variables were analyzed using a standard mixed-effect model for a crossover study. The model included sequence, treatment, and period as fixed effects, Baseline as a covariate, where applicable, and subject nested within sequence as a random effect. Variance was modeled as a function of treatment group, allowing heteroscedasticity. For each comparison, the 2-sided 95% confidence intervals (CIs) and p-values for the differences of the mean responses were calculated. The primary analysis included an analysis of study sensitivity, abuse liability, and study specificity.

The following criteria were tested in an ascending order to assess the drug abuse potential of

BRV:

• Study sensitivity

- Validation of the study: ALP has statistically larger mean response than placebo on the following scales:
  - Drug Liking VAS
  - Overall Drug Liking VAS
  - ARCI MBG
  - ARCI PCAG
  - Subjective Effects VAS: Good Drug Effects
  - Subjective Effects VAS: High

Placebo was first compared to the higher dose of ALP (3mg). If the 95% CIs of differences of the Emax and placebo did not include zero, then a contrast was to be performed between placebo and the smaller dose of ALP (1.5mg). The sponsor proposed that the study was considered valid if on at least 3 of 6 endpoints the 95% CIs of differences of the Emax of either dose of ALP and placebo did not include zero, and a non-descending dose response was observed (comment of this reviewer: should be for all of the six endpoints).

• Abuse liability analyses
- Comparison of ALP and BRV: All doses of BRV have statistically lower mean response than each dose of ALP (from ALP 3 mg to ALP 1.5 mg).
- Comparison of BRV and placebo: All doses of BRV show no higher abuse potential than placebo. This is demonstrated by comparing each mean response with BRV to twice the response of placebo.

• Study Specificity
- Comparison of LEV and placebo: If possible abuse potential has not been completely ruled out by the previous analyses; the specificity of the study is assessed by comparing placebo to an unscheduled comparator (LEV). This comparison helps confirm appropriate specificity in the study and provides additional comparative information for interpretation of signal intensity.

The secondary analysis included comparisons of LEV and BRV, as well as analysis of the secondary and supportive variables.

Although measures were separated into primary, secondary, and supportive variables, conclusions regarding the abuse potential of BRV considered the whole profile of subjective effects across all of the primary, secondary, and supportive measures and not responses on individual scales.

For all pharmacodynamic variables, except ARCI PCAG and VAS, which may not be normally distributed, non-parametric analyses were performed. A permutation test was used to estimate the contrasts of interest. Only pairwise comparisons were computed. The permutation test was chosen over the Wilcoxon test for its ability to retain the ties in its analysis.

ADJUSTMENT FOR TYPE I ERROR:
The adjusted p-values are not applicable here.

2.2.1.6 Changes in the Conduct of the Study

Two amendments were made to the protocol prior to the start of the study (ie, before any subjects were consented or enrolled).

The following changes were made to the study design in Amendment 1 (dated 9/29/2008):

• The original "double-blind" study design was modified to a "triple-dummy" design. (b) (4) [redacted] Therefore, a triple-dummy design (ie, separate placebos for BRV, LEV and ALP) was implemented to maintain the blind.

• A secondary objective was added. The negative control, LEV, was included as an unscheduled comparator to assess the abuse potential of BRV compared to that of LEV.

A second amendment was made to the protocol (Amendment 2, dated 11/7/2008), in order to incorporate changes requested by Health Canada.

2.2.1.7 Sponsor's Summary and Conclusions

The sponsor's results of the primary and key secondary analyses are shown in Appendix 1. The following summary and conclusions from the sponsor were from the sponsor's Synopsis:

- All 44 subjects who were randomized to the Treatment Phase were included in the ITT and per-protocol populations. Subjects with protocol deviations affecting the pharmacodynamic or pharmacokinetic variables were partially excluded from these analyses. Thirty-six subjects completed the study, and 8 subjects discontinued early.
- The study was considered valid because on all 6 designated endpoints, both doses of ALP had statistically larger mean response than placebo. An ascending dose response was observed, other than for Drug Liking VAS, which was slightly lower for 3mg ALP compared to 1.5mg ALP. In addition, both doses of ALP showed significantly greater effects compared to placebo on all primary and secondary variables, including measures of:

  - Balance of Effects: Drug Liking, Overall Drug Liking, and Take Drug Again VASs
  - Positive/Euphoria Effects: High and Good Drug Effects VASs and ARCI MBG
  - Sedative Effects: ARCI PCAG and ARCI BG Emin
  - Other Subjective Effects: Any Drug Effects and Dizziness VASs

  Alprazolam also showed significant negative effects (Bad Drug Effects and ARCI LSD) and modest stimulant-like effects (ARCI Amphetamine and ARCI BG E_{max}), particularly at the 3mg dose.
- Brivaracetam showed differences from ALP on some positive effects measures; most notably it was associated with less euphoria at all doses (ARCI MBG). On Good Drug Effects and High VASs, 50mg BRV had significantly lower effects compared to both ALP doses, while 200mg BRV was different from 3mg but not 1.5mg ALP (High VAS). The 50mg dose of BRV also showed significantly less Drug Liking than ALP. In addition, all BRV doses showed significantly fewer sedative effects compared to ALP and fewer stimulant-like effects, in particular compared to the 3mg dose. On measures of balance effects, BRV was not significantly different from ALP; however, 1000mg BRV showed a small but statistically

greater effect on some balance measures compared to ALP. Any Drug Effects were lower for 50mg BRV but not differentbetween 200mg and 1000mg BRV compared to ALP.

- All doses of BRV showed significantly greater effects compared to placebo on all primary and secondary variables, including measures of balance of effects, positive/euphoria effects, sedative effects, and other subjective effects. Negative and very mild stimulant-like effects (on ARCI Amphetamine but not ARCI BG E_{max} other than the 200mg dose) were also observed compared to placebo.

2.2.2 Reviewer's Assessment

2.2.2.1 REVIEWER's ANALYSES

In reviewing this NDA, this reviewer noted the sponsor reported that

> *"A total of 44 subjects (100.0%) were randomized to the Treatment Phase, took at least 1 dose of study medication and were included in the intent-to-treat (ITT) and perprotocol populations. Fifteen subjects who had protocol deviations affecting the pharmacodynamic variables were partially excluded from the per-protocol population (only the missing or affected period(s) were excluded from the analysis)."*

This reviewer checked that for every PD measurement, the number of subjects is different between ITT and PP set for each treatment, but the total number for all treatments between ITT and PP set is the same, n=44 as shown in Appendix 2.

Also in Appendix 2 this reviewer also list a descriptive comparison about the subject disposition in PP and completers for treatment balance by sequence and periods. There are a total of 35 period-differences in 8 sequences between the PP and completers sets.

This reviewer verified the sponsor's primary and some secondary analyses.

This reviewer noted that the sponsor's primary analyses were neither on completers population nor appeared being a paired test (based on the sponsor's SAS codes submitted on 1/30/2015 in response to our Information Request). Therefore, this reviewer performed analyses using the paired-data of the completers under the sponsor's analysis model. This reviewer's analyses are shown in Appendix 2.

This reviewer provided a descriptive summary of the PD measures for drug abuse in Appendix 2.

2.2.2.2 SUMMARY AND CONCLUSIONS

Statistical Issues

- The missing rate of subjects from the study was 18%. The sponsor did not replace the 8 non-completers, leading to an unbalanced Williams square design in estimation of mean differences.
- Although the difference between positive control and placebo was observed greater than 24 VAS points for drug-liking (at the moment) in this study, a margin should be pre-defined for subjects' qualification.
- The sponsor's analyses were based on per protocol set using apparently not a paired test. The primary analysis should be a paired test on completers population.

- The assay sensitivity showed significant difference from placebo at both doses 1.5 mg and 3.0 mg of alprazolam, although the mean difference at the lower dose is numerically larger than that at the high dose as observed for drug-liking (at the moment) VAS scores (but not for other primary endpoints).
- The null hypothesis should be: there is drug abuse potential and the alternative hypothesis should be: there is no drug abuse potential.

Conclusions and Recommendations

The assay sensitivity showed significant difference from placebo at both doses 1.5 mg and 3.0 mg of alprazolam, although the mean difference at the lower dose is numerically larger than that at the higher dose as observed for drug-liking (at the moment) VAS scores (but not for other primary endpoints).

Based on the data of study N01295, significant difference of BRIVARACETAM at all testing doses (50, 200, and 1000 mg) from placebo are observed as that of the positive control alprazolam (1.5 and 3.0 mg) for the primary endpoints.

The significant difference of BRV at all testing doses (50, 200, and 1000 mg) from placebo are the range of 19-30 VAS points of drug-liking (at the moment). The minimum of these differences is greater than 11 points which was a suggested threshold between a testing drug and placebo in a drug-abuse study by Chen and Bonson (J Biopharm Stat 23:2, 294-306, 2013). The results suggest the drug-abuse potential of BRV.

Moreover, there are no significant differences of BRV at all testing doses (50, 200, and 1000 mg) from the positive control ALP (1.5 and 3.0 mg) in drug-liking (at the moment) VAS. These results are supportive to the abuse property of BRV (50-1000 mg).

Positive dose responses are generally observed in the testing drug BRV 50-1000 mg and the positive control ALP 1.5-3.0 mg. Positive dose responses are also observed in differences of the testing drug BRV 50-1000 mg from placebo, the positive control ALP (1.5-3.0 mg), and LEV 4000 mg, respectively, in most primary and some key secondary endpoints.

The onsets of liking effect of these drugs were various from 1-4 hours for drug-liking (at the moment) and High, and up to ~7 for ARCI PCAG.

Both brivaracetam and levetiracetam at 4000 mg were similar based on the measures in this review, although levetiracetam is currently an unscheduled antiepileptic drug and is not labeled as a drug with abuse potential.

These results of this reviewer's analysis are supportive to BRV's abuse potential, consisting with the findings by the sponsor.

Labeling Recommendations

The statistical review addresses statements in the label (section 9: DRUG ABUSE AND DEPENDENCE) concerning:

1. In Label 9.2, it is said that:

(b) (4)

This is suggested to revise as:

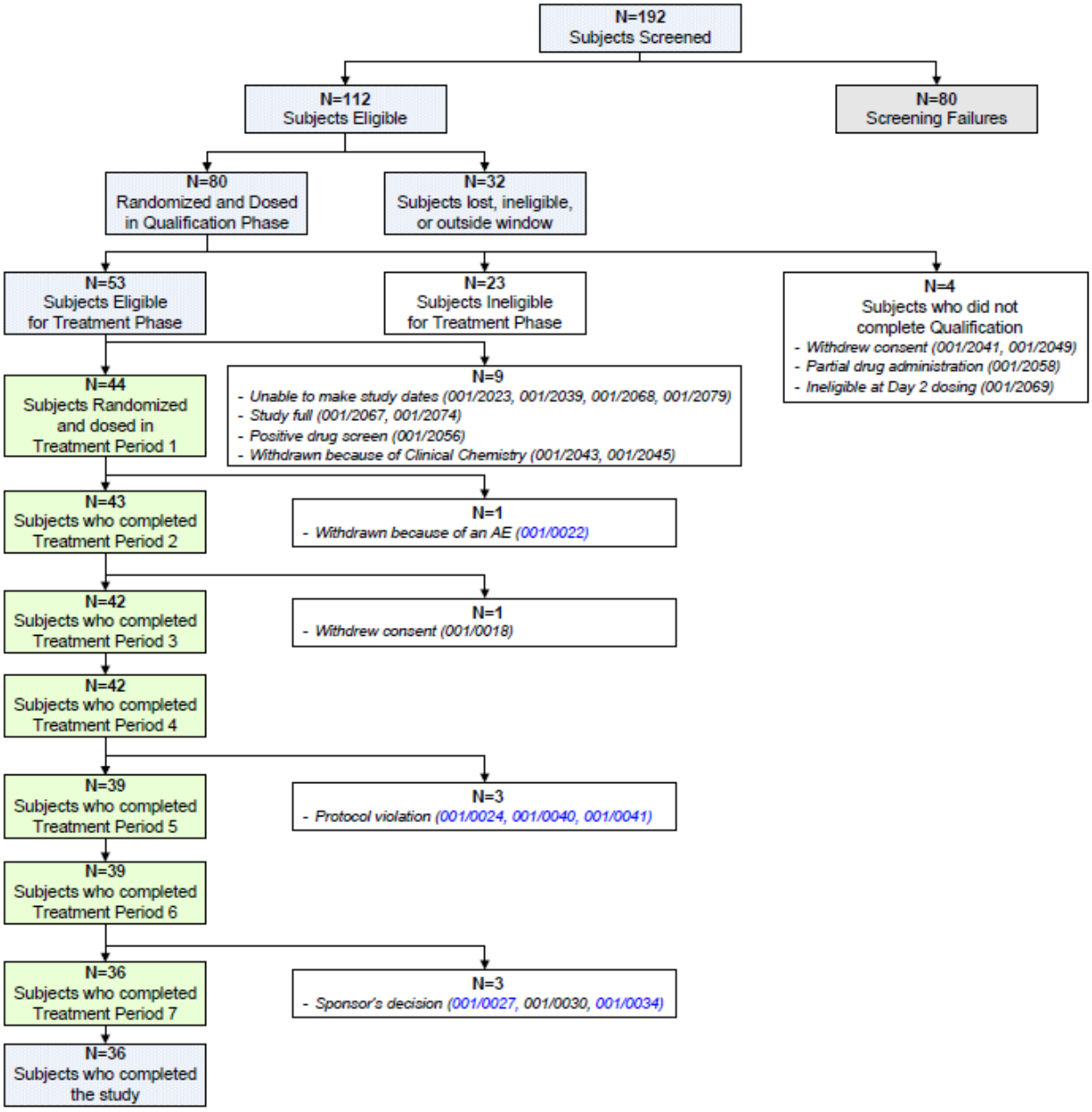
(b) (4)

3 Appendix

Appendix1: The sponsor's Results

Patient Disposition, Demographic and Baseline Characteristics

Figure 2. Flowchart of subject disposition



Source: sponsor's n01295-csr.pdf Figure 7:1.

Of the 76 subjects who completed the QP, 44 qualified for and were randomized to the Treatment Phase (ITT Population). Thirty-six subjects (36/44=81.8%) completed the study and 8 subjects (8/44=18.2%) discontinued.

In addition, one subject (Subject 001/0015) dropped 1 white tablet during Treatment Period 6 (3mg ALP). Although the white tablet was likely placebo for LEV (as the subject received 3mg ALP during that period; orange capsules), the subject was partially excluded from the per-protocol population (as exclusion was performed on blinded data). At the same period, the subject had also missed the pharmacodynamic assessment at 1 hour postdose. Seven subjects had deviations related to the pharmacodynamic assessments that resulted in partial exclusion from the per-protocol population. These were primarily related to missed or incomplete assessments:

- Subject 001/0001: The 23-hour postdose assessment was performed > 2 hours early due to an incorrect computer timestamp and therefore the exact time of the assessment was unknown. However, this occurred at Visit 2 (Day 3 of QP).
- Subject 001/0005: At Visit 4 (Treatment Period 2, Day 1; placebo), the 0.5 hour postdose assessment was not completed in its entirety (ARCI), and the 1-hour postdose assessment was not performed.
- Subject 001/0012: At Visit 3 (Treatment Period 1, Day 1; 3mg ALP) the 1-hour and 2-hour postdose assessments were not performed, and the ARCI assessment at 0.5 hours postdose was not completed in its entirety.
- Subject 001/0019: The Visit 6 (Treatment Period 4, Day 1; 3mg ALP) ARCI assessment at 1 hour postdose was not performed, and the VASs were only partially completed (due to the occurrence of an adverse event).
- Subject 001/0025: At Visit 8 (Treatment Period 6, Day 1; 3mg ALP), the 2-hour assessment was not performed.
- Subject 001/0031: The Visit 6 (Treatment Period 4, Day 1; 1.5mg ALP) 0.5 hour postdose assessment was incomplete and the Visit 8 (Treatment Period 6, Day 1; 3mg ALP) 1 hour postdose assessment was not performed.
- Subject 001/0042: At Visit 2 (QP Day 2) the 0.5 hour postdose ARCI assessment was only partially completed. In addition, the subject did not complete the 1 hour postdose assessment at Visit 6 (Treatment Period 4, Day 1; 1.5mg ALP). Finally, the subject also had a pharmacokinetic deviation; the 1 hour postdose sample was not drawn at Visit 9 (Treatment Period 7, Day 1; 200mg BRV) due to difficulty with the phlebotomy procedure and the subject was partially excluded from the pharmacokinetic population.

Table 4. Demographic data – ITT population (N=44)

Characteristic	Overall ITT Population (N=44)
Gender, n (%)	
Female	10 (22.7)
Male	34 (77.3)
Race, n (%)	
White	29 (65.9)
Black or African American	12 (27.3)
Asian	3 (6.8)
Age (years), mean (SD)	35.4 (9.35)
Weight (kg), mean (SD)	76.1 (11.88)
Height (cm), mean (SD)	172.7 (9.01)
BMI (kg/m^2), mean (SD)	25.4 (2.46)
BSA (m^2), mean (SD)	1.9 (0.19)

BMI=Body Mass Index; BSA=Body Surface Area; ITT=intent-to-treat; SD=standard deviation
Source: sponsor's n01295-csr.pdf Table 7:1.

Most subjects were cannabis users, although 16 subjects used other CNS depressants. The other CNS depressants used were primarily benzodiazepines (ALP, diazepam, lorazepam, femazapam, and clonazepam); however, a few subjects had previously used gammahydroxybutyrate or Quaalude.

Table 5. Sensitivity summary of ANOVA/ANCOVA results for alprazolam versus placebo (Emax) – Per Protocol population)

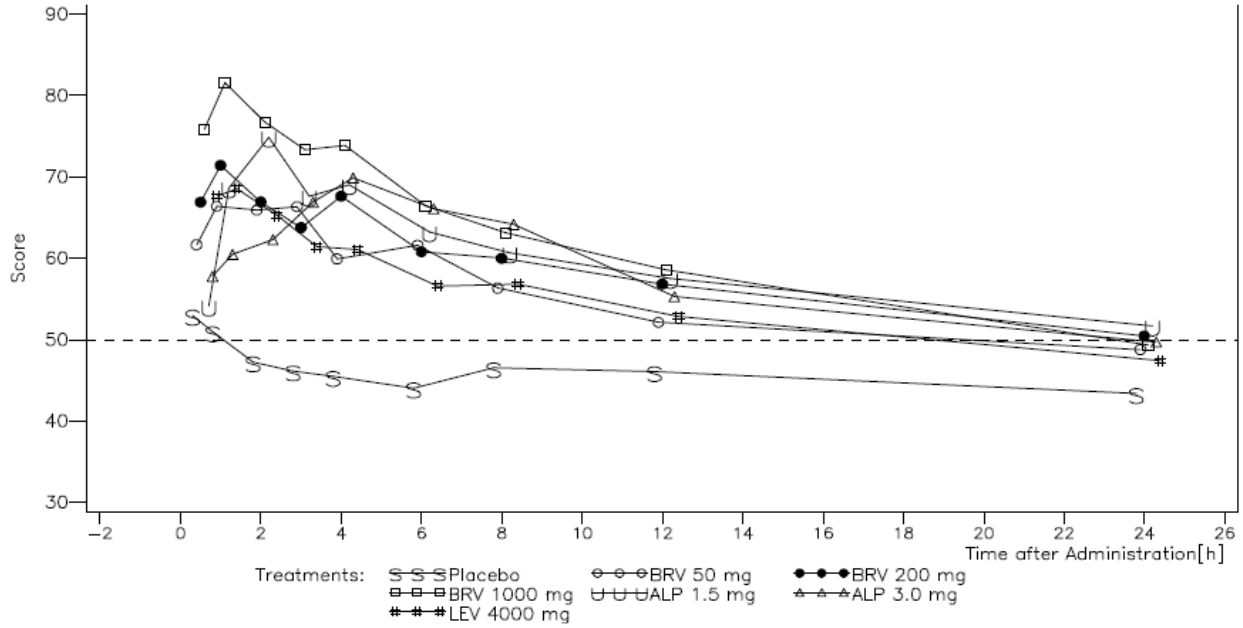
Pharmacodynamic variable	Estimate of difference [95% CI]	
	Alprazolam 1.5mg – placebo	Alprazolam 3mg – placebo
Balance effects		
Drug Liking VAS (primary)	30.31 (21.9, 38.7)	26.90 (18.4, 35.4)
Overall Drug Liking VAS (primary)	22.57 (12.8, 32.3)	24.78 (14.2, 35.3)
Positive effects		
ARCI MBG (secondary)	4.52 (3.1, 6.0)	6.19 (4.7, 7.7)
High VAS (primary)	56.68 (45.4, 68.0)	57.74 (47.1, 68.4)
Good Drug Effects VAS (secondary)	41.46 (30.6, 52.3)	44.18 (33.5, 54.9)
Sedative effects		
ARCI PCAG (primary)	6.25 (5.1, 7.4)	7.39 (6.3, 8.5)

Source: sponsor's ins-13-017.pdf Table 8:1.

Primary variables

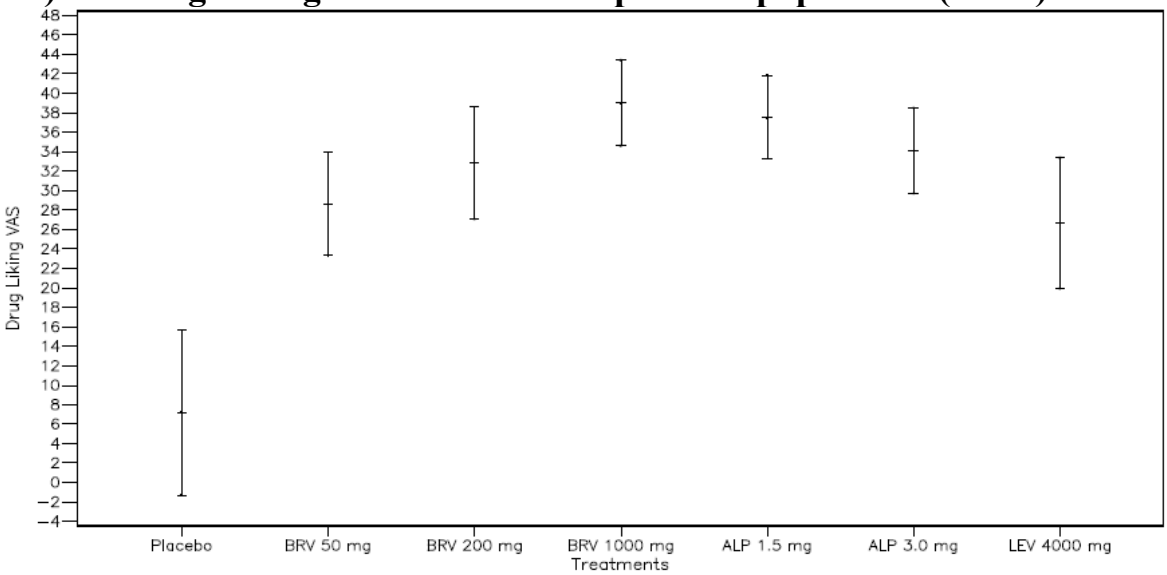
Drug Liking VAS (Balance of Effects)

Figure 3. Mean Drug Liking VAS scores over time by treatment – Per-protocol population (N=44)



ALP=alprazolam; BRV=brivaracetam; LEV=levetiracetam; VAS=visual analog scale
Drug Liking VAS: At this moment, my liking for the drug is (0=Strong Disliking, 100=Strong Liking).
Source: sponsor's n01295-csr.pdf Figure 8:1.

Figure 4. Least squares means of treatments effects from ANOVA (95% CI) for Drug Liking VAS Emax – Per-protocol population (N=44)



ALP=alprazolam; ANOVA=analysis of variance; BRV=brivaracetam; CI=confidence interval; Emax=maximum effect; LEV=levetiracetam; VAS=visual analog scale

Drug Liking VAS: At this moment, my liking for the drug is (0=Strong Disliking, 100=Strong Liking).

Least squares means are expressed as differences from the neutral value (50) of the scale. Actual values can be obtained by adding 50 to the least squares mean values.

Source: sponsor's n01295-csr.pdf Figure 8:2.

Table 6. Summary of ANOVA results for Drug Liking VAS Emax – Per-protocol population (N=44)

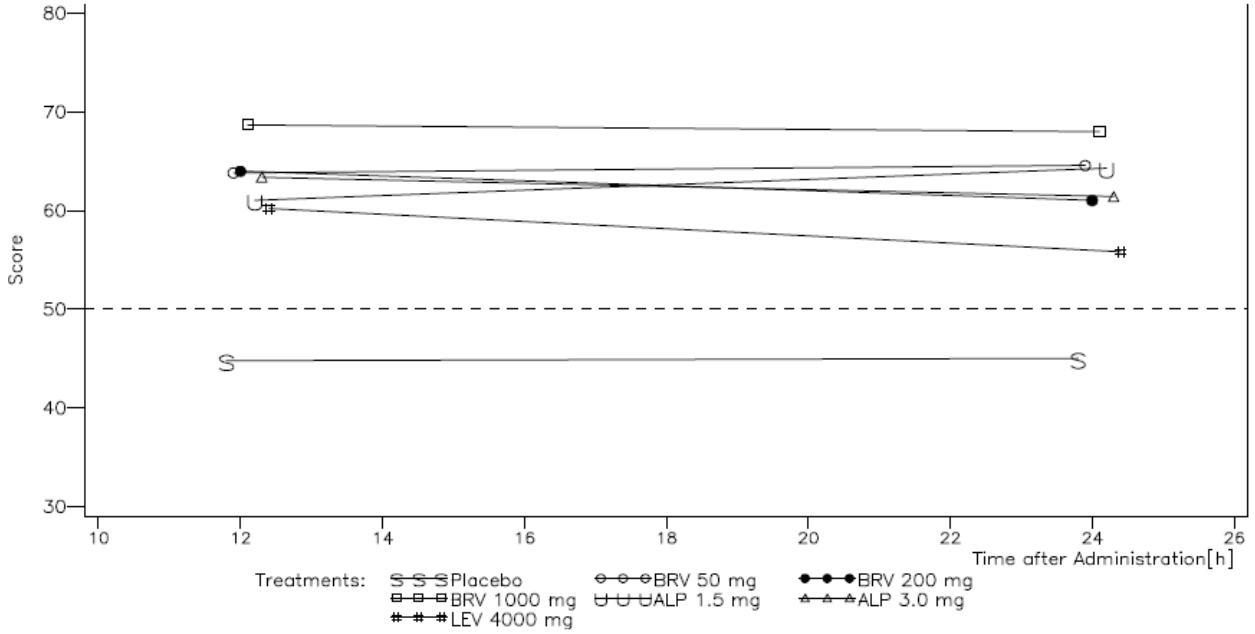
Pairwise comparison	Estimate of difference	95% CI of difference	P-value
Placebo versus alprazolam			
Alprazolam 1.5mg – placebo	30.3	21.9, 38.7	0.000
Alprazolam 3mg – placebo	26.9	18.4, 35.4	0.000
Brivaracetam versus alprazolam			
Brivaracetam 50mg – alprazolam 1.5mg	-8.9	-14.1, -3.6	0.001
Brivaracetam 200mg – alprazolam 1.5mg	-4.7	-10.3, 1.0	0.108
Brivaracetam 1000mg – alprazolam 1.5mg	1.5	-2.7, 5.7	0.485
Brivaracetam 50mg – alprazolam 3mg	-5.5	-10.8, -0.1	0.045
Brivaracetam 200mg – alprazolam 3mg	-1.2	-7.0, 4.6	0.675
Brivaracetam 1000mg – alprazolam 3mg	4.9	0.5, 9.3	0.028
Brivaracetam versus placebo			
Brivaracetam 50mg – placebo	21.4	12.4, 30.4	0.000
Brivaracetam 200mg – placebo	25.7	16.4, 34.9	0.000
Brivaracetam 1000mg – placebo	31.8	23.3, 40.3	0.000
Brivaracetam versus levetiracetam			
Brivaracetam 50mg – levetiracetam 4000mg	2.0	-5.4, 9.3	0.600
Brivaracetam 200mg – levetiracetam 4000mg	6.2	-1.5, 13.9	0.115
Brivaracetam 1000mg – levetiracetam 4000mg	12.4	5.6, 19.1	0.000
Levetiracetam versus placebo and alprazolam			
Levetiracetam 4000mg – placebo	19.5	9.6, 29.4	0.000
Levetiracetam 4000mg – alprazolam 1.5mg	-10.8	-17.5, -4.2	0.002
Levetiracetam 4000mg – alprazolam 3mg	-7.4	-14.2, -0.7	0.031

Source: sponsor's n01295-csr.pdf Table 8:3.
Emax=maximum effect; SD=standard deviation; VAS=visual analog scale.

Overall Drug Liking VAS (Balance of Effects)

The mean overall drug-liking VAS scores at 12 and 24 hours.

Figure 5. Mean Overall Drug Liking VAS scores at 12 and 24 hours by treatment – Per-protocol population (N=44)



Source: sponsor's n01295-csr.pdf Figure 8:3.

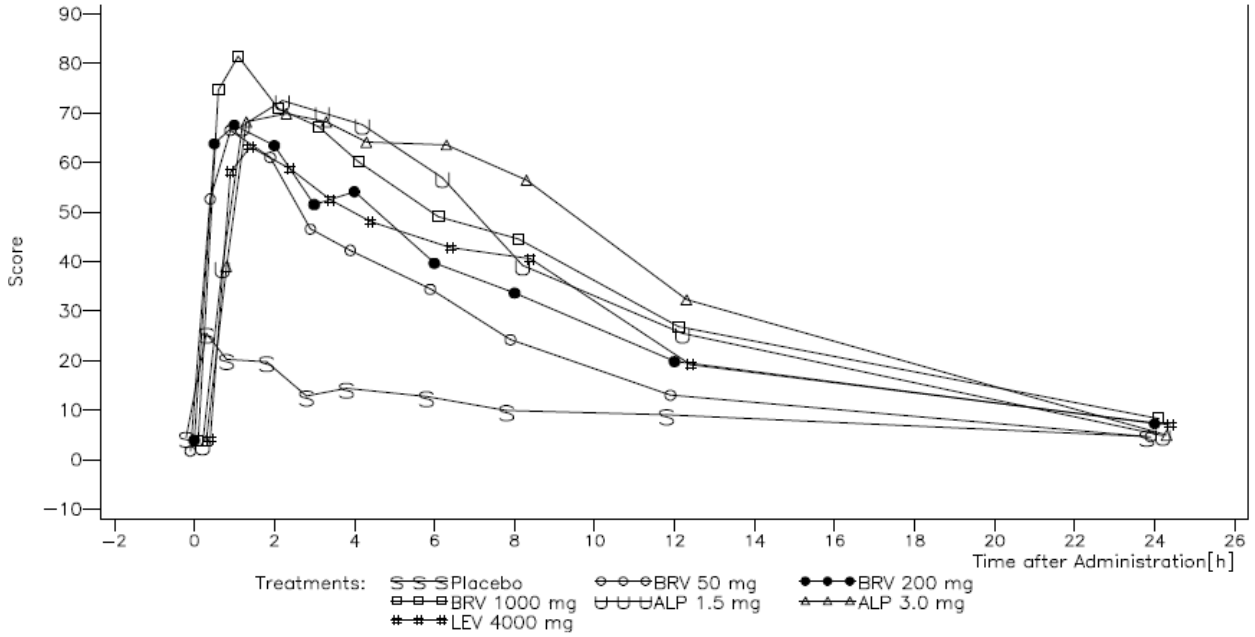
Table 7. Summary of ANOVA results for Overall Drug Liking VAS Emax – Per-protocol population (N=44)

Pairwise comparison	Estimate of difference	95% CI of difference	P-value
Placebo versus alprazolam			
Alprazolam 1.5mg – placebo	22.6	12.8, 32.3	0.000
Alprazolam 3mg – placebo	24.8	14.2, 35.3	0.000
Brivaracetam versus alprazolam			
Brivaracetam 50mg – alprazolam 1.5mg	-2.0	-9.2, 5.3	0.597
Brivaracetam 200mg – alprazolam 1.5mg	-1.1	-8.8, 6.6	0.781
Brivaracetam 1000mg – alprazolam 1.5mg	7.1	0.1, 14.2	0.048
Brivaracetam 50mg – alprazolam 3mg	-4.2	-12.5, 4.2	0.327
Brivaracetam 200mg – alprazolam 3mg	-3.3	-12.1, 5.5	0.459
Brivaracetam 1000mg – alprazolam 3mg	4.9	-3.3, 13.1	0.238
Brivaracetam versus placebo			
Brivaracetam 50mg – placebo	20.6	10.6, 30.6	0.000
Brivaracetam 200mg – placebo	21.5	11.1, 31.9	0.000
Brivaracetam 1000mg – placebo	29.7	19.8, 39.6	0.000
Brivaracetam versus levetiracetam			
Brivaracetam 50mg – levetiracetam 4000mg	2.6	-6.2, 11.5	0.559
Brivaracetam 200mg – levetiracetam 4000mg	3.5	-5.8, 12.8	0.459
Brivaracetam 1000mg – levetiracetam 4000mg	11.7	3.0, 20.5	0.009
Levetiracetam versus placebo and alprazolam			
Levetiracetam 4000mg – placebo	18.0	7.0, 28.9	0.001
Levetiracetam 4000mg – alprazolam 1.5mg	-4.6	-13.1, 3.9	0.288
Levetiracetam 4000mg – alprazolam 3mg	-6.8	-16.2, 2.6	0.156

Source: sponsor's n01295-csr.pdf Table 8:5.

Subjective Effects VAS: High (Positive Effects)

Figure 6. Mean High VAS scores over time by treatment – Per-protocol population (N=44)



Source: sponsor's n01295-csr.pdf Figure 8:5.

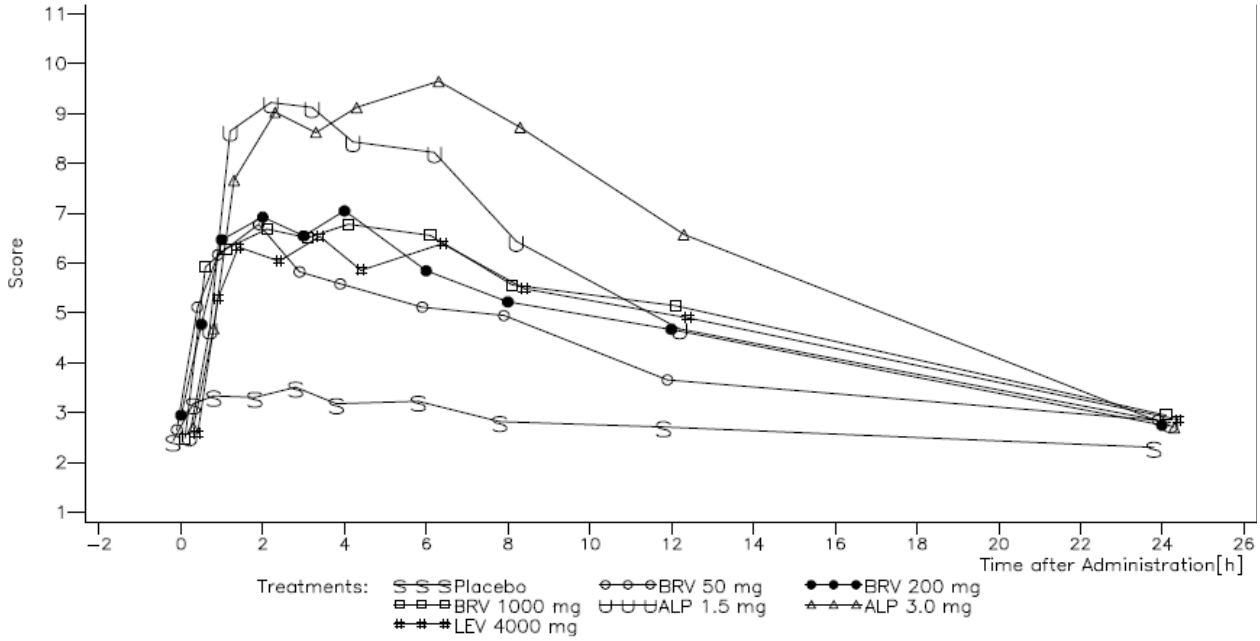
Table 8. Summary of ANCOVA results for High VAS Emax – Per-protocol population (N=44)

Pairwise comparison	Estimate of difference	95% CI of difference	P-value
Placebo versus alprazolam			
Alprazolam 1.5mg – placebo	56.7	45.4, 68.0	0.000
Alprazolam 3mg – placebo	57.7	47.1, 68.4	0.000
Brivaracetam versus alprazolam			
Brivaracetam 50mg – alprazolam 1.5mg	-12.0	-19.0, -4.9	0.001
Brivaracetam 200mg – alprazolam 1.5mg	-6.2	-12.7, 0.2	0.059
Brivaracetam 1000mg – alprazolam 1.5mg	1.0	-5.8, 7.8	0.765
Brivaracetam 50mg – alprazolam 3mg	-13.0	-19.1, -7.0	0.000
Brivaracetam 200mg – alprazolam 3mg	-7.3	-12.6, -2.0	0.008
Brivaracetam 1000mg – alprazolam 3mg	-0.03	-5.7, 5.7	0.993
Brivaracetam versus placebo			
Brivaracetam 50mg – placebo	44.7	32.7, 56.7	0.000
Brivaracetam 200mg – placebo	50.4	38.7, 62.2	0.000
Brivaracetam 1000mg – placebo	57.7	45.8, 69.6	0.000
Brivaracetam versus levetiracetam			
Brivaracetam 50mg – levetiracetam 4000mg	-0.5	-9.4, 8.4	0.916
Brivaracetam 200mg – levetiracetam 4000mg	5.3	-3.2, 13.7	0.223
Brivaracetam 1000mg – levetiracetam 4000mg	12.5	3.8, 21.3	0.005
Levetiracetam versus placebo and alprazolam			
Levetiracetam 4000mg – placebo	45.2	32.6, 57.7	0.000
Levetiracetam 4000mg – alprazolam 1.5mg	-11.5	-19.4, -3.6	0.004
Levetiracetam 4000mg – alprazolam 3mg	-12.6	-19.5, -5.6	0.000

Source: sponsor's n01295-csr.pdf Table 8:7.

ARCI PCAG scale (Sedative Effects)

Figure 7. Mean ARCI PCAG scores over time by treatment – Per-protocol population (N=44)



Source: sponsor's n01295-csr.pdf Figure 8:7.

Table 9. Summary of ANCOVA results for ARCI PCAG Emax – Per-protocol population (N=44)

Pairwise comparison	Estimate of difference	95% CI of difference	P-value
Placebo versus alprazolam			
Alprazolam 3mg – placebo	6.3	5.1, 7.4	0.000
Alprazolam 1.5mg – placebo	7.4	6.3, 8.5	0.000
Brivaracetam versus alprazolam			
Brivaracetam 50mg – alprazolam 1.5mg	-3.0	-4.0, -1.9	0.000
Brivaracetam 200mg – alprazolam 1.5mg	-2.1	-3.2, -1.1	0.000
Brivaracetam 1000mg – alprazolam 1.5mg	-2.0	-3.1, -1.0	0.000
Brivaracetam 50mg – alprazolam 3mg	-4.1	-5.1, -3.1	0.000
Brivaracetam 200mg – alprazolam 3mg	-3.2	-4.3, -2.2	0.000
Brivaracetam 1000mg – alprazolam 3mg	-3.2	-4.2, -2.1	0.000
Brivaracetam versus placebo			
Brivaracetam 50mg – placebo	3.3	2.0, 4.5	0.000
Brivaracetam 200mg – placebo	4.2	2.9, 5.4	0.000
Brivaracetam 1000mg – placebo	4.2	2.9, 5.5	0.000
Brivaracetam versus levetiracetam			
Brivaracetam 50mg – levetiracetam 4000mg	-0.5	-1.6, 0.7	0.425
Brivaracetam 200mg – levetiracetam 4000mg	0.4	-0.7, 1.5	0.489
Brivaracetam 1000mg – levetiracetam 4000mg	0.5	-0.7, 1.6	0.441
Levetiracetam versus placebo and alprazolam			
Levetiracetam 4000mg – placebo	3.8	2.5, 5.0	0.000
Levetiracetam 4000mg – alprazolam 1.5mg	-2.5	-3.5, -1.5	0.000
Levetiracetam 4000mg – alprazolam 3mg	-3.6	-4.6, -2.6	0.000

Emax=maximum effect; HYD=hydrocodone bitartrate q24h film coated tablet; Hydrocodone solution=hydrocodone bitartrate, USP powder, administered as a 240 mL oral solution; IQR=inter-quartile range; PD=pharmacodynamic; VAS=visual analog scale

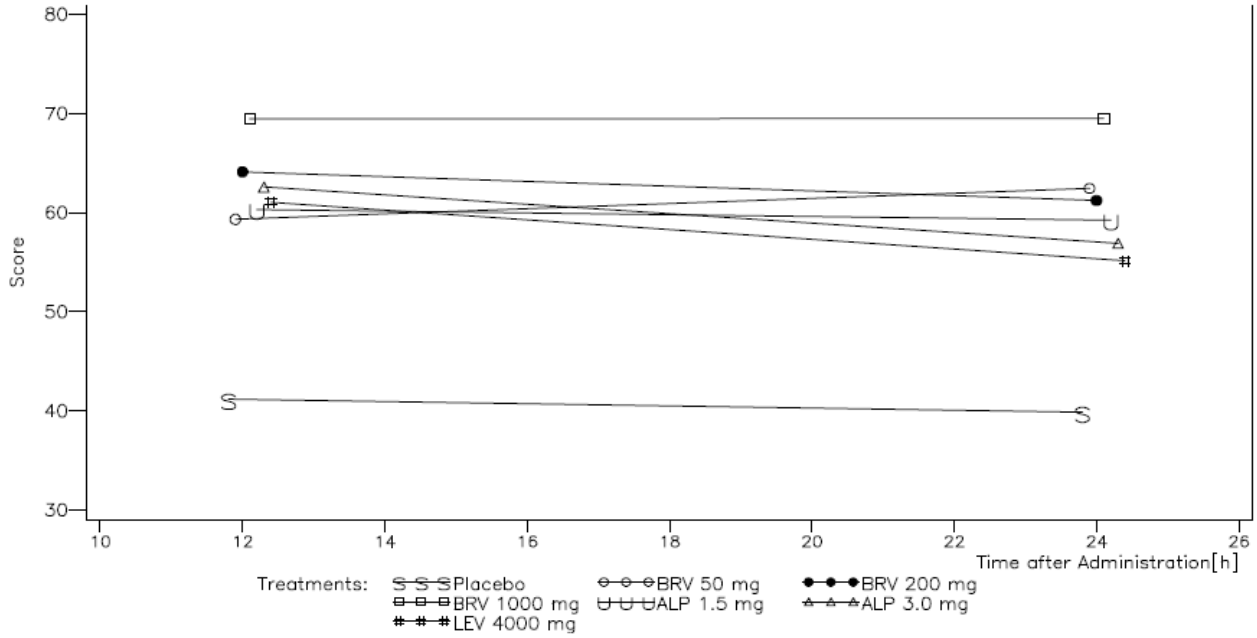
Overall Treatment Effect was assessed using Friedman's test. Pairwise treatment comparisons were assessed using the Wilcoxon sign-rank test on the within-subject differences.

P values shown in bold are significant ($P<0.05$).

Source: sponsor's n01295-csr.pdf Table 8:9.

Secondary Endpoints: Take Drug Again VAS (Balance of Effects)

Figure 8. Mean Take Drug Again VAS scores at 12 and 24 hours by treatment – Per-protocol population (N=44)



Source: sponsor's n01295-csr.pdf Figure 8:9.

Appendix 2: This Reviewer's Analyses

This reviewer found out that the sponsor's ITT population was the Per Protocol population (n=44).

Patients disposition Table

Frequency Percent Row Pct Col Pct	Table of SSEL by DSCTRT								
		DSCTRT(Subj Stat: Actual Drug Taken)							
	SSEL(Subj Stat: Status)	ALP 1.5 mg	ALP 3.0 mg	BRV 1000 mg	BRV 200 mg	BRV 50 mg	LEV 4000 mg	Placebo	Total
	Completed	6 13.64 16.67 100.00	6 13.64 16.67 85.71	5 11.36 13.89 83.33	6 13.64 16.67 100.00	4 9.09 11.11 66.67	5 11.36 13.89 62.50	4 9.09 11.11 80.00	36 81.82
	Discontinued	0 0.00 0.00 0.00	1 2.27 12.50 14.29	1 2.27 12.50 16.67	0 0.00 0.00 0.00	2 4.55 25.00 33.33	3 6.82 37.50 37.50	1 2.27 12.50 20.00	8 18.18
	Total	6 13.64	7 15.91	6 13.64	6 13.64	6 13.64	8 18.18	5 11.36	44 100.00

Drug-liking Emax-Difference in Sequence and Period between PP and Completers:

35 periods in 8 sequences

TRTSEQ	trtperiod	ppcount	compcount	diffcount	seqnumber
1273645	1	4	3	1	1
1273645	2	4	3	1	1
1273645	3	4	3	1	1
1726354	1	3	2	1	2
1726354	2	3	2	1	2
1726354	3	3	2	1	2
1726354	4	3	2	1	2
4352617	1	3	2	1	3
4352617	2	3	2	1	3
4352617	3	3	2	1	3
4352617	4	3	2	1	3
4536271	1	3	2	1	4
4536271	2	3	2	1	4
4536271	3	3	2	1	4
4536271	4	3	2	1	4
4536271	5	3	2	1	4
4536271	6	3	2	1	4
5463721	1	3	2	1	5
5463721	2	3	2	1	5
5463721	3	3	2	1	5
5463721	4	3	2	1	5
5463721	5	3	2	1	5
5463721	6	3	2	1	5
5647312	1	3	2	1	6
5647312	2	3	2	1	6
5647312	3	3	2	1	6
5647312	4	3	2	1	6
5647312	5	3	2	1	6
5647312	6	3	2	1	6
6574132	1	3	2	1	7
6574132	2	3	2	1	7
6574132	3	3	2	1	7
6574132	4	3	2	1	7
7615243	1	4	3	1	8

Treatment sequence:
1=Placebo,
2=BRV 50 mg,
3=BRV 200 mg,
4=BRV 1000 mg,
5=ALP 1.5 mg,
6=ALP 3.0 mg,
7=LEV 4000 mg,

ppcount=number of subjects in PP set
compcount=number of subjects in Completers set

Number of PP subjects for each endpoint measure

endpoint	num_pp
Amphetamine Scale	44
Any Drug Effects	44
BG Scale	44
Bad Drug Effects	44
Dizziness	44
Drug Liking	44
Good Drug Effects	44
High	44
LSD Scale	44
MBG Scale	44
Overall Drug Liking	44
PCAG Scale	44
Take Drug Again	44

Subjects disposition: Endpoints Measurements by Treatment, PP set

Frequency Percent Row Pct Col Pct	Table of PHDSCATL by PHDTRT									
	PHDSCATL(PD Data: Subcategory of Question)	PHDTRT(PD Data: Actual Drug Taken)								
		ALP 1.5 mg	ALP 2.0 mg	ALP 3.0 mg	BRV 1000 mg	BRV 200 mg	BRV 50 mg	LEV 4000 mg	Placebo	Total
	Amphetamine Scale	41 0.84 10.96 7.69	44 0.90 11.76 7.69	41 0.84 10.96 7.69	41 0.84 10.96 7.69	40 0.82 10.70 7.69	41 0.84 10.96 7.69	43 0.88 11.50 7.69	83 1.71 22.19 7.69	374 7.69
	Any Drug Effects	41 0.84 10.96 7.69	44 0.90 11.76 7.69	41 0.84 10.96 7.69	41 0.84 10.96 7.69	40 0.82 10.70 7.69	41 0.84 10.96 7.69	43 0.88 11.50 7.69	83 1.71 22.19 7.69	374 7.69
	BG Scale	41 0.84 10.96 7.69	44 0.90 11.76 7.69	41 0.84 10.96 7.69	41 0.84 10.96 7.69	40 0.82 10.70 7.69	41 0.84 10.96 7.69	43 0.88 11.50 7.69	83 1.71 22.19 7.69	374 7.69
	Bad Drug Effects	41 0.84 10.96 7.69	44 0.90 11.76 7.69	41 0.84 10.96 7.69	41 0.84 10.96 7.69	40 0.82 10.70 7.69	41 0.84 10.96 7.69	43 0.88 11.50 7.69	83 1.71 22.19 7.69	374 7.69
	Dizziness	41 0.84 10.96 7.69	44 0.90 11.76 7.69	41 0.84 10.96 7.69	41 0.84 10.96 7.69	40 0.82 10.70 7.69	41 0.84 10.96 7.69	43 0.88 11.50 7.69	83 1.71 22.19 7.69	374 7.69

Drug Liking	41 0.84 10.96 7.69	44 0.90 11.76 7.69	41 0.84 10.96 7.69	41 0.84 10.96 7.69	40 0.82 10.70 7.69	41 0.84 10.96 7.69	43 0.88 11.50 7.69	83 1.71 22.19 7.69	374 7.69
Good Drug Effects	41 0.84 10.96 7.69	44 0.90 11.76 7.69	41 0.84 10.96 7.69	41 0.84 10.96 7.69	40 0.82 10.70 7.69	41 0.84 10.96 7.69	43 0.88 11.50 7.69	83 1.71 22.19 7.69	374 7.69
High	41 0.84 10.96 7.69	44 0.90 11.76 7.69	41 0.84 10.96 7.69	41 0.84 10.96 7.69	40 0.82 10.70 7.69	41 0.84 10.96 7.69	43 0.88 11.50 7.69	83 1.71 22.19 7.69	374 7.69
LSD Scale	41 0.84 10.96 7.69	44 0.90 11.76 7.69	41 0.84 10.96 7.69	41 0.84 10.96 7.69	40 0.82 10.70 7.69	41 0.84 10.96 7.69	43 0.88 11.50 7.69	83 1.71 22.19 7.69	374 7.69
MBG Scale	41 0.84 10.96 7.69	44 0.90 11.76 7.69	41 0.84 10.96 7.69	41 0.84 10.96 7.69	40 0.82 10.70 7.69	41 0.84 10.96 7.69	43 0.88 11.50 7.69	83 1.71 22.19 7.69	374 7.69
Overall Drug Liking	41 0.84 10.96 7.69	44 0.90 11.76 7.69	41 0.84 10.96 7.69	41 0.84 10.96 7.69	40 0.82 10.70 7.69	41 0.84 10.96 7.69	43 0.88 11.50 7.69	83 1.71 22.19 7.69	374 7.69
PCAG Scale	41 0.84 10.96 7.69	44 0.90 11.76 7.69	41 0.84 10.96 7.69	41 0.84 10.96 7.69	40 0.82 10.70 7.69	41 0.84 10.96 7.69	43 0.88 11.50 7.69	83 1.71 22.19 7.69	374 7.69
Take Drug Again	41 0.84 10.96 7.69	44 0.90 11.76 7.69	41 0.84 10.96 7.69	41 0.84 10.96 7.69	40 0.82 10.70 7.69	41 0.84 10.96 7.69	43 0.88 11.50 7.69	83 1.71 22.19 7.69	374 7.69
Total	533 10.96	572 11.76	533 10.96	533 10.96	520 10.70	533 10.96	559 11.50	1079 22.19	4862 100.00

Sequence balance-completer

Frequency Percent Row Pct Col Pct	Table of PHDSCATL by SEQTRT														
		SEQTRT													
PHDSCATL	1273645	1726354	2137465	2314756	3241576	3425167	4352617	4536271	5463721	5647312	6574132	6751423	7162534	7615243	Total
Drug Liking	9 1.67 8.33 20.00	6 1.11 5.56 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	6 1.11 5.56 20.00	6 1.11 5.56 20.00	6 1.11 5.56 20.00	6 1.11 5.56 20.00	6 1.11 5.56 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	108 20.00
High	9 1.67 8.33 20.00	6 1.11 5.56 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	6 1.11 5.56 20.00	6 1.11 5.56 20.00	6 1.11 5.56 20.00	6 1.11 5.56 20.00	6 1.11 5.56 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	108 20.00
Overall Drug Liking	9 1.67 8.33 20.00	6 1.11 5.56 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	6 1.11 5.56 20.00	6 1.11 5.56 20.00	6 1.11 5.56 20.00	6 1.11 5.56 20.00	6 1.11 5.56 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	108 20.00
PCAG Scale	9 1.67 8.33 20.00	6 1.11 5.56 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	6 1.11 5.56 20.00	6 1.11 5.56 20.00	6 1.11 5.56 20.00	6 1.11 5.56 20.00	6 1.11 5.56 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	108 20.00
Take Drug Again	9 1.67 8.33 20.00	6 1.11 5.56 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	6 1.11 5.56 20.00	6 1.11 5.56 20.00	6 1.11 5.56 20.00	6 1.11 5.56 20.00	6 1.11 5.56 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	9 1.67 8.33 20.00	108 20.00
Total	45 8.33	30 5.56	45 8.33	45 8.33	45 8.33	45 8.33	30 5.56	30 5.56	30 5.56	30 5.56	30 5.56	45 8.33	45 8.33	45 8.33	540 100.00

Period balance-completer

Frequency Percent Row Pct Col Pct	Table of PHDSCATL by PHDPERL							
		PHDPERL						
PHDSCATL	Trt Period 1	Trt Period 2	Trt Period 3	Trt Period 4	Trt Period 5	Trt Period 6	Trt Period 7	Total
Drug Liking	16 2.96 14.81 20.00	16 2.96 14.81 20.00	15 2.78 13.89 20.00	15 2.78 13.89 20.00	15 2.78 13.89 20.00	16 2.96 14.81 20.00	15 2.78 13.89 20.00	108 20.00
High	16 2.96 14.81 20.00	16 2.96 14.81 20.00	15 2.78 13.89 20.00	15 2.78 13.89 20.00	15 2.78 13.89 20.00	16 2.96 14.81 20.00	15 2.78 13.89 20.00	108 20.00
Overall Drug Liking	16 2.96 14.81 20.00	16 2.96 14.81 20.00	15 2.78 13.89 20.00	15 2.78 13.89 20.00	15 2.78 13.89 20.00	16 2.96 14.81 20.00	15 2.78 13.89 20.00	108 20.00
PCAG Scale	16 2.96 14.81 20.00	16 2.96 14.81 20.00	15 2.78 13.89 20.00	15 2.78 13.89 20.00	15 2.78 13.89 20.00	16 2.96 14.81 20.00	15 2.78 13.89 20.00	108 20.00
Take Drug Again	16 2.96 14.81 20.00	16 2.96 14.81 20.00	15 2.78 13.89 20.00	15 2.78 13.89 20.00	15 2.78 13.89 20.00	16 2.96 14.81 20.00	15 2.78 13.89 20.00	108 20.00
Total	80 14.81	80 14.81	75 13.89	75 13.89	75 13.89	80 14.81	75 13.89	540 100.00

Sequence balance-PP

Frequency Percent Row Pct Col Pct	Table of PHDSCATL by SEQTRT														
		SEQTRT(Pat: Treatment Sequence)													
PHDSCATL(PD Data: Subcategory of Question)	1273645	1726354	2137465	2314756	3241576	3425167	4352617	4536271	5463721	5647312	6574132	6751423	7162534	7615243	Total
Drug Liking	32 1.71 8.56 20.00	24 1.28 6.42 20.00	27 1.44 7.22 20.00	27 1.44 7.22 20.00	27 1.44 7.22 20.00	27 1.44 7.22 20.00	24 1.28 6.42 20.00	26 1.39 6.95 20.00	26 1.39 6.95 20.00	26 1.39 6.95 20.00	24 1.28 6.42 20.00	27 1.44 7.22 20.00	27 1.44 7.22 20.00	30 1.60 8.02 20.00	374 20.00
High	32 1.71 8.56 20.00	24 1.28 6.42 20.00	27 1.44 7.22 20.00	27 1.44 7.22 20.00	27 1.44 7.22 20.00	27 1.44 7.22 20.00	24 1.28 6.42 20.00	26 1.39 6.95 20.00	26 1.39 6.95 20.00	26 1.39 6.95 20.00	24 1.28 6.42 20.00	27 1.44 7.22 20.00	27 1.44 7.22 20.00	30 1.60 8.02 20.00	374 20.00
Overall Drug Liking	32 1.71 8.56 20.00	24 1.28 6.42 20.00	27 1.44 7.22 20.00	27 1.44 7.22 20.00	27 1.44 7.22 20.00	27 1.44 7.22 20.00	24 1.28 6.42 20.00	26 1.39 6.95 20.00	26 1.39 6.95 20.00	26 1.39 6.95 20.00	24 1.28 6.42 20.00	27 1.44 7.22 20.00	27 1.44 7.22 20.00	30 1.60 8.02 20.00	374 20.00
PCAG Scale	32 1.71 8.56 20.00	24 1.28 6.42 20.00	27 1.44 7.22 20.00	27 1.44 7.22 20.00	27 1.44 7.22 20.00	27 1.44 7.22 20.00	24 1.28 6.42 20.00	26 1.39 6.95 20.00	26 1.39 6.95 20.00	26 1.39 6.95 20.00	24 1.28 6.42 20.00	27 1.44 7.22 20.00	27 1.44 7.22 20.00	30 1.60 8.02 20.00	374 20.00
Take Drug Again	32 1.71 8.56 20.00	24 1.28 6.42 20.00	27 1.44 7.22 20.00	27 1.44 7.22 20.00	27 1.44 7.22 20.00	27 1.44 7.22 20.00	24 1.28 6.42 20.00	26 1.39 6.95 20.00	26 1.39 6.95 20.00	26 1.39 6.95 20.00	24 1.28 6.42 20.00	27 1.44 7.22 20.00	27 1.44 7.22 20.00	30 1.60 8.02 20.00	374 20.00
Total	160 8.56	120 6.42	135 7.22	135 7.22	135 7.22	135 7.22	120 6.42	130 6.95	130 6.95	130 6.95	120 6.42	135 7.22	135 7.22	150 8.02	1870 100.00

Period balance-PP

Frequency Percent Row Pct Col Pct	Table of PHDSCATL by PHDPERL								
	PHDPERL(PD Data: Period)								
PHDSCATL(PD Data: Subcategory of Question)	Qualification Phase	Trt Period 1	Trt Period 2	Trt Period 3	Trt Period 4	Trt Period 5	Trt Period 6	Trt Period 7	Total
Drug Liking	88 4.71 23.53 20.00	44 2.35 11.76 20.00	43 2.30 11.50 20.00	43 2.30 11.50 20.00	42 2.25 11.23 20.00	39 2.09 10.43 20.00	39 2.09 10.43 20.00	36 1.93 9.63 20.00	374 20.00
High	88 4.71 23.53 20.00	44 2.35 11.76 20.00	43 2.30 11.50 20.00	43 2.30 11.50 20.00	42 2.25 11.23 20.00	39 2.09 10.43 20.00	39 2.09 10.43 20.00	36 1.93 9.63 20.00	374 20.00
Overall Drug Liking	88 4.71 23.53 20.00	44 2.35 11.76 20.00	43 2.30 11.50 20.00	43 2.30 11.50 20.00	42 2.25 11.23 20.00	39 2.09 10.43 20.00	39 2.09 10.43 20.00	36 1.93 9.63 20.00	374 20.00
PCAG Scale	88 4.71 23.53 20.00	44 2.35 11.76 20.00	43 2.30 11.50 20.00	43 2.30 11.50 20.00	42 2.25 11.23 20.00	39 2.09 10.43 20.00	39 2.09 10.43 20.00	36 1.93 9.63 20.00	374 20.00
Take Drug Again	88 4.71 23.53 20.00	44 2.35 11.76 20.00	43 2.30 11.50 20.00	43 2.30 11.50 20.00	42 2.25 11.23 20.00	39 2.09 10.43 20.00	39 2.09 10.43 20.00	36 1.93 9.63 20.00	374 20.00
Total	440 23.53	220 11.76	215 11.50	215 11.50	210 11.23	195 10.43	195 10.43	180 9.63	1870 100.00

Since the sponsor's primary analyses were neither on completers population nor appeared a paired test, this reviewer carried out paired-data analyses on the primary endpoints and some key secondary points using the completers data under the sponsor's analysis model as summarized in Table 11 below. These results are supportive to BRV's abuse potential, consisting with the findings by the sponsor.

Table 11. Summary of Paired-data Analysis for Primary and Some Secondary Endpoints VAS Emax –Completers population (N=36)

Difference	ALP 1.5 mg	ALP 3.0 mg	BRV 50 mg	BRV 200 mg	BRV 10000 mg	LEV 4000 mg
Drug-Liking VAS[1]						
drug-PLB (stderr) 95% CI p-value	28.4 (4.8) (18.6,38.3) <.0001	24.3 (4.9) (14.3, 34.4) <.0001	19.3 (5.1) (8.9, 29.8) 0.0007	24.7 (5.2) (14.2, 35.3) <.0001	29.8 (4.8) (19.9, 39.7) <.0001	19.1 (5.6) (7.7, 30.5) 0.0015
drug-A1.5 (stderr) 95% CI p-value			-8.4 (2.6) (-13.7,-3.0) 0.0031	-3.2 (2.7) (-8.7, 2.3) 0.2461	1.7 (2.2) (-2.9, 6.3) 0.4635	-8.7 (3.6) (-16.0, -1.4) 0.0204
drug-A3 (stderr) 95% CI p-value			-5.2 (3.0) (-11.1,0.8) 0.0898	0.0 (3.1) (-6.3, 6.4) 0.9909	4.9 (2.4) (-0.2, 10.0) 0.0588	-5.5 (3.9) (-13.3, 2.3) 0.1631
drug-LEV (stderr) 95% CI p-value			0.7 (3.9) (-7.4, 8.7) 0.864	5.8 (3.9) (-2.3, 13.8) 0.1515	10.6 (3.9) (2.7, 18.5) 0.0103	
Overall Drug-Liking VAS[1]						
drug-PLB (stderr) 95% CI p-value	22.5 (5.0) (12.2,32.7) 0.0001	25.1 (5.5) (14.0, 36.2) <.0001	22.2 (5.6) (10.9,33.5) 0.0003	23.7 (5.5) (12.6, 34.8) 0.0001	30.1 (5.5) (19.0, 41.2) <.0001	20.2 (6.1) (7.9, 32.5) 0.0018
drug-A1.5 (stderr) 95% CI p-value			-0.2 (4.3) (-9.0,8.6) 0.956	1.1 (4.6) (-8.3, 10.5) 0.8201	7.2 (4.0) (-1.0, 15.5) 0.0827	-2.4 (5.7) (-14.0, 9.3) 0.6808
drug-A3 (stderr) 95% CI p-value			-2.5 (5.2) (-13.1,8.1) 0.6362	-1.2 (5.4) (-12.2, 9.8) 0.8271	5.0 (4.9) (-5.1,15.1) 0.3184	-4.6 (6.4) (-17.6, 8.4) 0.4753
drug-LEV (stderr) 95% CI p-value			1.7 (5.7) (-10.1,13.4) 0.7745	3.0 (5.9) (-9.2, 15.1) 0.6208	9.2 (5.3) (-1.9, 20.2) 0.0994	
High VSA[1]						
drug-PLB (stderr) 95% CI p-value	54.7 (5.6) (43.2,66.2) .0001	55.7 (5.3) (447, 66.6) .0001	41.9 (6.1) (29.5,54.3) .0001	48.7 (5.8) (36.9, 60.5) .0001	53.5 (6.0) (41.3, 65.7) .0001	43.6 (6.3) (30.8, 56.3) .0001
drug-A1.5 (stderr) 95% CI p-value			-12.3 (4.0) (-20.3,-4.2) 0.0037	-5.7 (3.7) (-13.1,1.7) 0.1266	-1.1 (3.6) (-8.4, 6.2) 0.761	-10.8 (4.4) (-19.6,-1.9) 0.0192
drug-A3 (stderr) 95% CI p-value			-13.3 (3.4) (-20.2,-6.3) 0.0005	-6.7 (2.8) (-12.4, -1.0) 0.0234	-2.1 (3.0) (-8.2, 4.1) 0.5015	-11.7 (3.7) (-19.4,-4.0) 0.0043
drug-LEV (stderr) 95% CI p-value			-1.1 (4.8) (-10.9, 8.7) 0.8222	5.5 (4.4) (-3.6, 14.6) 0.2288	10.0 (4.8) (0.2, 19.9) 0.0453	
ARCI PCAG[1]						
drug-PLB (stderr) 95% CI p-value	6.4 (0.8) (4.9, 8.0) .0001	7.6 (0.7) (6.1, 9.1) .0001	3.4 (0.7) (1.9, 4.9) .0001	4.2 (0.7) (2.8, 5.6) .0001	4.1 (0.7) (2.7, 5.6) .0001	3.9 (0.7) (2.4, 5.3) .0001
drug-A1.5 (stderr) 95% CI p-value			-3.1 (0.7) (-4.4, -1.7) .0001	-2.3 (0.7) (-3.6, -0.9) 0.0015	-2.4 (0.7) (-3.7, -1.0) 0.0011	-2.6 (0.6) (-3.9, -1.3) 0.0003
drug-A3 (stderr) 95% CI p-value			-4.1 (0.6) (-5.4, -2.9) .0001	-3.3 (0.6) (-4.6, -2.1) .0001	-3.4 (0.6) (-4.7, -2.1) .0001	-3.7 (0.6) (-4.9, -2.5) .0001
drug-LEV (stderr) 95% CI p-value			-0.4 (0.4) (-1.3, 0.4) 0.3059	0.3 (0.3) (-0.4, 1.1) 0.3296	0.3 (0.5) (-0.8, 1.3) 0.5799	
Take Drug Again[2]						
drug-PLB (stderr)	18.5 (6.0)	22.4 (6.0)	21.2 (6.3)	25.2 (6.3)	31.5 (6.6)	23.2 (6.0)

95% CI p-value	(6.2, 30.7) 0.0043	(10.2, 34.5) 0.0007	(8.3, 34.0) 0.002	(12.3, 38.0) 0.0003	(18.2, 44.8) <.0001	(11.0,35.5) 0.0005
drug-A1.5 (stderr) 95% CI p-value			3.4 (5.3) (-7.5, 14.2) 0.5286	7.3 (5.6) (-4.1, 18.6) 0.2018	13.5 (5.5) (2.4, 24.6) 0.0187	5.4 (5.2) (-5.3,16.0) 0.3099
drug-A3 (stderr) 95% CI p-value			-0.5 (5.3) (-11.2,10.2) 0.9241	3.4 (5.4) (-7.6, 14.3) 0.5376	9.6 (5.3) (-1.2, 20.4) 0.0808	1.5 (4.8) (-8.5,11.4) 0.7633
drug-LEV (stderr) 95% CI p-value			-2.4 (4.8) (-12.4, 7.6) 0.621	1.6 (5.1) (-8.9, 12.1) 0.7602	7.9 (5.0) (-2.2,18.1) 0.1212	

Note: PLB=placebo; A1.5= ALP 1.5 mg; A3= ALP 3.0 mg; LEV= LEV 4000 mg.
[1] Primary endpoint
[2] Secondary endpoint

Summary of endpoint measures for drug abuse (Completers Set)

Endpoint	treatment	n	mean	stderr	stddev	min	Q1	median	Q3	max
Amphetamine Scale	ALP 1.5 mg	36	5.22	0.46	2.79	1	3.5	5	6.5	11
	ALP 3.0 mg	36	6.50	0.46	2.74	2	4	6	8	11
	BRV 1000 mg	36	5.19	0.53	3.20	1	3	4	8.5	11
	BRV 200 mg	36	4.72	0.43	2.59	1	3	4	6	11
	BRV 50 mg	36	4.50	0.40	2.40	0	3	4	6	11
	LEV 4000 mg	36	4.75	0.55	3.30	0	3	3.5	7	11
	Placebo	36	3.14	0.37	2.19	0	2	3	4	10
Any Drug Effects	ALP 1.5 mg	36	93.25	1.92	11.52	50	92	100	100	100
	ALP 3.0 mg	36	91.03	2.21	13.28	51	84.5	100	100	100
	BRV 1000 mg	36	89.78	3.31	19.88	0	89	99.5	100	100
	BRV 200 mg	36	89.42	2.47	14.82	52	80.5	99.5	100	100
	BRV 50 mg	36	80.08	3.76	22.55	2	66.5	85	100	100
	LEV 4000 mg	36	81.50	4.41	26.48	0	70	96	100	100
	Placebo	36	36.83	5.89	35.34	0	0	49.5	59.5	100
BG Scale	ALP 1.5 mg	36	6.97	0.31	1.87	4	6	7	7.5	12
	ALP 3.0 mg	36	7.61	0.28	1.69	4	6	7	9	12
	BRV 1000 mg	36	7.11	0.36	2.16	4	6	7	8	13
	BRV 200 mg	36	7.11	0.35	2.08	4	6	6.5	8	13
	BRV 50 mg	36	7.11	0.33	2.00	4	6	7	8	13
	LEV 4000 mg	36	7.39	0.40	2.38	4	6	7	8.5	13
	Placebo	36	6.53	0.32	1.93	4	6	6	7	13
Bad Drug Effects	ALP 1.5 mg	36	53.61	5.38	32.30	0	40	50.5	82	100
	ALP 3.0 mg	36	70.67	4.02	24.12	1	51	72.5	90.5	100
	BRV 1000 mg	36	33.64	5.58	33.47	0	1	24.5	57.5	100
	BRV 200 mg	36	33.86	4.85	29.12	0	0.5	36	51	100
	BRV 50 mg	36	31.92	4.34	26.07	0	3.5	44.5	51	76
	LEV 4000 mg	36	38.81	5.77	34.63	0	2	46.5	58.5	100
	Placebo	36	16.17	4.20	25.18	0	0	1	38	100
Dizziness	ALP 1.5 mg	36	63.53	5.85	35.12	0	42	76	91.5	100
	ALP 3.0 mg	36	73.39	4.93	29.59	3	56	81.5	100	100
	BRV 1000 mg	36	53.44	5.86	35.14	0	21	61	81.5	100
	BRV 200 mg	36	51.86	5.04	30.23	0	40.5	57	74	100
	BRV 50 mg	36	44.69	5.37	32.23	0	12	50.5	66.5	100
	LEV 4000 mg	36	50.81	5.93	35.58	0	7	56.5	80	100
	Placebo	36	17.61	4.39	26.31	0	0	0	50	78
Drug Liking	ALP 1.5 mg	36	87.64	2.43	14.57	50	76	95	100	100
	ALP 3.0 mg	36	83.64	3.01	18.05	50	72.5	90.5	100	100
	BRV 1000 mg	36	89.08	2.63	15.77	51	75.5	100	100	100

	BRV 200 mg	36	84.19	2.83	16.97	44	73.5	91	100	100
	BRV 50 mg	36	78.97	3.14	18.83	50	60.5	79	99	100
	LEV 4000 mg	36	78.64	3.76	22.58	1	64.5	80.5	100	100
	Placebo	36	57.36	4.28	25.69	0	51	51	59	100
Good Drug Effects	ALP 1.5 mg	36	84.64	3.21	19.23	0	75.5	89	100	100
	ALP 3.0 mg	36	87.56	2.65	15.92	49	74.5	96	100	100
	BRV 1000 mg	36	87.92	2.92	17.53	30	79.5	99.5	100	100
	BRV 200 mg	36	87.94	2.51	15.06	51	77.5	93.5	100	100
	BRV 50 mg	36	79.53	3.73	22.36	1	65	86.5	100	100
	LEV 4000 mg	36	77.11	4.36	26.18	0	66	80.5	99.5	100
	Placebo	36	41.56	5.81	34.88	0	0.5	51	56.5	100
High	ALP 1.5 mg	36	88.08	3.16	18.97	1	81	95.5	100	100
	ALP 3.0 mg	36	89.14	2.06	12.37	54	78.5	93.5	100	100
	BRV 1000 mg	36	86.92	3.49	20.92	0	78.5	97.5	100	100
	BRV 200 mg	36	82.28	2.94	17.66	47	69	84	100	100
	BRV 50 mg	36	75.67	4.11	24.67	2	63	82.5	94.5	100
	LEV 4000 mg	36	77.22	4.25	25.51	0	62	83	99	100
	Placebo	36	30.31	5.69	34.11	0	0	8.5	56	100
LSD Scale	ALP 1.5 mg	36	6.11	0.41	2.45	3	4	5.5	7.5	12
	ALP 3.0 mg	36	7.17	0.42	2.51	1	5	7	9.5	12
	BRV 1000 mg	36	5.22	0.34	2.02	3	4	5	6	11
	BRV 200 mg	36	5.00	0.40	2.38	2	4	4	6.5	11
	BRV 50 mg	36	4.64	0.29	1.74	2	4	4	5	10
	LEV 4000 mg	36	4.97	0.39	2.35	1	4	4	5.5	11
	Placebo	36	3.67	0.19	1.12	2	3	4	4	7
MBG Scale	ALP 1.5 mg	36	7.89	0.82	4.92	1	3.5	7	12.5	16
	ALP 3.0 mg	36	9.75	0.64	3.81	3	7	10	12.5	16
	BRV 1000 mg	36	7.58	0.83	4.98	1	3	6	12	16
	BRV 200 mg	36	6.58	0.85	5.08	0	2	6	10	16
	BRV 50 mg	36	5.69	0.77	4.63	0	1.5	5	8.5	16
	LEV 4000 mg	36	6.64	0.94	5.66	0	1	4.5	13	16
	Placebo	36	3.61	0.61	3.64	0	1	2.5	5	15
Overall Drug Liking	ALP 1.5 mg	36	67.42	4.45	26.73	0	54.5	69	88.5	100
	ALP 3.0 mg	36	70.25	4.85	29.10	0	55	76	95	100
	BRV 1000 mg	36	75.19	3.53	21.17	20	56	78.5	96.5	100
	BRV 200 mg	36	69.19	4.13	24.78	0	55	73.5	85	100
	BRV 50 mg	36	68.08	4.63	27.79	0	51	68.5	95	100
	LEV 4000 mg	36	65.81	4.89	29.32	0	51	70.5	90	100
	Placebo	36	45.61	4.74	28.42	0	48.5	50	51	100
PCAG Scale	ALP 1.5 mg	36	10.75	0.42	2.52	3	10	11.5	12	14
	ALP 3.0 mg	36	11.89	0.36	2.19	5	11	12	13	15
	BRV 1000 mg	36	8.44	0.54	3.22	1	6	9	11	13
	BRV 200 mg	36	8.53	0.56	3.38	3	6	8	12	15
	BRV 50 mg	36	7.75	0.57	3.43	1	5.5	8.5	10.5	15
	LEV 4000 mg	36	8.19	0.58	3.48	1	6	8	11	15
	Placebo	36	4.22	0.49	2.93	1	2	4	4.5	12
Take Drug Again	ALP 1.5 mg	36	62.53	5.54	33.25	0	50.5	69.5	91	100
	ALP 3.0 mg	36	66.64	5.76	34.57	0	43.5	76.5	99.5	100
	BRV 1000 mg	36	75.72	4.86	29.17	0	64.5	81.5	100	100
	BRV 200 mg	36	69.75	5.34	32.05	0	51	77	98.5	100
	BRV 50 mg	36	66.11	5.77	34.63	0	51	68	99	100
	LEV 4000 mg	36	67.92	5.52	33.12	0	51	75.5	97.5	100
	Placebo	36	43.42	5.99	35.95	0	1	50	57.5	100

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