CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207318Orig1s000

STATISTICAL REVIEW(S)

Memorandum

Subject: Violations on Study Entry Criteria regarding Concomitant Medication Use in Study ACP-103-020

Introduction

The OSI reviewer addressed a concern that in the pivotal study (ACP-103-020), there were many study subjects who entered the study without meeting the Exclusion Criteria #08 and #13, which are the study entry criteria about the use of concomitant medications. According to the OSI reviewer, "Finalization of the monitoring plan prior to study initiation may have prevented some of the observations related to inadequate monitoring including enrollment of 49/199 (24%) subjects not meeting eligibility criteria."

In the submitted raw data of Inclusion/Exclusion Criteria, there were 55 patients had at least one of the exclusion and inclusion criteria, out of whom 45 randomized patients (44 mITT patients) had at least one of the two exclusion criteria regarding use of concomitant medications. It is noted that the sponsor's study report (Listing 16.2.1.6) did not include all the 45 patients, but only 25. The 25 patients were a subset of the 44 patients.

The clinical team requested that the statistical reviewer examine the issue. This reviewer discussed with the clinical reviewer, Paul Andreason, the potential impact of the concomitant medication use listed in the exclusion and inclusion criteria on efficacy. The clinical reviewer does not think the use of concomitant medications will be an issue with the efficacy evaluation for the treatment of psychosis with Parkinson's Disease.

Conclusion

The efficacy results obtained on the mITT patients with a removal of either the 44 mITT patients or the 24 mITT patients showed a similar trend as in the primary efficacy analysis, although in both cases the efficacy estimate was smaller than in the primary efficacy analysis. Statistically, this reviewer does not see an influential impact of the removal of the 25 or 44 patients on the efficacy.

1. **Removing 25 randomized patients who had exclusion criteria #08 and #13 (listed in the sponsor's CSR (Listing 16.2.1.6)**

There were 25 patients listed in the sponsor's report (Listing 16.2.1.6 of the CSR) as violations of Exclusion Criteria #08 and #13. One patient (ACP-103-020-013-103) was not an ITT patient because the patient did not have a post-baseline score, and thus was not included in the set of the sponsor's ITT population (Section 1 above). Thus the rest of this patient, i.e., 24 patients, were included in the mITT analysis set (N=185).

This reviewer conducted a sensitivity analysis for this purpose. When the 24 patients are removed from the primary efficacy analysis, a slightly less efficacious result was seen. However, the removal of the 24 patients from the primary analysis did not affect the primary efficacy conclusion. The estimated treatment effect, estimated difference of pimavanserin from placebo, was -2.7, which was smaller by 0.4 points than the estimate (-3.1) from the primary efficacy analysis.

2. **Removing 45 randomized patients who had exclusion criteria #08 and #13**

This reviewer conducted a sensitivity analysis for this purpose. When the 44 patients are removed from the primary efficacy analysis, a slightly less efficacious result was seen. However, the removal of the 44 patients from the primary analysis did not affect the primary efficacy conclusion. The estimated treatment effect, estimated difference of pimavanserin from placebo, was -2.2, which was smaller by 0.9 points than the estimate (-3.1) from the primary efficacy analysis.

Eiji Ishida, DBI/OB/OTS/CDER

Primary Statistical Reviewer

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/s/

EIJI ISHIDA
04/29/2016

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 207,318
Drug Name:	Pimavanserin (Nuplazid™)
Indication(s):	Psychosis associated with Parkinson's Disease
Applicant:	Acadia Pharmaceuticals Inc.
Date(s):	September 1, 2015 (Submission Stamp date);
	May 1, 2016 (PDUFA due date)
Review Priority:	Priority
Biometrics Division:	Division of Biometrics I
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1 EXECUTIVE SUMMARY

The single pivotal study (Study ACP-103-020) has established statistical evidence that pimavanserin 40 mg is efficacious as a treatment of Parkinson's Disease Psychosis (PDP) and does not worsen Parkinson's Disease status. No major issue that may affect the main statistical conclusions was found.

The primary efficacy endpoint was the change from baseline to Week 6 in score of a novel instrument SAPS-PD (Scale for the Assessment of Positive Symptoms for Parkinson's Disease). The SAPS-PD assesses Parkinson's Disease Psychosis (PDP) for Hallucination and Delusion symptoms. Based on SAPS-PD, pimavanserin 40 mg has been shown to be more efficacious than placebo for an acute treatment of PDP.

The key secondary endpoint was the change from baseline to Week 6 in UPDRS Parts II and III Combined score, the respective part of which assesses activities in daily life and motor functions of Parkinson's Disease patients. A non-inferiority of pimavanserin to placebo has been concluded based on a non-inferiority test with a non-inferiority margin of 5 points. To be specific, pimavanserin ruled out >2.72 points worse than placebo based on the 95% confidence interval of the treatment effect relative to placebo.

A Psychopharmacologic Drugs Advisory Committee (PDAC) meeting will be held on March 29, 2016. One of the questions addressed to the PDAC may likely be about whether the treatment effect observed in this study, 3 points in SAPS-PD as an observed effect (a difference of pimavanserin from placebo in least square mean estimate), is clinically meaningful. This review may provide information on clinical effectiveness of the candidate new treatment.

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2 INTRODUCTION

Acadia Pharmaceuticals Inc. filed a new drug application (NDA) of pimavanserin for an indication of Psychosis associated with Parkinson's Disease (PDP). The candidate drug is pimavanserin 40 mg. In the NDA filing, the sponsor included one pivotal study and three supportive studies for evaluation of efficacy and safety. At Type C Meeting, held on April 9, 2013, the FDA agreed to the sponsor's plan to file the NDA based on data from the single, positive study (ACP-103-020) and supportive data from other studies (see Table 1).

The pivotal study Study ACP-103-020, titled "A Multi-Center, Placebo-Controlled, Double-Blind Trial to Examine the Safety and Efficacy of Pimavanserin in the Treatment of Psychosis in Parkinson's Disease", was conducted in US and Canada with 199 randomized patients. The sponsor evaluated efficacy of a fixed dose of 40 mg pimavanserin compared to placebo in the 6-week dosing duration. The sponsor claims this study established pimavanserin efficacy for the PDP indication.

A supportive study, Study ACP-103-012, conducted in US, Europe (mostly Eastern Europe) and India with 298 randomized patients, had two fixed doses of pimavanserin 10 mg and 40 mg to be compared to placebo in the 6-week dosing duration. The sponsor was unable to establish efficacy of pimavanserin in Study ACP-103-012 (Refer to Appendix A3 for this reviewer's brief summary of efficacy results). Another supportive study, Study ACP-103-014, had two fixed doses of pimavanserin 10 mg and 20 mg compared to placebo in the 6-week dosing duration. This study was early terminated when 123 patients of the planned 280 patients were enrolled. The third supportive study, Study ACP-103-006, conducted in US with 60 randomized patients, was a flexible dose placebo-controlled study (20 mg, 40 mg and 60 mg) in the 4-week dosing duration.

The present statistical review evaluates efficacy of pimavanserin for the labeling claim, based on the single, pivotal study (Study ACP-103-020). It is noted that at the planning stage of the pivotal study, the agency required that the sponsor evaluate motor symptoms of Parkinson's Disease in their planned antipsychotic efficacy studies of pimavanserin.

2.1 Overview

Study ACP-103-020 was a multicenter, randomized, fixed-dose, double-blind, placebo-controlled efficacy study in which 199 subjects were randomized across 66 centers (63 in the US and 3 in Canada). The sponsor evaluated efficacy of a fixed dose of 40 mg pimavanserin compared to placebo in the 6-week dosing duration. The sponsor defined the ITT population (later renamed as 'mITT') as consisting of randomized patients who had their baseline score and at least one post-baseline score of the primary efficacy measure. The number of subjects of the mITT population was 185 (95 patients for pimavanserin and 90 patients for placebo).

According to the sponsor, the study population has been largely the same for all pimavanserin studies for the PDP indication; the entry criteria have been consistent with the NINDS/NIMH

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established diagnostic criteria for PDP, as published by a Movement Disorder Society task force in 2007. However, according to the sponsor, the entry criteria for severity/frequency of psychosis of Study ACP103-020 are higher than for those of Studies ACP-103-012 and -014 (See Table 1). Specifically, in Study ACP-103-020, the study patients had to meet the condition of "A total NPI-H+D score ≥6 OR a score of ≥4 on either the H or D domain", while in Study ACP-103-012 that of "A score of ≥4 on either the H or D domain."

Table 1: Major Study Elements of Pimavanserin Placebo-Controlled Phase III Studies for PDP

Study	ACP-103-020	ACP-103-012	ACP-103-014
	Pivotal	Supportive	
N = # randomized patients	N = 199	N = 298	N = 123 (The planned N was 280, but was terminated early)
Dosing Duration (weeks)	6	6	6
Dose (daily)	Fixed dose 40 mg	Fixed doses 10 mg and 40 mg	Fixed doses 10 mg and 20 mg
Primary Efficacy Endpoint [Hypothesis test result]	Change from Baseline in SAPS-PD [Significant]	Change from Baseline in SAPS H+D [Not Significant]	Change from Baseline in SAPS H+D [N/A]
Key Secondary Endpoint [Hypothesis test result]	Change from Baseline in UPDRS II+III [Non-inferiority established]	Change from Baseline in UPDRS II+III [Not tested due to non-significant result in primary efficacy]	Change from Baseline in UPDRS II+III [N/A]
Region	US and Canada	US, Europe (Mostly Eastern) and India	US and Europe
Major difference in Study Population	**NPI-H+D: Entry Criteria at Screening**		
	A total NPI-H+D score ≥6 OR a score of ≥4 on either the H or D domain	A score of ≥4 on either the H or D domain	
	SAPS-PD: Entry Criteria at Baseline		
	A SAPS global item score (global H or D) of ≥3 and a score of ≥3 on at least one other non-global item	N/A	

NPI=Neuropsychiatric Inventory; SAPS= Scale for the Assessment of Positive Symptoms; H=Hallucinations; D=Delusions; PD=Parkinson's Disease
Source: Reviewer's documents based on CSR, Study Protocol and SAP.

The primary efficacy measure of Study ACP-103-020 was SAPS-PD[1], a scale the sponsor proposed at Type C Meeting with the FDA held on April 26, 2010. This scale was developed based on SAPS (Scale for the Assessment of Positive Symptoms) as a novel instrument to assess Parkinson's Disease Psychosis (PDP). As shown in Table 1, the primary efficacy measure used

[1] Fernandez, et. al (2008) Movement Disorders, Vol.23 No4. 2008. Pp484-500

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in Studies ACP-103-012 and -014 was SAPS-H+D, which is a 20-item scale for assessing Hallucinations and Delusions from SAPS. SAPS-PD consists of 9 items selected from the 20 items of SAPS-H+D.

The FDA required the sponsor to adequately assess for worsening of Parkinson's Disease in any PDP study of ACP-103 (pimavanserin), and that the sponsor formally conduct a non-inferiority test to demonstrate that pimavanserin is not inferior to placebo on some measure of PD status. The sponsor chose UPDRS II+III (UPDRS Part II (activities of daily living) and Part III (motor examination)) scores to pre-specify the required non-inferiority test. (See Section 3.2.2 for the selected non-inferiority margin).

The sponsor's Clinical Study Report (CSR) of Study ACP-103-020 indicates that an estimated pimavanserin treatment effect (relative to placebo in mean change from baseline score of SAPS-PD) was 3.06, and that a statistically significant difference (pimavanserine's superiority to placebo) was established at the p-value of 0.0014. It also indicates that non-inferiority of pimavanserin to placebo on Parkinson's Disease status was concluded based on the combined score of the UPDRS II+III.

2.2 Data Sources

The pimavanserin NDA submission is located at the FDA server:

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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The sponsor submitted all NDA efficacy study data in the original submission. The sponsor collected clinical study data of Study ACP103-020 in their legacy database (raw data), and generated legacy analysis data from the raw data. Prior to the NDA submission, the sponsor converted the legacy data to SDTM datasets. The submission of Study ACP103-020 contained the raw datasets (legacy data), and their converted legacy analysis datasets and CDISC SDTM datasets. This reviewer noticed that treatment assignment information was not included in the raw data but only in the legacy analysis datasets and SDTM datasets, and found through the communications with the sponsor that the randomization schedule and the raw data were directly merged into legacy analysis datasets and SDTM data sets. This reviewer confirmed that the planned treatment assignments of the randomization schedule match the actual treatment assignments of the legacy analysis datasets and SDTM datasets.

Given the treatment assignments incorporated into the submitted raw data, this reviewer verified that the analysis results the sponsor obtained from the legacy analysis data are consistent with the raw data that the treatment assignments of the randomization schedule are incorporated into.

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3.2 Evaluation of Efficacy

The primary objective of this study was to demonstrate the antipsychotic efficacy of pimavanserin in subjects with Parkinson's Disease Psychosis (PDP) as measured by a decrease in the severity and/or frequency of hallucinations and/or delusions. One key secondary endpoint was pre-specified to demonstrate that pimavanserin does not worsen motor symptoms of Parkinson's Disease (PD) in PDP subjects; for this purpose a non-inferiority test was planned based on the UPDRS II+III combined score. The multiple test procedure for the primary efficacy and key secondary endpoints was agreed upon with the FDA.

3.2.1 Study Population and Baseline Severity/Frequency of Psychosis

General Characteristics of Study Population

The study subjects' psychotic symptoms developed after the diagnosis of Parkinson's disease was established. These symptoms must include visual hallucinations and/or auditory hallucinations, and/or delusions. Their psychotic symptoms had to be present for at least one month. Study subjects actively experienced psychotic symptoms each week during the month prior to the Screening visit (Inclusion criteria 3 and 4).

Severity of Study Population (Table 2 and Table 3)

The study subjects' symptoms had to be severe enough to warrant treatment with an antipsychotic agent, which were documented at screening by items A (Delusions) and B (Hallucinations) of the NPI[2], referred as NPI-H+D. A score of 4 or greater on either the Hallucinations (Frequency x Severity) or Delusions (Frequency x Severity) scales OR a total combined score of 6 or greater was required (Inclusion criteria 5).

In addition, at the baseline visit, study subjects must have met a criterion based on SAPS-PD: a SAPS Hallucinations or Delusions global item (H7 or D13) score $\geq$3 AND a score $\geq$3 on at least one other non-global item (Inclusion criteria 6). The items A and B of the NPI and SAPS-PD are provided in this review (see Appendix).

The two tables (Table 2 and Table 3) display the severity of all randomized patients based on NPI-H+D (or NPI A and B) and the baseline severity of mITT patients by treatment group based on the SAPS-PD total score. Both mean NPI-H+D total score and mean SAPS-PD score are almost the same for the two treatment groups.

Out of 185 mITT patients at baseline, 58 patients had a NPI-Delusion score of zero (Figure 1) and 33 patients had a SAPS-PD Delusion score of zero (Figure 2), while 4 patients had a score of zero in both NPI-Hallucination and SAPS-PD Hallucination as seen in both figures. Thus, the study patients may have been less severe in their delusion symptoms. This fact may also be seen in the lower mean score of NPI-Delusion of 4.84 in contrast with that of 7.21 in NPI-Hallucination. A similar observation may be made for the SAPS-PD Delusion and Hallucination scores (Figure 2).

[2] NPI: Neuropsychiatric Inventory

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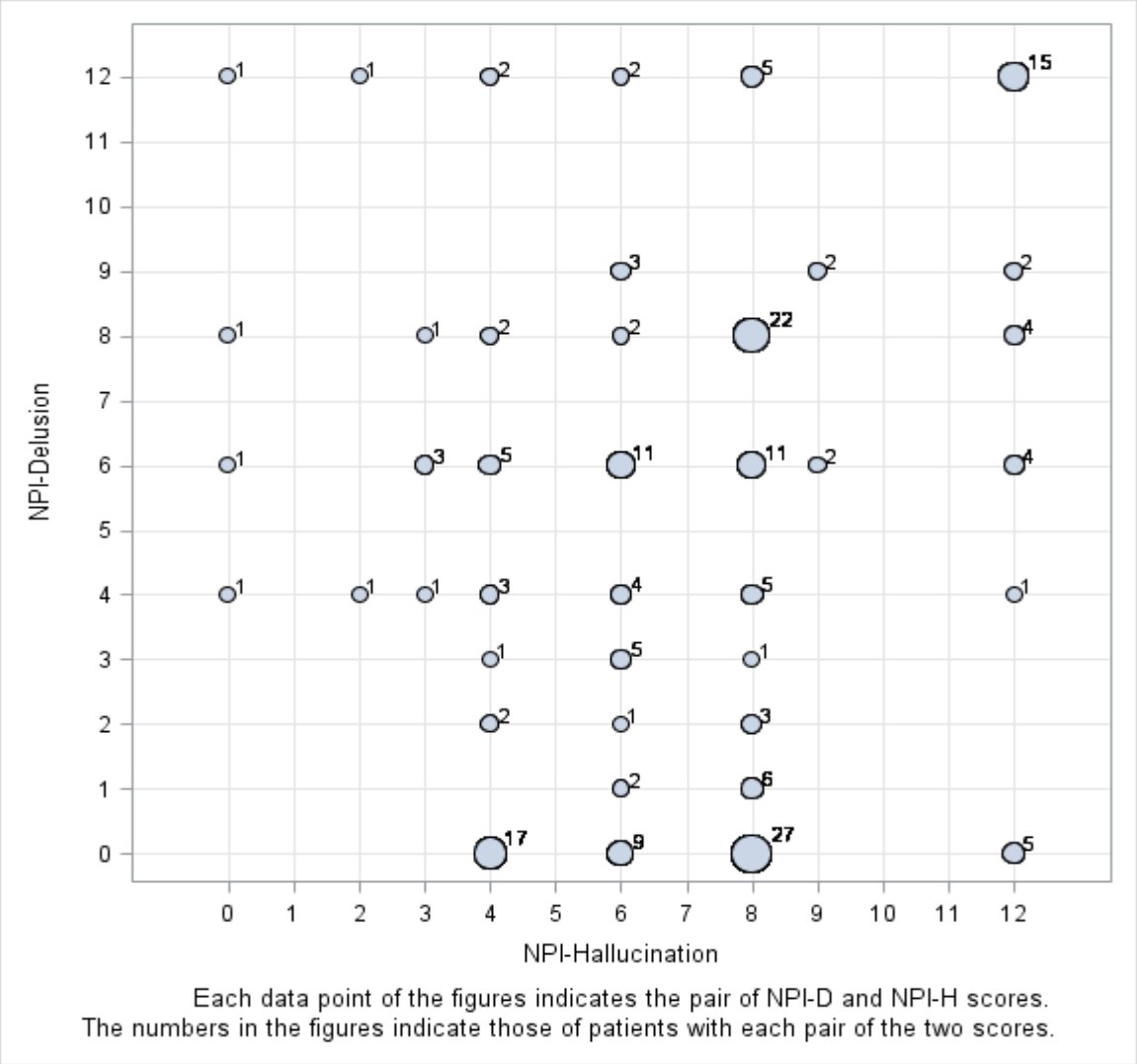
Figure 1: Distribution of NPI-H+D by Hallucination/Delusion at Screening (185 mITT Patients)



Note: The numbers of the plots indicate those of subjects.
Source: Reviewer's analysis

Table 2: NPI-H+D Score at Screening and at Baseline by Treatment Group

Screening entry criteria for NPI: A total NPI-H+D score ≥6 OR A score of ≥4 on either the H or D domain	NPI-H+D Screening/Baseline Score		
	Screened patients (N=199)	mITT Population (N=185)	
	Prior to randomization	Pimavanserin (N=95)	Placebo (N=90)
Mean NPI-H+D Delusion score (SD)	4.84 (4.14)	4.8 (4.21)	4.9 (4.09)
Mean NPI-H+D Hallucination score (SD)	7.21 (2.80)	7.1 (2.81)	7.3 (2.83)
Mean NPI-H+D Total score (SD)	12.06 (5.58)	11.8 (5.85)	12.2 (5.33)

SD denotes standard deviation.
Source: Reviewer's analysis

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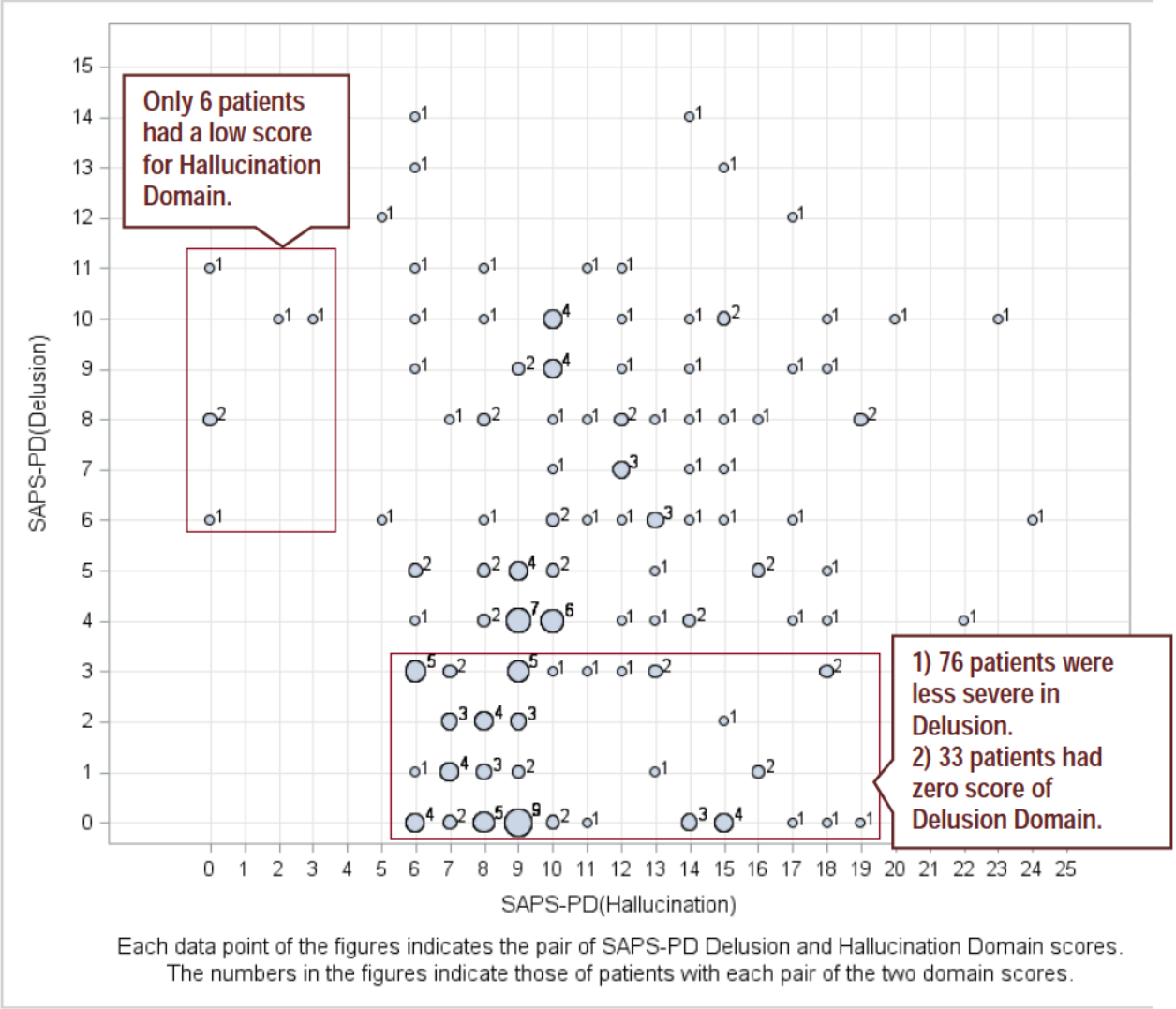
Table 3: SAPS-PD Baseline Score of mITT Patients (Total Score and Domain Scores)

Randomization entry criteria for SAPS-PD: A SAPS global item score (global H or D) of ≥3 AND A score of ≥3 on at least one other non-global item	SAPS-PD Baseline Score - mITT Population (N=185)	
	Pimavanserin (N=95)	Placebo (N=90)
Mean SAPS-PD Delusion score (SD)	4.76 (3.59)	4.78 (3.82)
Mean SAPS-PD Hallucination score (SD)	11.13 (4.58)	9.96 (3.80)
Mean SAPS-PD Total score (SD)	15.88 (6.12)	14.73 (5.55)

SD denotes standard deviation.
Source: Reviewer's analysis

Figure 2: Distribution of SAPS-PD Hallucination and Delusion Domain Scores at Baseline (N=185)



Note: The numbers of the plots indicate those of subjects.
Source: Reviewer's analysis

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3.2.2 Study Design and Endpoints

Study Design

The pivotal study, Study ACP-103-020, was a six-week, multi-center, randomized, double-blind, placebo-controlled study. The study was conducted on an outpatient basis. The baseline disease severity was characterized based on NPI-H+D[3], assessed at the screening visit and SAPS-PD (the modified 9-item SAPS[4] for Hallucinations and Delusions) assessed at the baseline (pre-randomization) visit. A total of the planned sample size was 200, and the randomization was performed at an equal ratio for pimavanserin or placebo group. The planned efficacy assessments were scheduled to be performed at Day 15 (Week 2), Day 29 (Week 4) and Day 43 (Week 6). There was only one planned post-baseline assessment for UPDRS Parts II and III to evaluate motor functions, which was on Day 43 (Week 6). A follow-up visit (Day 71) was scheduled 4 weeks after the last regular study visit for those subjects who do not continue into an open-label extension protocol.

Primary Efficacy Endpoint

The primary efficacy endpoint was pre-specified to be the mean change from pre-dose baseline (Day 1) at Week 6 in SAPS-PD, consisting of Hallucination and Delusion scales. This endpoint assesses an improvement in hallucination and delusion symptoms of Parkinson's Disease as one clinical entity over the 6-week treatment duration.

The sponsor planned to have a Type C Meeting (a teleconference scheduled to be held on April 26, 2010) and had the following question (Question 1) in the meeting package:

Does the Agency agree that modification of the primary endpoint based on a 9-item subset of the SAPS-H+D scale is supported by the baseline (pre-treatment) data from pimavanserin and clozapine studies and is appropriate for the planned Phase 3 trial?

The FDA's preliminary comment was as follows:

Yes, the modified primary efficacy endpoint is acceptable. We agree that the 9-item subset of the SAPS-H+D scale appears to be supported by the factor analysis on the baseline data from the studies. The modified primary endpoint appears to have improved clinical relevance and face validity, compared to the 20-item scale.

The sponsor cancelled the teleconference, determining that receiving the Agency's preliminary comments were sufficient for them.[5]

[3] NPI: Neuropsychiatric Inventory- Hallucination and Delusion
[4] SAPS: Scale for the Assessment of Positive Symptoms
[5] DARRTS: Meeting Cancellation Form, dated April 28, 2010. (IND68384)

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Key Secondary Endpoint

The key secondary endpoint is the mean change from Baseline in the combined UPDRS Part II and III scores (UPDRS-II+III) at Week 6.

The non-inferiority margin in the UPDRS Parts II and III Combined Score was discussed with the FDA during the 29 June 2006 Type C teleconference[6]. It was agreed that a change of approximately 5 points or greater is currently considered to be the minimal clinically important change in the UPDRS motor score.

Sample Size Estimation

The following is the sponsor's description of the sample size calculation:
"The primary endpoint is the difference in the mean absolute change in the combined scores for the modified 9-item SAPS (Scale for the Assessment of Positive Symptoms) Hallucinations and Delusions domains (SAPS-PD) between the active arm and the control arm from Day 1 (Baseline) to Day 43 (Week 6).

Assuming a clinically meaningful treatment difference in the mean change in the modified 9-item SAPS-PD Scores of 3.00 from Day 1 (Baseline) to Day 43 (Week 6) and using an estimated standard deviation of 6.5, a total of 100 subjects per treatment arm is required to achieve a 90% chance that the comparison (i.e., 40 mg pimavanserin versus placebo) will be significant at the alpha level of 0.05 for a 2-sided t-test.

As currently planned, the Phase III study will also be powered to detect a 5-point margin of difference from placebo on the key secondary endpoint, UPDRS (Unified Parkinson's Disease Rating Scale) Parts II and III. In a similarly designed study ACP-103-012, at the end of the 6-week study period, the standard deviations of UPDRS change from Baseline were 9.25 and 9.42 points in the placebo and pimavanserin 40 mg groups, respectively. Assuming a common standard deviation of 9.4 points, and conservatively assuming that the mean change from Baseline in UPDRS at Day 43 (Week 6) in the pimavanserin 40 mg group is 0.5-point greater (worse) than the placebo group, 100 subjects per treatment group will have a 92% power to demonstrate that the pimavanserin 40 mg group is not inferior to the placebo group within a margin of 5 points at a 1-sided 0.025 significance level."

3.2.3 Statistical Methodologies

3.2.3.1 Primary Efficacy

Primary Analysis for Primary Efficacy

Mean change from baseline in SAPS-PD was analyzed using a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) method. The model included the fixed, categorical effects of treatment (placebo or pimavanserin; 2 levels), visit (Weeks 2, 4 and 6; 3 levels) and treatment-by-visit interaction, as well as the continuous, fixed covariate of

[6] DARRTS: The meeting minutes is dated 10 July 2006. (IND68384)

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baseline score. An unstructured covariance matrix was used to model the within-subject errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. The significance test was based on least-square means comparison at the Week 6 using a 2-sided $\alpha = 0.05$. The primary analysis used observed measurements alone and no missing data were imputed.

Sensitivity Analysis for Primary Efficacy

In the primary efficacy analysis, missing data are assumed to follow the same distribution as observed data. Since this assumption may not be true, it may be important to evaluate efficacy under a scenario that missing data have values that are less efficacious than the observed data. The sponsor pre-specified a few sensitivity analyses, two of which may be important to mention in this review: ANCOVA with the WOCF (worst observation carried forward) imputation, which assumes that the missing data may be set equal to the worst observation of the patient and ANCOVA with the LOCF (last observation carried forward) imputation, which assumes that the missing data may be set equal to the last observation of the patient.

3.2.3.2 Key Secondary Endpoint and Analysis

The key secondary endpoint was the mean change from baseline to Week 6 in the combined score of the UPDRS Part II (activities of daily living) and Part III (motor examination). There was only one post-baseline assessment, and the primary analysis was the ANCOVA analysis (OC, i.e., completers only) with the mITT analysis set. To control the study-wise type I error rate, the test for key secondary endpoint was planned to be performed only when the null hypothesis for the primary efficacy endpoint was rejected at the significance level of 0.05 (two-sided).

3.2.3.3 Some Other Secondary/Supportive Endpoints and Analysis

Clinical Global Impressions - Severity (CGI-S) and - Improvement (CGI-I)

The sponsor planned to analyze the difference between pimavanserin versus placebo in Least Square mean changes from baseline (CGI-S) and in Least Square mean score at Week 6 (CGI-I) using MMRM as well as ANCOVA with LOCF and OC in the mITT analysis set.

SAPS-H+D (20-Item) Score

The sponsor planned to analyze the difference between pimavanserin versus placebo in SAPS-H+D Least Square mean changes from baseline using MMRM as well as ANCOVA with LOCF and OC in the mITT analysis set.

Combined SAPS Hallucinations and Delusions Global Rating of Severity (GSAPS-H+D)

The sponsor planned to analyze the difference between pimavanserin versus placebo in GSAPS-H+D LS-mean changes from baseline will be analyzed using MMRM as well as ANCOVA with LOCF and OC in the mITT analysis set.

SAPS Subscales and Global Rating Score

The sponsor planned to analyze the SAPS Hallucinations domain score (SAPS-H) and Delusions domain score (SAPSD), which is based on SAPS-H+D and the global rating severity scores

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within each sub-scale (GSAPS-H, GSAPS-D). The analysis was conducted using MMRM as well as ANCOVA with LOCF and OC in the mITT analysis set.

3.2.3.4 Center Effects

More than 50 centers participated in this study and many centers had a small number of subjects. However, as the primary efficacy endpoint was rated using a centralized rater service, study center was not pooled. The primary analysis did not include center effect as a factor in its analysis model.

3.2.4 Patient Disposition, Demographic and Baseline Characteristics

Demographic Characteristics (Table 4)

The summary statistics of the study demographic characteristics are provided in the table below.

Table 4: Demographic Characteristics

mITT population	Placebo (N=90)	Pimavanserin (N=95)	Total (N=185)
Gender n (%)			
Male	52 (57.8)	64 (67.4)	116 (62.7)
Female	38 (42.2)	31 (32.6)	69 (37.3)
Age (years)			
Mean (SD)	72.4 (7.92)	72.4 (6.55)	72.4 (7.23)
Age Categories n (%)			
<65 Years	11 (12.2)	11 (11.6)	22 (11.9)
65-75 years	50 (55.6)	53 (55.8)	103 (55.7)
>75 Years	29 (32.2)	31 (32.6)	60 (32.4)
Race Category n (%)			
White	85 (94.4)	90 (94.7)	175 (94.6)
Non-White	5 (5.6)	5 (5.3)	10 (5.4)

SD denotes standard deviation.
Source: Table 14.1.2.1.1 of the CSR

Randomization and Primary Analysis Set

Randomization: A total of 199 eligible patients were randomized to pimavanserin or placebo at an equal ratio (N=94 for placebo and N=105 for pimavanserin).

Primary Analysis Set: The sponsor's primary analysis set was the modified intent-to-treat (mITT) population defined as a set of randomized patients who have their baseline score of SAPS-PD and at least one post-baseline score of SAPS-PD. The sponsor excluded 14 of 199 randomized patients from their mITT analysis population[7]. This reviewer verified that the removal of the excluded patients from the mITT analysis for primary efficacy does not favor pimavanserin for its efficacy evaluation. The sponsor's mITT population had 185 subjects (N=90 for placebo and N=95 for pimavanserin).

[7] The unique subject ID's of the 14 patients who were excluded from mITT population were: ACP-103-020-038-104, ACP-103-020-039-103, ACP-103-020-301-108, ACP-103-020-303-122, ACP-103-020-318-104, ACP-103-020-320-104, and ACP-103-020-330-101.

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Patient Disposition (Table 5)

The patient disposition and the number of patients who had efficacy assessment at Week 6 are provided in the following table.

Table 5: Patient Disposition for Primary Efficacy Assessment with Discontinuation Reason

Treatment group (# Randomized subjects)	**Placebo** (N=94)	**Pimavanserin** (N=105)	**Total** (N=199)
Excluded from mITT population	4	10	14
Sponsor mITT population	90	95	185
SAPS-PD observed at Week 6	86	87	173
SAPS-PD observation missing at Week 6	4	8	12
# Discontinued Patients	7	16	23
Reason for Discontinuation from Study (Sponsor mITT population)			
Adverse event	2	10	12
Voluntary withdrawal of consent	2	3	5
At discretion of ACADIA	2	2	4
Subject fails to comply with protocol requirements	0	1	1
Investigator's decision	1	0	1

Source: Table 14.1.2.1.1 of the CSR and Reviewer's analysis

3.2.5 Results and Conclusions

3.2.5.1 Primary Efficacy Endpoint (based on SAPS-PD)

Primary Analysis (Table 6)

The study efficacy conclusion was drawn from the primary analysis result. As listed in Table 6, pimavanserin's efficacy for the PDP (Hallucination and Delusion) was statistically demonstrated at the 0.05 significance level (2-sided test).

Table 6: Primary Efficacy Analysis Result (SAPS-PD Change Score from Baseline at Week 6)

Pimavanserin Difference from Placebo in LS Mean of Change from Baseline score (Week 6)				
LS Mean Estimate		Difference from Placebo in LS Mean Estimate (SE)	95% Confidence Interval	P value
Pimavanserin (SE)	Placebo (SE)			
-5.79 (0.66)	-2.73 (0.67)	-3.06 (0.94)	(-4.91, -1.20)	0.0014

Note: A negative change from baseline indicates an improvement. LS (Least Square) Mean estimates were obtained from an application of the pre-specified MMRM.

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Table 7 provides visit-wise LS mean estimates, and the difference of pimavanserin from placebo in LS mean estimate and its 95% confidence interval with the nominal p value.

Table 7: Visit-wise Efficacy based on Change Score from Baseline of SAPS-PD (via Primary Analysis Model)

LS Mean Estimate by Treatment group (Change from baseline score at Weeks 2, 4 and 6)					
Treatment group	Visit	LS Mean Estimate (SE)	Difference from Placebo in LS Mean Estimate (SE)	95% Confidence Interval	P value
Pimavanserin	Week 2	-3.1 (0.60)	-0.21 (0.86)	(-1.9,-1.5)	0.8092
	Week 4	-5.0 (0.61)	-1.82 (0.87)	(-3.5, -0.1)	0.0369
	Week 6	-5.8 (0.66)	-3.06 (0.94)	(-4.9, -1.2)	0.0014
Placebo	Week 2	-2.9 (0.61)			
	Week 4	-3.2 (0.61)			
	Week 6	-2.7 (0.67)			

Note: LS (Least Square) Mean estimates were obtained from an application of the pre-specified MMRM. SE denotes standard error. Confidence interval and p-values were obtained without adjusting for multiplicity. Source: Reviewer's analysis

Sensitivity Analysis (Table 8)

The table below lists two of the sponsor's sensitivity analyses using the mITT population. The ANCOVA using an imputation of WOCF (worst observation carried forward) was an approach that is the least favorable to pimavanserin of the sponsor's pre-specified sensitivity analyses, a scenario that all missing observations were the worst of each patient's observed values. The result of ANCOVA (WOCF) does not suggest that the conclusion from the primary analysis may be questioned. The ANCOVA (LOCF) is equivalent to an ANCOVA using last observed values. The result of ANCOVA (LOCF) suggests that the dropouts only favored pimavanserin efficacy estimation by the amount of 0.15, a difference between -3.06 (primary analysis) and -2.91 (ANCOVA (LOCF)).

Table 8: SAPS-PD – Sensitivity Analyses versus Primary Analysis

	Method	LS Mean Change from Baseline at Week 6 (SE)		Difference from Placebo (pimavanserin – placebo)	95% Confidence Interval	p-value
		Pimavanserin	Placebo			
Primary Analysis	MMRM	-5.79 (0.66)	-2.73 (0.67)	-3.06 (0.94)	(-4.91, -1.20)	0.001
Sensitivity Analysis	ANCOVA (LOCF)	-5.56 (0.65)	-2.65 (0.67)	-2.91 (0.93)	(-4.76, -1.07)	0.002
	ANCOVA (WOCF)	-5.43 (0.65)	-2.65 (0.67)	-2.78 (0.94)	(-4.63, -0.93)	0.003

Note: LS (Least Square) Mean estimates were obtained from an application of the pre-specified MMRM. SE denotes standard error. Source: Table 13 of the CSR and Reviewer's analysis.

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Observed Data used in Primary Efficacy Evaluation (Table 9)

The overall rate of dropouts for the efficacy assessment at Week 6 was around 6.5%, and there was not a large difference in the rate of missing observations between Pimavanserin and Placebo groups. The observed raw mean changes from baseline in SAPS-PD score show an improvement of 6.3 in SAPS-PD score (Pimavanserin) and 2.7 (Placebo). At Week 6, the observed raw mean difference between the two treatment groups was 3.6 points in favor of pimavanserin.

Table 9: SAPS-PD – Raw Mean Scores of Pimavanserin and Placebo Groups by Visit

	SAPS-PD Observed Visit-wise Raw Score of mITT Patients (N=185)					
Treatment group	Visit	N (% of Remaning Patients)	SAPS-PD total score Mean change score from baseline (SD)	SAPS-PD total score Mean observed score (SD)	SAPS-PD Delusion score Mean observed score (SD)	SAPS-PD Hallucination score Mean observed score (SD)
Pimavanserin	Baseline	95	-	15.9 (6.12)	4.8 (3.59)	11.1 (4.58)
	Week 2	94 (98.9)	-3.3 (6.13)	12.6 (7.45)	3.5 (3.59)	9.1 (5.29)
	Week 4	88 (92.6)	-5.3 (6.19)	10.8 (7.20)	3.0 (3.30)	7.8 (5.00)
	Week 6	87 (91.6)	-6.3 (5.88)	9.7 (7.11)	2.7 (3.02)	7.0 (5.14)
Placebo	Baseline	90	-	14.7 (5.55)	4.8 (3.82)	10.0 (3.80)
	Week 2	90 (100)	-2.7 (6.08)	12.1 (6.39)	3.6 (3.39)	8.5 (4.47)
	Week 4	89 (98.9)	-3.0 (6.41)	11.7 (6.11)	3.5 (3.26)	8.2 (4.50)
	Week 6	86 (95.6)	-2.7 (7.03)	11.8 (7.17)	3.6 (3.95)	8.3 (4.43)

SD denotes standard deviation.
Source: Reviewer's analysis

Table 10: Sponsor Supportive Analysis Results (SAPS-H+D)

Pimavanserin vs Placebo at Week 6 Change from baseline score in Supportive endpoints					
Efficacy Measure	LS Mean Estimate (SE)		Difference from Placebo in LS Mean Estimate (SE)	95% Confidence Interval	P value
	Pimavanserin	Placebo			
SAPS-H+D	-6.51 (0.72)	-3.14 (0.73)	-3.37 (1.03)	(-5.40, -1.35)	0.0012
SAPS-H	-4.18 (0.49)	-2.10 (0.49)	-2.08 (0.70)	(-3.46, -0.71)	0.0032
SAPS-D	-2.28 (0.38)	-1.12 (0.38)	-1.16 (0.54)	(-2.22, -0.10)	0.0325
GSAPS-H+D	-1.95 (0.26)	-1.02 (0.26)	-0.93 (0.37)	(-1.65, -0.21)	0.0117
GSAPS-H	-1.16 (0.15)	-0.50 (0.15)	-0.66 (0.21)	(-1.08, -0.25)	0.0020
GSAPS-D	-0.80 (0.15)	-0.53 (0.15)	-0.27 (0.21)	(-0.68, 0.14)	0.1890

Note: The analysis method was the same as the primary efficacy analysis (MMRM). SE denotes standard error. GSAPS denotes Combined SAPS-Hallucinations and Delusions Global Rating of Severity.
Source: Tables 14.2.3.5.1, 14.2.3.7.1, 14.2.3.8.1, 14.2.3.6.1, 14.2.3.9.1 and 14.2.3.10.1 of the CSR

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Supportive Analysis (Table 10)

The sponsor planned and performed supportive analyses using SAPS-H+D (20-item SAPS score for hallucination and delusion). See Section 3.2.3.3 of this review. Overall, these analysis results are supportive for the primary efficacy analysis conclusion. It is noted that the numerical results for the delusion domain appear to be slightly less supportive compared to those for the hallucination domain.

3.2.5.2 Key Secondary Endpoint (based on UPDRS II+III)

Primary Analysis and Non-inferiority Test (Table 11)

The key secondary endpoint was the mean change from baseline to Week 6 in the combined score of the UPDRS Part II (activities of daily living) and Part III (motor examination) using the ANCOVA analysis (OC) for the mITT analysis set. Essentially, this analysis is equivalent to an analysis using only completersbecause there was only one post-baseline assessment (at week 6). It is noted that there were only a few missing observations at the endpoint visit in total (Table 12).

Since the upper limit (2.72) of the 2-sided 95% CI for the treatment difference did not exceed the pre-specified non-inferiority margin of 5 units, non-inferiority of pimavanserin 40 mg compared to placebo was established (Table 11). The sponsor concluded that the result suggests that there was no clinically meaningful difference in the activities of daily living and the motor examinations of the subjects taking pimavanserin 40 mg when compared with the subjects taking placebo.

Table 11: Primary Analysis Results of Key Secondary Endpoint: Parkinson's Disease Status (UPDRS II+III)

Key Secondary Endpoint: Pimavanserin vs Placebo at Week 6 Change score from baseline in UPDRS II+III Combined score				
ANCOVA (OC) LSM Estimate (SE)		Difference from Placebo in LSM Estimate (SE)	95% Confidence Interval	P value
Pimavanserin [N=92]	Placebo [N=88]			
-1.40 (0.86)	-1.69 (0.88)	0.29 (1.23)	(-2.14, 2.72)	0.8140

Note: A negative change from baseline indicates an improvement. The analysis result is based on ANCOVA (OC) model with treatment group as a factor and baseline score as a covariate. OC denotes Observed Cases. SE denotes standard error. N denotes the number of patients who had a baseline score and the endpoint score at Week 6.
Source: Reviewer's analysis

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Table 12: Raw Mean Change Score from Baseline at Week 6 (UPDRS II+III)

Mean change from baseline at Week 6 (SD)	Pimavanserin (N=95)		Placebo (N=90)	
UPDRS II+III combined score	-1.36 (8.16)	n=92	-1.73 (8.76)	n=88
UPDRS II (Activities in Daily Living) score	-0.52 (3.32)	n=92	-0.88 (3.33)	n=88
UPDRS III (Motor Examination) score	-0.80 (7.12)	n=93	-0.86 (7.09)	n=88

SD denotes standard deviation. N denotes the numbers of mITT patients, and n those of patients who had the endpoint score at Week 6.
Source: Tables 27 and 28 of the CSR and Reviewer's analysis

Correlation between SAPS-PD and UPDRS II+III (Table 13, Figure 3)

Out of 185 mITT patients, 175 patients had an assessment at Week 6 in both SAPS-PD and UPDRS II+III.

In Figure 3, a graph of scatterplots between the changes from baseline at Week 6 of the SAPS-PD and UPDSR II and III combined scores is provided for these 175 patients. It seems that there is no tendency suggesting that patients improve on psychosis but worsen on Parkinson's Disease status.

Mean changes from baseline at Week 6 of both scores are listed for these 175 patients in Table 13.

Table 13: Mean Changes from Baseline at Week 6 of SAPS-PD total score and UPDRS II+III combined score (N=175)

Mean change from baseline at Week 6 (SD)	Pimavanserin (N=95)		Placebo (N=90)	
SAPS-PD total score	-6.14 (6.11)	n=88	-2.70 (7.00)	n=87
UPDRS II+III combined score	-1.64 (7.89)		-1.76 (8.80)	

Note: n denotes number of patients who had both scores at Week 6; SD denotes standard deviation.
Source: Reviewer's analysis

3.2.5.3 Other Secondary Efficacy Endpoints (Table 14, Table 15)

The MMRM analysis results of secondary efficacy endpoints based on CGI-S and CGI-I are listed in Table 14 and Table 15. Both results are supportive for pimavanserin's efficacy.

Table 14: Secondary Efficacy (CGI-S)

Pimavanserin Difference from Placebo in Mean change from baseline score of CGI-S at Weeks 2, 4 and 6			
Visit	LS Mean Estimate (SE)	95% Confidence Interval	P value
Week 2	-0.02 (0.15)	(-0.32,-0.27)	0.8730
Week 4	-0.41 (0.18)	(-0.76, -0.06)	0.0224
Week 6	-0.58 (0.17)	(-0.92, -0.25)	0.0007

SE denotes standard error.
Source: Table 14.2.2.2.1 of the CSR and Reviewer's analysis

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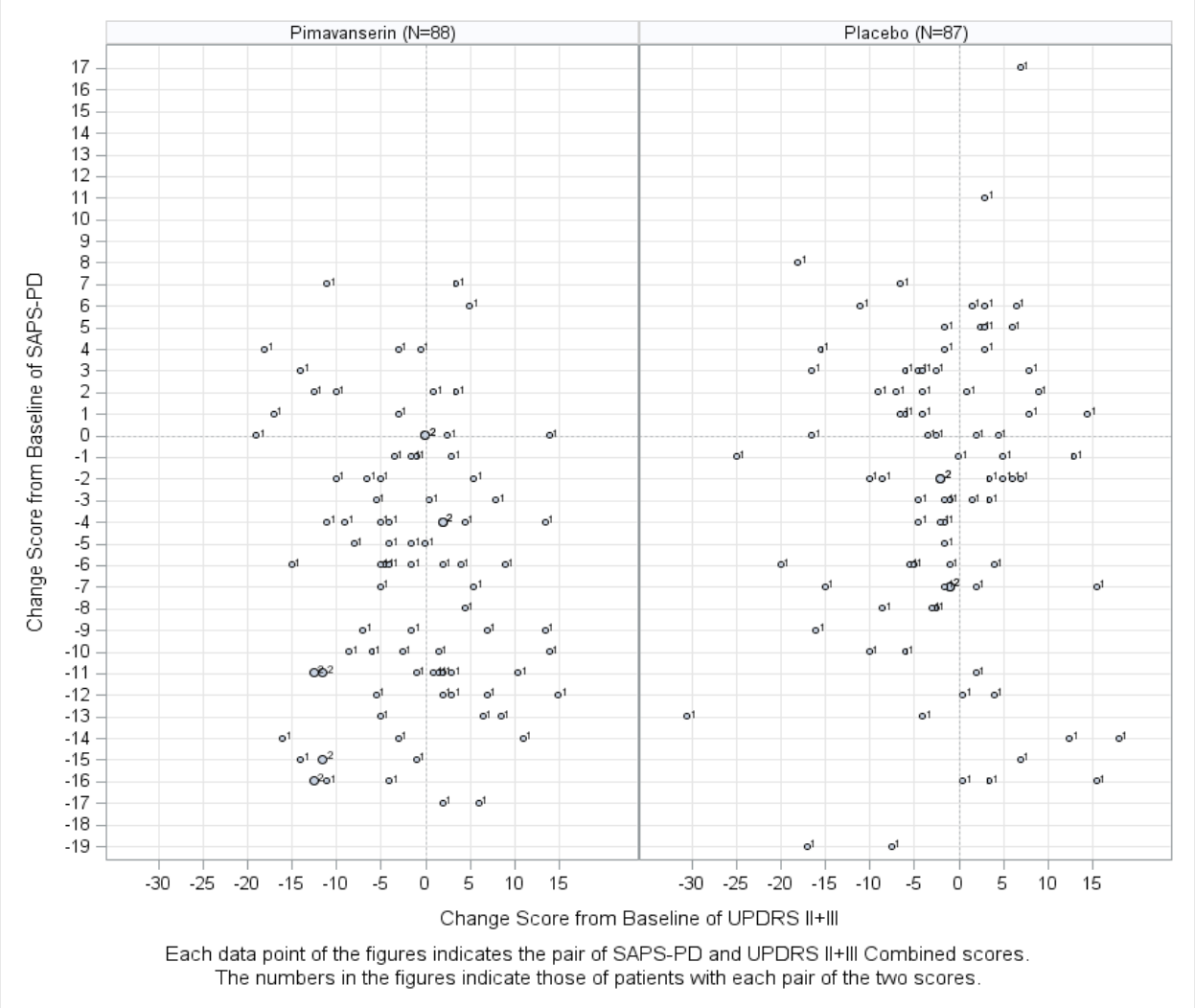
Table 15: Secondary Efficacy (CGI-I)

Pimavanserin Difference from Placebo in Mean score of CGI-I at Weeks 2, 4 and 6			
Visit	LS Mean Estimate (SE)	95% Confidence Interval	P value
Week 2	-0.01 (0.18)	(-0.36,-0.33)	0.9363
Week 4	-0.50 (0.19)	(-0.88, -0.12)	0.0098
Week 6	-0.67 (0.20)	(-1.06, -0.27)	0.0011

SE denotes standard error.
Source: Table 14.2.2.3.1 of the CSR and Reviewer's analysis

Figure 3: Scatterplots of SAPS-PD and UPDRS II+III Change Scores from Baseline to Week 6 by Treatment Group (N=175)



Source: Reviewer's analysis

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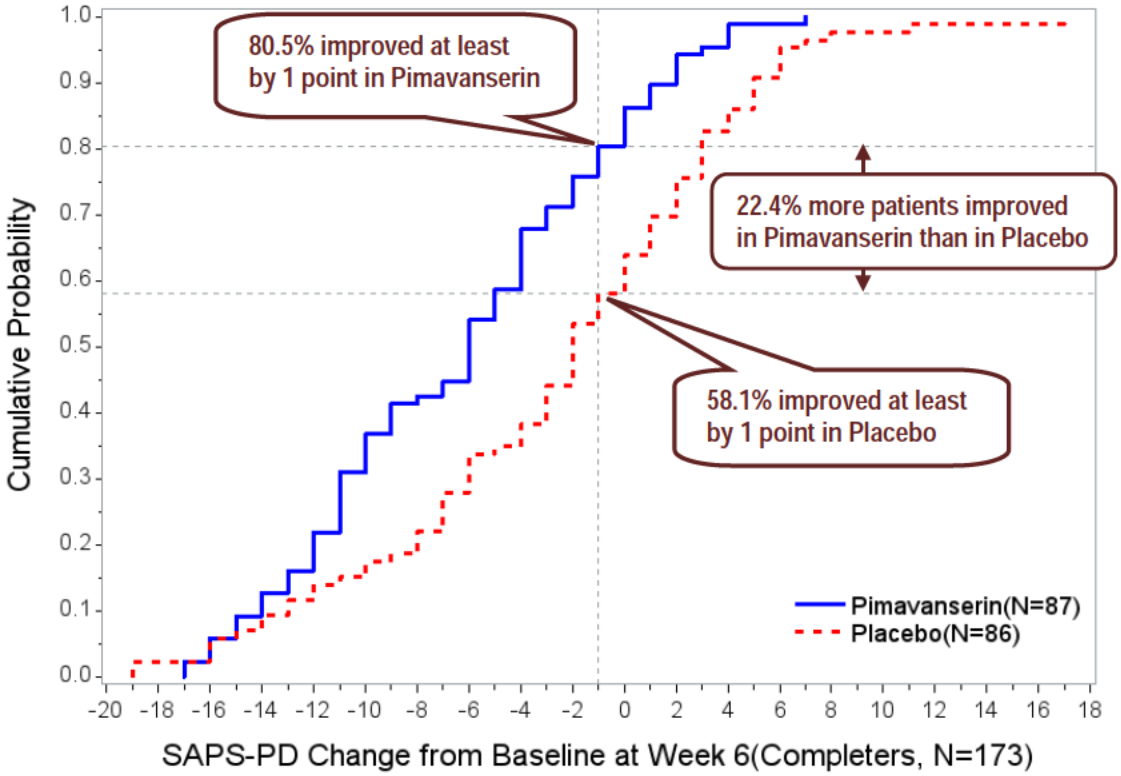
3.3 Exploratory Analysis

The exploratory analyses provided in this section are based on the mITT patients (N=185). Analyses of this section are all *post hoc*, and cannot be interpreted as conclusive or generalizable. The statistical results (estimates, confidence intervals, p values) shown in this section should not be used to draw any general conclusion. This section only provides descriptive information about the study efficacy data.

3.3.1 Empirical Cumulative Distribution of SAPS-PD Change from Baseline Score (Figure 4)

The empirical cumulative distribution plots provide visualized efficacy of pimavanserin in comparison with placebo. Figure 4 shows the benefit of pimavanserin as a treatment of PDP. A patient improves when the change from baseline score is less than zero. As shown in the figure, 80.5% of pimavanserin completers and 58.1% of placebo completers improved. A cumulative probability of pimavanserin was around 16% higher on average than that of placebo, and the placebo response seems to have been considerably high.

Figure 4: Empirical Cumulative Distribution Function Plots by Treatment at Week 6 (Observed Change Scores from Baseline in SAPS-PD) (Completers, N=173)



Note: A patient improves if the change from baseline score to Week 6 is less than 0.
Source: Reviewer's analysis

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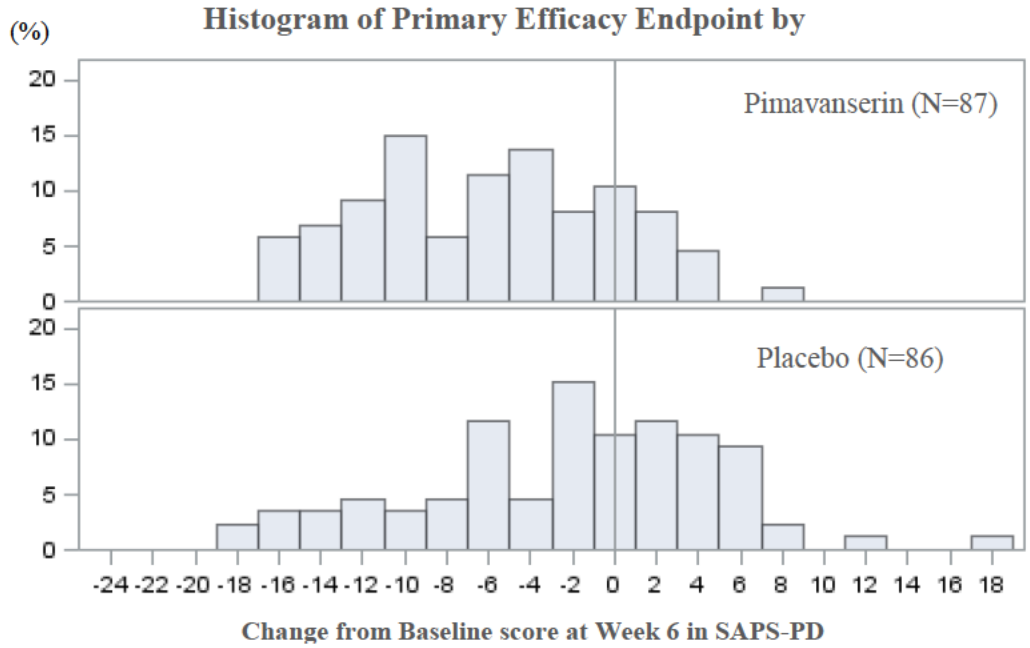
Figure 5 shows the histogram of primary endpoint scores (change from baseline to Week 6 in SAPS-PD) for 173 completers. The distributional ranges are similar for both treatment groups, but the histogram of pimavanserin group does not look skewed, while that of placebo group is skewed left, which is an indication that pimavanserin is more efficacious than placebo.

Figure 5: Empirical Distribution of Change from Baseline to Week 6 in SAPS-PD (for 173 Completers)



Source: Reviewer´s analysis

3.3.2 Scatterplots of Individual and Global Item Sums of SAPS-PD at Week 6 (Figure 5)

SAPS-PD is a new scale for evaluating psychosis (hallucination and delusion) that is adopted from SAPS-H+D. SASP-PD consists of 9 items: 5 Hallucination domain scores (4 individual items and one global item) and 4 Delusion domain scores (3 individual items and one global item)). In the original SAPS[8] (consisting of 4 domains of Hallucination, Delusion, Bizarre Behavior and Positive Formal Thought Disorder), it is said that the global item scores additionally cover other positive symptoms than the individual items of the respective domain capture. Therefore, the associative relationship between the sum of 7 individual items and the sum of 2 global items of SAPS-PD may not show a strong associative relationship.

Figure 6 shows scatterplots of the sum of 7 individual item scores versus the sum of 2 global item scores for the 173 completers. Each circle denotes a configuration of the changes from baseline in the paired sums. The number next to each circle denotes the number of patients with the given configuration; a larger circle indicates more patients. In both treatment groups, there seems to be positive correlation, but the global item scores were not highly correlated with the sum of the 7 individual item scores. Evidence of pimavanserin efficacy is visualized in the plots.

[8] Scale for the Assessment of Positive Symptoms (SAPS) by Nancy C. Andreasen, 1984

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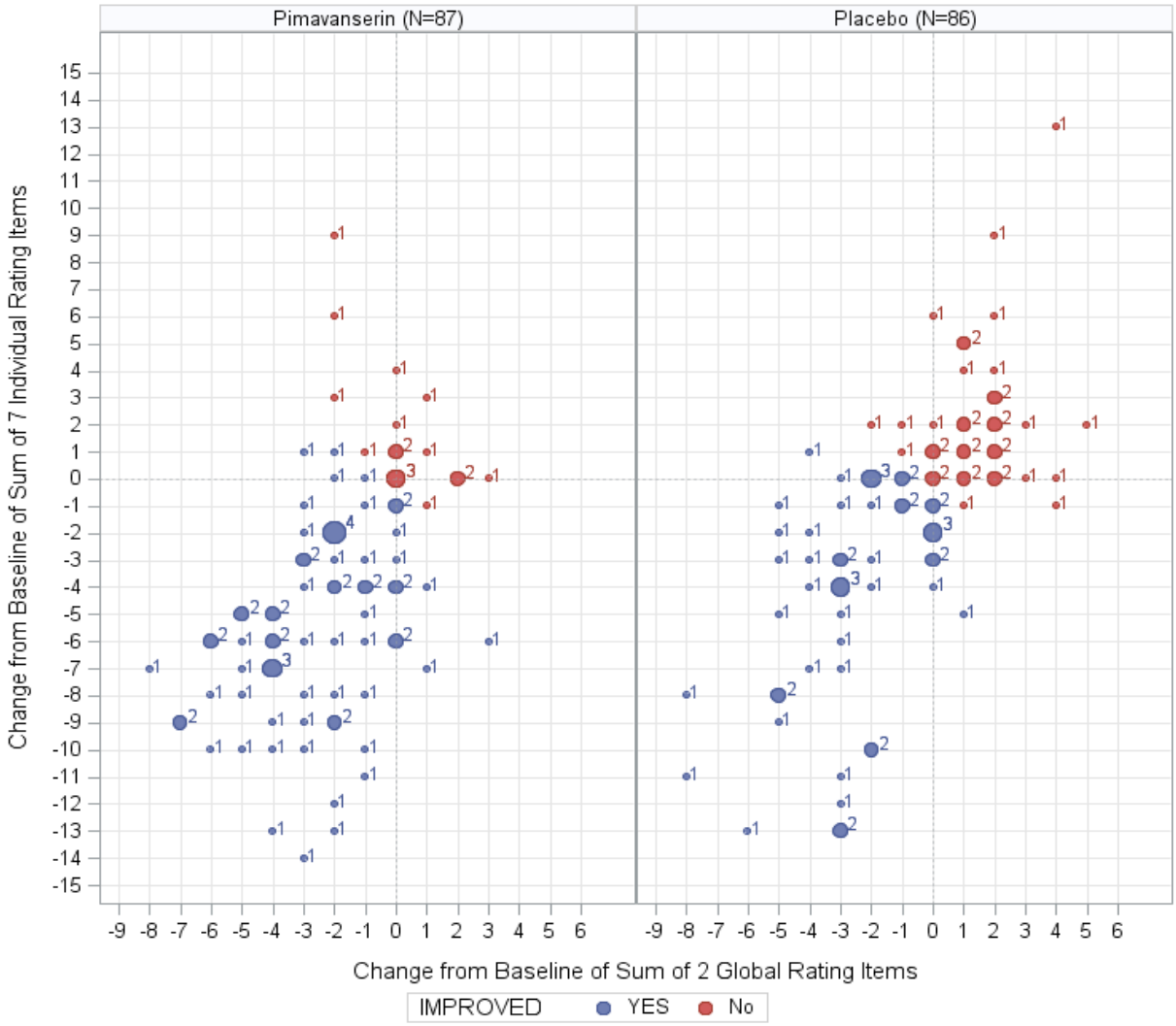
"Improved patients (those with negative changes from baseline in the SAPS-PD (the sum of all 9 items)" are colored in blue, and "non-improved patients" in red. It appears that pimavanserin had a better efficacy than placebo both in *improved patients* and *non-improved patients*. Clearly, a much higher proportion of patients improved in pimavanserin than in placebo, but some placebo patients had a great improvement that is as good as pimavanserin patients who improved greatly.

Figure 6: Scatterplots of Individual versus Global Sums of SAPS-PD by Treatment at Week 6 (Completers, N=173)



Each data point of the figures indicates the pair of change from baseline scores of 2 Global ratings and Sum of 7 Individual ratings. The numbers in the figures indicate the numbers of patients. IMPROVED means the change from baseline in SAPS-PD (9 items) was negative.

Source: Reviewer's analysis

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3.3.3 Exploratory Efficacy Analysis of Sum of 7 Individual Items of SAPS-PD (Table 16)

The SAP-PD (9-item SAPS) consists of 7 individual items measuring hallucination and delusion symptoms and 2 (Hallucination and Delusion) global items. This reviewer analyzed the sum of 7 individual items of SAPS-PD, using the same analysis method as in the primary analysis; the difference from placebo in the LS mean estimate was -2.01 with a p value of 0.0022. The difference from placebo in the LS mean estimate for the primary endpoint (sum of the 9 items) was -3.06.

Table 16: Pimavanserin Efficacy for Sum of 7 individual item scores of SAPS-PD

PIM 40 mg vs Placebo at Week 6/Change from baseline score in Supportive endpoints				
LSM Estimate (SE)		Difference from Placebo in LSM Estimate (SE)	95% Confidence Interval	P value
Pimavanserin	Placebo			
-3.80 (0.45)	-1.79 (0.46)	-2.01 (0.64)	(-3.28, -0.74)	0.0022

Note: The analysis method was the same as the primary efficacy analysis (MMRM). SE denotes standard error.
Source: Reviewer's analysis

A similar analysis for the sum of the two global item scores also shows a statistical significance with a p value of 0.0117. The difference from placebo in LS mean estimate was -0.93. This analysis is provided by the sponsor in their supportive analyses. The result is displayed in Table 10 of this review (under the title of GSAPS H+D).

3.3.4 Exploratory Efficacy Analysis of SAPS-PD Hallucination and Delusion Domains

Table 17 and Table 18 display the MMRM analysis result for each of the domains (Delusion and Hallucination) of SAPS-PD for the primary analysis set (N=185).

The scatter plots shown in Figure 7 and Figure 8 provide a visualized positive correlation for 173 completers between the sum of individual scores and the global score for each domain. By construct, the global score measures patient overall delusion or hallucination severity that may not be covered by the individual scores. A visual inspection of the plots may give an impression that in delusion and hallucination, respectively, the pimavanserin efficacy came more from patients who did not improve (indicated by circles in red) rather than from those who improved (indicated by circles in blue). Interestingly, many patients had no improvement or worsening outcome at Week 6 (a score of zero in change from baseline in SAPS-PD) in each of the domains, which was not seen in the figure for the SAPS-PD total score (Figure 6).

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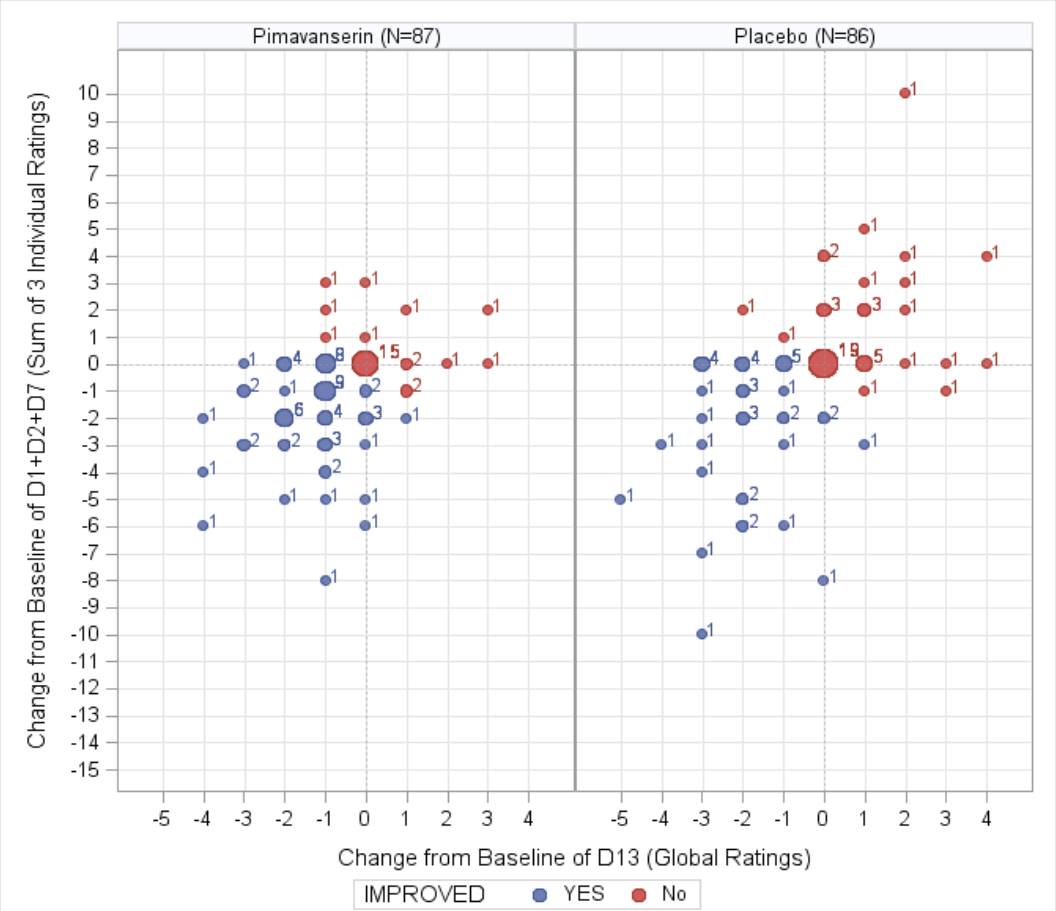
3.3.4.1 Delusion Domain (Sum of 4 Delusion items of SAPS-PD) (Table 17, Figure 7)

Table 17: Delusion Domain of SAPS-PD – Exploratory Efficacy Analysis (mITT Population, N=185)

Pimavanserin vs Placebo at Week 6 (Change from baseline score of SAPS-PD Delusion Domain score)				
LS Mean Estimate (SE)		Difference from Placebo in LS Mean Estimate (SE)	95% Confidence Interval	P value
Pimavanserin	Placebo			
-1.95 (0.32)	-1.01 (0.32)	-0.94 (0.45)	(-1.83, -0.04)	0.0403

Note: The analysis method was the same as the primary efficacy analysis (MMRM). SE denotes standard error.
Source: Reviewer's analysis

Figure 7: Scatterplots of Individual Item Score Sum versus Global Score for Delusion Domain of SAPS-PD by Treatment at Week 6 (Completers, N=173)



Each data point of the figures indicates the pair of change from baseline scores in the global rating and the sum of 3 individual ratings. The numbers in the figures indicate the numbers of patients. IMPROVED means change from baseline in sum of all 4 delusion items was negative.

Source: Reviewer's analysis

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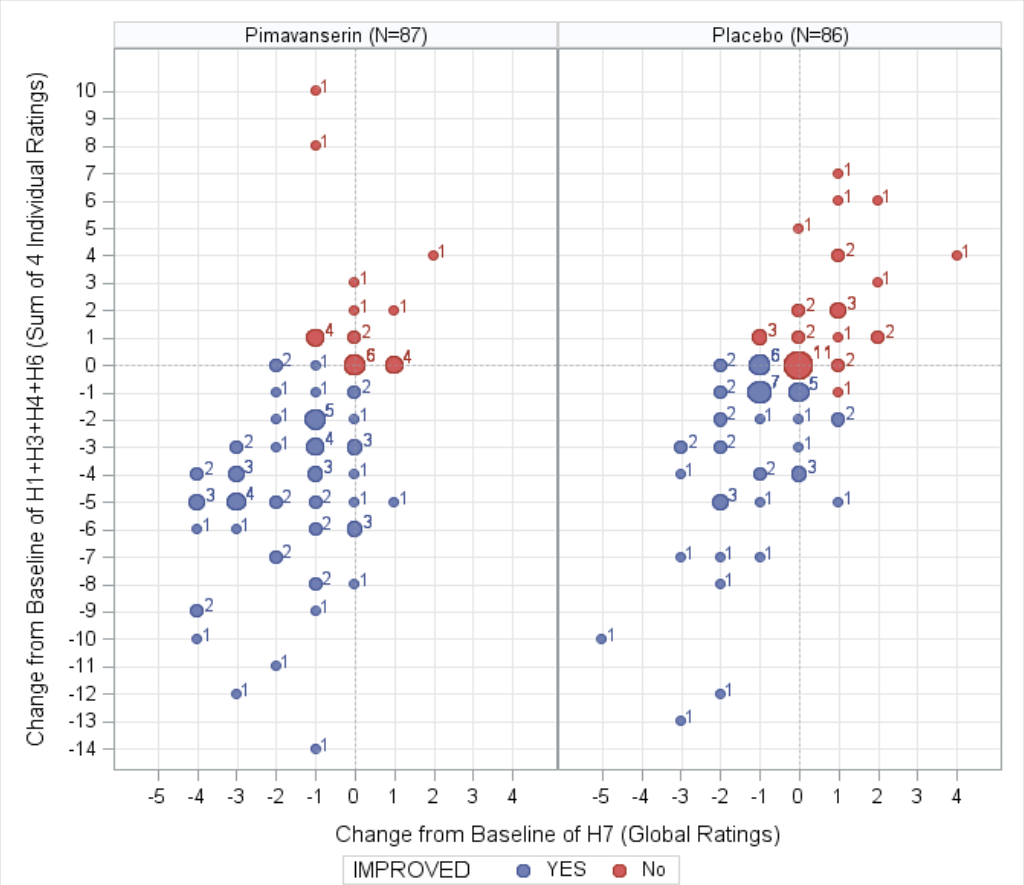
3.3.4.2 Hallucination Domain (Sum of 5 items of SAPS-PD) (Table 18, Figure 8)

Table 18: Hallucination Domain of SAPS-PD – Exploratory Efficacy Analysis (mITT Population, N=185)

PIM 40 mg vs Placebo at Week 6 (Change from baseline score of SAPS-PD Hallucination Domain score)				
LS Mean Estimate (SE)		Difference from Placebo in LS Mean Estimate (SE)	95% Confidence Interval	P value
Pimavanserin	Placebo			
-3.81 (0.46)	-1.80 (0.46)	-2.01 (0.65)	(-3.30, -0.72)	0.0024

Note: The analysis method was the same as the primary efficacy analysis (MMRM). SE denotes standard error.
Source: Reviewer's analysis

Figure 8: Scatterplots of Individual Item Score Sum versus Global Score for Hallucination Domain of SAPS-PD by Treatment at Week 6 (Completers, N=173)



Each data point of the figures indicates the pair of change from baseline scores in global rating and sum of 4 individual ratings. The numbers in the figures indicate the numbers of patients. IMPROVED means change from baseline in sum of all 5 hallucination items was negative.

Source: Reviewer's analysis

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3.4 Evaluation of Safety

Safety evaluation was not conducted in this review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region (Table 19)

The sponsor included subgroup summary statistics for gender, race (white or non-white), age group (sponsor specified thresholds of 65 and 75 years of age). The sponsor concluded that their subgroup analyses show a consistent trend for superiority of pimavanserin over placebo regardless of subject age, gender (page 63 of the CSR). This reviewer has no objection to the sponsor's conclusion. As this study was conducted in US and Canada with only 5 patients from Canada, a subgroup analysis by region/country is not performed.

For each treatment group, the summary statistics of observed scores and change from baseline scores of SAPS-PD were included in the CSR (Tables 14.2.3.14 - 14.2.3.16). For a reference purpose provided below is a table of selected summary statistics of the sponsor's subgroups (gender, race and age group) from the sponsor's CSR tables.

Table 19: Sponsor Subgroup Analysis (Gender, Race, Country and Age Group)

Observed (Raw) data Primary Endpoint (SAPS-PD)		Mean Change from Baseline at Week 6 (SD)				
		Pimavanserin	#Subjects	Placebo	#Subjects	Total Number of Subjects at Week 6
Primary Analysis Set mITT population (N=185)		-6.3 (5.88)	87	-2.7 (7.03)	86	173
Gender	Male	-7.3 (5.54)	56	-3.0 (6.82)	50	106
	Female	-4.7 (6.20)	31	-2.2 (7.38)	36	67
Race	White	-6.0 (5.81)	82	-2.3 (6.83)	81	163
	Non-white	-11.4 (5.18)	5	-7.8 (9.04)	5	10
Age Group	< 65 years of age	-5.0 (4.60)	10	-5.4 (5.14)	11	21
	≥ 65 and < 75 years of age	-6.5 (6.14)	47	-2.3 (6.77)	47	94
	> 75 years of age	-6.6 (5.96)	30	-5.4 (8.00)	28	58

SD denotes standard deviation.
Source: Tables 14.2.3.14 - 14.2.3.16 of the CSR

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4.2 Other Special/Subgroup Populations

4.2.1 MMSE (Mini Mental State Exam)

The sponsor conducted a subgroup analysis based on MMSE baseline score. The result is provided in the following table.

Table 20: Sponsor Subgroup Analysis by MMSE baseline score

Observed (Raw) data Primary Endpoint (SAPS-PD)		Mean Change from Baseline at Week 6 (SD)				
		Pimavanserin	#Subjects	Placebo	#Subjects	Total Number of Subjects at Week 6
Primary Analysis Set mITT population (N=185)		-6.3 (5.88)	87	-2.7 (7.03)	86	173
MMSE	≥25	-6.0 (5.78)	60	-3.3 (7.38)	67	127
	<25	-7.1 (6.14)	27	-0.5 (5.18)	19	46

Source: Table 14.2.3.17 of the CSR

4.2.2 Subgroup by Delusion Baseline Severity (Figure 9, Table 21, Table 22)

As seen in Figure 2, at baseline, 114 patients had a score in SAPS-PD Delusion in the lower range (0 – 5 points), which may suggest that those patients were enrolled in the study for hallucination but not for delusion.

This reviewer created a subgroup based on delusion severity at baseline using SAPS-PD Delusion Domain score. The criteria this reviewer used to categorize patients with a delusion baseline status of 'severe' or 'less severe' are as follows: Those who had at least 3 points both in the delusion global score and the sum of delusion non-global scores are in a status of "severe in delusion." A patient who did not have at least 3 points both in the global score and the sum of non-global scores in SAPS-PD Delusion Domain at baseline may be categorized as "less severe in delusion."

Figure 9 visualizes an improvement from baseline at Week 6 in SAPS-PD Delusion Domain score. It plots individual pairs of baseline and Week 6 scores of SAPS-PD Delusion Domain. Patients who are located above the 45 degree line drawn in the figure were those who improved at Week 6 endpoint (Baseline score > Week 6 score). Pairs plotted in red indicate patients who had relatively severer SAPS-PD Delusion score at baseline, and those in blue indicate patients who had less severe SAPS-PD Delusion score at baseline.

Table 21 shows mean baseline score and raw mean change score from baseline of SAPS-PD Delusion Domain score (ranging from 0 – 20 points with 4 item scores) by treatment group for overall patients (mITT population), and for severity subgroups. It appears that patients with less severe delusion at baseline contributed somewhat more to the treatment effect with respect to this domain.

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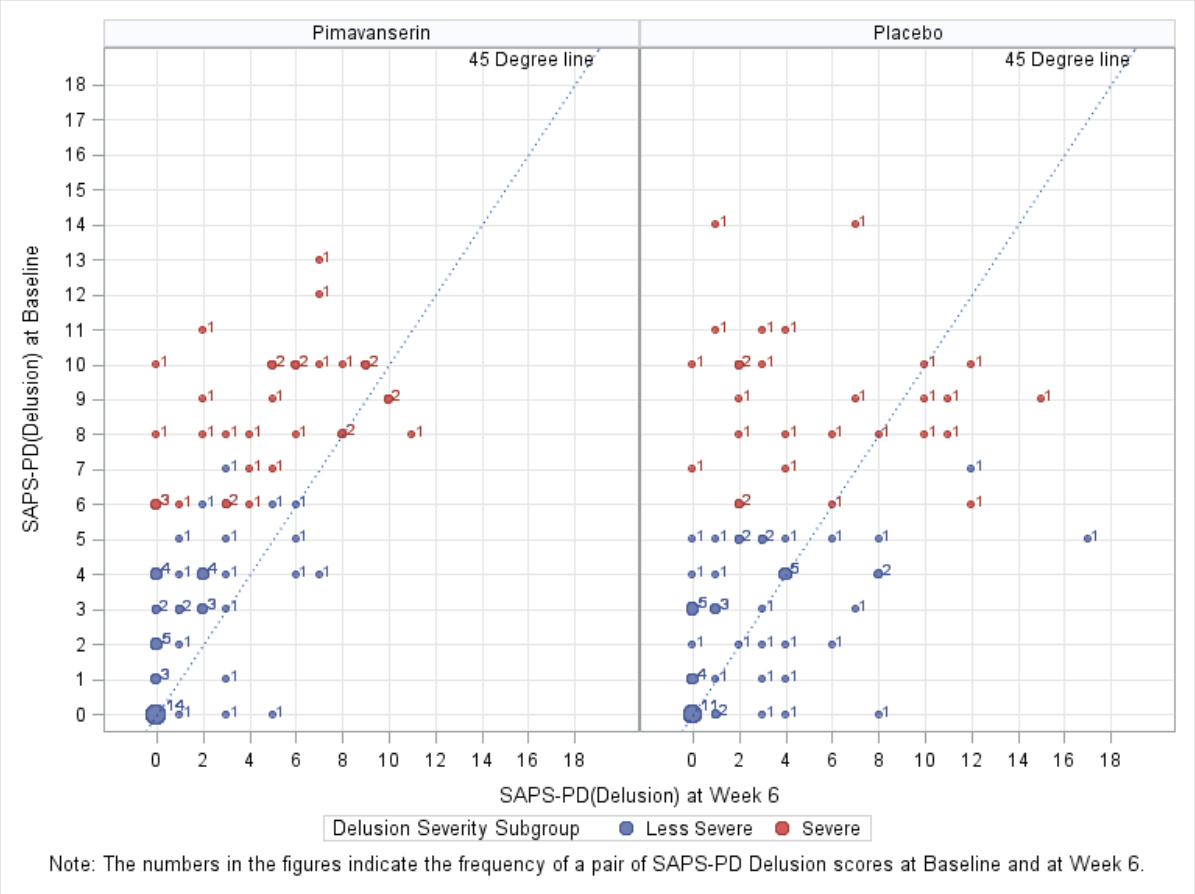
Figure 9: Mapping individual patient improvements on SAPS-PD Delusion Domain Score from Baseline to Week 6 by Delusion Severity (Completers, N=173)



Source: Reviewer's analysis

Table 21: Mean Baseline Sore and Raw Mean Change Score from Baseline of SAPS-PD Delusion Domain (Completers, N=173)

SAPS-PD Delusion	Pimavanserin			Placebo			Pimavanserin Mean Difference from Placebo in Change from Baseline
	N	Mean (SD)		N	Mean (SD)		
		Baseline	Change from Baseline		Baseline	Change from Baseline	
Overall	87	4.71 (3.60)	-2.01 (2.70)	86	4.56 (3.70)	-1.01 (4.09)	-1.00
Severe	31	8.71 (1.79)	-3.65 (3.01)	27	9.11 (2.04)	-3.37 (5.11)	-0.28
Less Severe	56	2.50 (2.11)	-1.11 (2.02)	59	2.47 (2.01)	0.07 (3.01)	-1.18
Removing patients who had a score of zero both at baseline and Week 6	42	3.33 (1.78)	-1.48 (2.22)	48	3.04 (1.80)	0.08 (3.34)	-1.56

Source: Reviewer's analysis

Table 22 shows the MMRM analysis result for the delusion subgroup analysis. This analysis is *post hoc* exploratory, and as such has a limitation in the generalizability of the result. The analysis may be underpowered and the inferential result should be carefully interpreted.

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However, the result seems to suggest that the subgroup of patients of less severe in delusion may have had more of a share in efficacy evidence shown in the overall delusion analysis based on the combined subgroups of severe and less severe patients. The magnitude of difference may not be clinically relevant for the indication of hallucination and delusion.

Table 22: Exploratory MMRM Analysis - Change Score from Baseline of SAPS-PD Delusion Domain (mITT Population, N=185)

Pimavanserin vs Placebo at Week 6 (Change from baseline score of SAPS-PD Delusion total score)				
Baseline Severity in SAPS-PD	LS Mean Estimate (SE)		Difference from Placebo in LS Mean Estimate (SE)	95% Confidence Interval
	Pimavanserin	Placebo		
Overall	-1.95 (0.32)	-1.01 (0.32)	-0.94 (0.45)	(-1.83, -0.04)
Severe	-3.83 (0.68)	-3.07 (0.72)	-0.76 (0.99)	(-2.74,1.22)
Less Severe	-1.00 (0.33)	0.10 (0.32)	-1.10 (0.46)	(-2.02,-0.19)

Note: The analysis method was MMRM with the same model as in the primary efficacy. SE denotes standard error.
Source: Reviewer's analysis

Note on Hallucination Severity Subgroup

A subgroup based on hallucination severity at baseline may not be meaningful. As shown in Figure 2, there were only a small number of patients in the mITT analysis set who had a considerably low (less than 4, say) baseline score of SAPS-PD Hallucination Domain.

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5 SUMMARY AND CONCLUSIONS

The single pivotal study (Study ACP-103-020) has established statistical evidence that pimavanserin 40 mg is efficacious as a treatment of Parkinson's Disease Psychosis (PDP) and does not worsen Parkinson's Disease status. No major issue that may affect the main statistical conclusions was found.

The primary efficacy endpoint was the change from baseline to Week 6 in score of a novel instrument SAPS-PD (Scale for the Assessment of Positive Symptoms for Parkinson's Disease). The SAPS-PD assesses Parkinson's Disease Psychosis (PDP) for Hallucination and Delusion symptoms. Based on SAPS-PD, pimavanserin 40 mg has been shown to be more efficacious than placebo for an acute treatment of PDP.

The key secondary endpoint was the change from baseline to Week 6 in UPDRS Parts II and III Combined score, the respective part of which assesses activities in daily life and motor functions of Parkinson's Disease patients. A non-inferiority of pimavanserin to placebo has been concluded based on a non-inferiority test with a non-inferiority margin of 5 points. To be specific, pimavanserin ruled out >2.72 points worse than placebo based on the 95% confidence interval of the treatment effect relative to placebo.

A Psychopharmacologic Drugs Advisory Committee (PDAC) meeting will be held on March 29, 2016. One of the questions addressed to the PDAC may likely be about whether the treatment effect observed in this study, 3 points in SAPS-PD as an observed effect (a difference of pimavanserin from placebo in least square mean estimate), is clinically meaningful. This review may provide information on clinical effectiveness of the candidate new treatment.

The following findings from exploratory and subgroup analyses, and other analyses, may help understand the clinical meaningfulness of the observed treatment effect.

1. Many study patients seem to have had relatively mild delusion symptoms at baseline. In addition, a number of patients had a score of zero for delusion in SAPS-PD (33 patients, 16.6% of 199 randomized patients) and in NPI-H+D (58 patients, 31.4% if 185 mITT patients). (See Figure 1 and Figure 2.)
2. Exploratory SAPS-PD subscale analysis: This reviewer noted that the maximum total score for the Hallucination domain is larger than that for the Delusion domain (25 vs 20). Despite that, when each subscale (Hallucination and Delusion) is evaluated on the mITT patients, the treatment effect for primary efficacy seems to have a relatively larger share in Hallucination than in Delusion (-2.01 vs -0.94 in Difference from Placebo in LS mean estimates. See Table 17 and Table 18). However, the clinical relevancy may be discussed by the clinical review team.
3. Exploratory analysis for severity subgroup (subgroup based on baseline SAPS-PD subscale scores): A subgroup analysis based on baseline severity in delusion may suggest that:

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a. Evidence of efficacy for delusion seems to have been dependent on improvements of patients who were less severe for delusion at baseline (See Table 21 and Table 22). However, the observed differences may not be clinically relevant.
b. Patients of both treatment groups who were severe in delusion at baseline seem to have had a large improvement on average in SAPS-PD Delusion Domain score, but the small difference between pimavanserin and placebo groups appears to be due to placebo response (See Table 22).

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APPENDICES

A1 NPI (A and B)

A Delusions:

If the screening question is confirmed, determine the frequency and severity of the delusions.

Frequency:

1. Occasionally – less than once per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – once or more per day.

Severity:

1. Mild – delusions present but seem harmless and produce little distress in the patient.
2. Moderate – delusions are distressing and disruptive.
3. Marked – delusions are very disruptive and are a major source of behavioral disruption. [If PRN medications are prescribed, their use signals that the delusions are of marked severity.]

B Hallucinations:

If the screening question is confirmed, determine the frequency and severity of the hallucinations.

Frequency:

1. Occasionally – less than once per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – once or more per day.

Severity:

1. Mild – hallucinations are present but harmless and cause little distress for the patient.
2. Moderate – hallucinations are distressing and are disruptive to the patient.
3. Marked – hallucinations are very disruptive and are a major source of behavioral disturbance. PRN medications may be required to control them.

A2 SAPS-PD

The SAPS-PD is a 9 item instrument derived from the 20 item SAPS. The SAPS was developed as a clinician reported outcome through a semi-structure interview with a patient. The entire SAP was administered to each patient and the 9 items to create the SAPS-PD was pulled out to form a score. The 9 items are:

- H1 Auditory Hallucinations
- H3 Voices Conversing
- H4 Somatic or Tactile Hallucinations
- H6 Visual Hallucinations
- H7 Global Rating of Severity of Hallucinations
- D1 Persecutory Delusions
- D2 Delusions of Jealousy
- D7 Ideas and Delusions of Reference
- D13 Global Rating of Severity of Delusions

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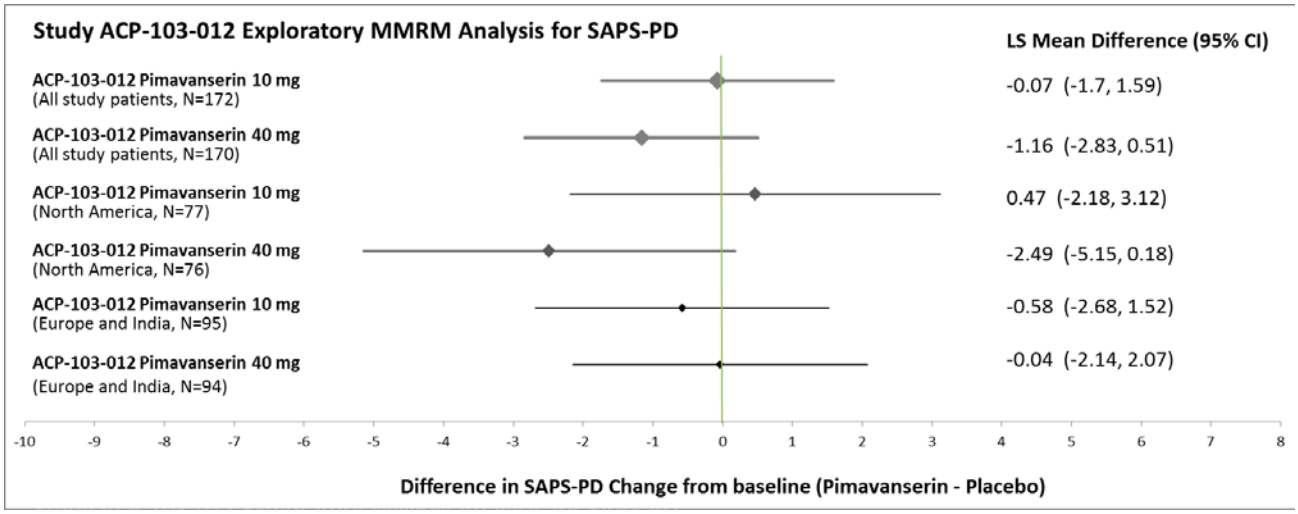
The range of scores for the SAPS-PD is 0-45 with a high score representing higher severity of psychosis. The responses were on a 0 through 5 NRS, with 0=none; 1=questionable, 2=mild, 3=moderate, 4=marked, and 5=severe. The SAPS was given to patients at baseline, Week 2, Week 4 and Week 6.

A3 Study ACP-103-012

Study ACP-103-012 investigated two pimavanserin doses: 10 mg and 40 mg. The following figure provides forest plots of pimavanserin's estimated difference from placebo (and the 95% confidence interval) in SAPS-PD change score from baseline obtained from the exploratory MMRM analysis (observed data only). The plots include results from subgroup analyses based on North America (US and Canada) and Outside of North America (Europe and India).

Figure 10: Study ACP-103-012 MMRM analysis results for SAPS-PD Change from Baseline at Week 6



Note: MMRM analysis was based on Observed data only (no imputation of missing data).

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/s/

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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 Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 207-318
Drug Name:	ACP-103
Indication:	Treatment of [redacted] (b) (4) Parkinson's disease psychosis (PDP)
Applicant:	Sponsor: ACADIA Pharmaceuticals, Inc. 3911 Sorrento Valley Boulevard San Diego, CA 92121-1402 Testing Facility: [redacted] (b) (4)
Documents Reviewed:	Electronic submission: Submitted on September 17 2015 Electronic data: Submitted on September 17 2015
Review Priority:	Standard
Biometrics Division:	Division of Biometrics - VI
Statistical Reviewer:	Hepei Chen
Concurring Reviewer:	Karl K. Lin, Ph.D.
Medical Division:	Division of Psychiatry Products
Reviewing Pharmacologist:	Amy Avila, Ph.D.
Date Submitted:	November 6, 2015
Keywords:	Carcinogenicity, Dose response

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1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were to evaluate the potential carcinogenic effects of ACP-103 when administered orally by gavage to rats/mice for 24 months. Results of this review have been discussed with the reviewing pharmacologist Dr. Avila.

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

2. Rat Study

Two separate experiments, one in male and one in female rats, were conducted. As indicated in Table 1, in each of these two experiments there were three treated groups and two identical vehicle control groups. Three hundred male and 300 female Crl:CD(SD) rats were assigned randomly to the treated and control groups in equal size of 60 rats per group. The dose levels for treated groups were 3, 10, and 30 mg/kg/day for males and 5, 15, and 50 mg/kg/day for females, respectively. In this review these dose groups were referred to as the low, mid, and high dose groups, respectively. The rats in the two identical vehicle control groups remained untreated and received the vehicle (deionized water) in the same manner as the treated groups. These vehicle control groups were referred to as the vehicle control1 and the vehicle control 2.

All treated animals were planned to be dosed for a minimum of 728 consecutive days (104 weeks), while the vehicle control group 2 males were dosed for a minimum of 723 non-consecutive days (103 weeks). However, the high dose group males were dosed for 674 consecutive days (96 weeks) due to increased mortality rates. The dosing of the group was stopped but it was allowed to continue. When the group size reached 15 animals, all surviving males in the high dose group were euthanized on study day 708 (Week 101). All surviving rats, both males and females, in the rest groups were euthanized during study Week 104.

Table 1. Experimental Design in Mouse Study

		Dose Level (mg/kg/day)		Number of Animals	
Group	Dose Level	Males	Females	Males	Females
1	Vehicle Control 1	0	0	60	60
2	Vehicle Control 2	0	0	60	60
3	Low	3	5	60	60
4	Mid	10	15	60	60
5	High	30	50	60	60

All animals were observed twice daily for mortality and morbidity. Clinical observations were recorded daily and detailed physical examinations, and palpable masses observations were recorded weekly. Body weights and food consumption were recorded weekly through study week 12 and biweekly thereafter. Blood samples for the preparation of blood smears were collected from all animals euthanized *in extremis* and from all animals at the scheduled necropsies (study weeks 101 and 104). Complete necropsies were conducted on all animals, and selected tissues were examined microscopically from all animals.

2.1. Sponsor's analyses

2.1.1. Survival analysis

The sponsor performed Kaplan-Meier estimates of group survival rates, by sex, and showed them graphically in its report. The generalized Wilcoxon test for survival was used to compare the homogeneity of survival rates across the groups at the 0.05 significance level. If the survival rates were significantly different, the generalized Wilcoxon test was used to make pairwise comparisons of each treated group with the control groups. A log-rank dose response trend test of survival rates was also performed including the control group and the active treatment groups. The trend test and pairwise comparisons were conducted with each control group individually and with the pooled control groups. The two control groups were also compared using the generalized Wilcoxon test. Survival times in which the status of the animal's death was classified as an accidental death, planned interim sacrifice or terminal sacrifice, were considered as censored values for the purpose of the Kaplan-Meier estimates and survival rate analyses.

Sponsor's findings:

In the sponsor's analysis, the numbers of rats surviving to their terminal necropsy were 18, 15, 18, 21, and 15 for males, and 19, 20, 21, 23, and 25 for females in the vehicle control 1, vehicle control 2, low, mid, and high dose groups, respectively. The sponsor's analysis showed no significant trend or increase/decrease in mortality across the combined vehicle control group and the three treated groups due to the test article for males or females.

2.1.2. Tumor data analysis

In the sponsor's analysis, the incidence of tumors was analyzed by Peto's mortality-prevalence method or death rate method, without continuity correction for each sex, incorporating the context (incidental or fatal) in which tumors were observed. The following fixed intervals were used for incidental tumor analyses: weeks 0-52, 53-78, 79-92, 93-end of study, and scheduled terminal sacrifice. Tumors classified as mortality-independent, such as, but not limited to, those of the mammary gland and skin, were analyzed with Peto's onset rate method incorporating the day of detection. For each sex, tumors that were detected, either by palpation or necropsy, after the first animal of that sex was terminally sacrificed were considered incidental and included in the scheduled terminal sacrifice interval for analyses.

For organs in which an exhaustive examination of animals was planned, the incidence of each tumor type was analyzed with a 1-sided trend test using the positive dose response. In addition, pairwise comparisons with the control groups were conducted for each active treatment group. All comparisons were conducted for each control group individually as well as for the pooled control groups. In addition, a two-sided comparison of control group 1 vs. control group 2 was conducted for all tumors. An exact permutation test was conducted for analyses of a tumor type with low tumor incidences across all treatment groups.

Adjustment for multiple testing:

The sponsor's analysis evaluated the positive trend test at the 0.005 and 0.025 (one-tailed) significance levels for common and rare tumors, respectively, and evaluated the high-dose to the control group comparisons at the 0.01 and 0.05 (one-tailed) significance levels for common and

rare tumors respectively as recommended in the FDA draft guidance for statistical design and analysis carcinogenicity studies. (2001). A rare tumor was defined as one in which the historical spontaneous tumor rate was less than 1%.

Sponsor's findings:

No significant findings were indicated in the sponsor's analysis in either sex.

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 using data provided by the sponsor electronically.

For animal carcinogenicity experiments with two identical controls, the FDA guidance for statistical design and analysis of carcinogenicity studies (2001) recommends that the two control groups be combined for statistical analysis of the data. Such a combination of the two identical control groups may increases the power of the test. Following the guidance recommendation, and the advice of the reviewing pharmacologist, this reviewer analyzed both the mortality and tumor data using the combined control group.

It was noticed that in this rat study, the males in the high dose group were dosed up to Week 96, and stayed in the study undosed until they were terminal sacrificed at week 101 while all males in the rest of groups were dosed up to Week 104. The five week period of stopping dosing to those animals was not taken into consideration in the determination of a weighted dose to be used for the group in the statistical analysis, because the weighted high dose level would be 27.7, which is only slightly different from the targeted dose level of 30.

2.2.1. Survival analysis

In the reviewer's analysis, the survival distributions of rats in all five groups, including the combined vehicle control group, and the three treated groups, were estimated using the Kaplan-Meier product limit method. For the combined vehicle control, low, mid, and high dose groups, the dose response relationship 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, the results of the tests for dose response relationship, and homogeneity of survivals for the combined vehicle control, low, mid, and high dose groups are given in Tables 1A and 1B in the appendix for male and female rats, respectively.

Reviewer's findings:

In the reviewer's analysis, the numbers of rats surviving to their terminal necropsy were 18, 15, 18, 21, and 15 for male, and 19, 20, 21, 23, and 25 for females in the vehicle control 1, vehicle control 2, low, mid, and high dose groups, respectively. No statistically significant dose response relationship or pairwise group comparisons in mortality were noted in both male and female rats.

2.2.2. Tumor data analysis

In the reviewer's analysis, the tumor data were analyzed for dose response relationships across the combined vehicle control and treated groups, and pairwise comparisons of the combined vehicle control with each of the treated groups. Both the dose response relationship tests and pairwise comparison tests were performed using the Poly-k tests described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993).

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

$$R^*_i = \sum w_{ij}$$

where w_{ij} is the weight for the j-th animal in the i-th treatment group, and the sum is over all animals in the group.

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

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

$w_{ij} = (t_{ij} / t_{sacr})^k$ to animals dying without the tumor

where t_{ij} is the time of death of the j-th animal in the i-th treatment group, and t_{sacr} is the planned (or intended) time of terminal sacrifice. The above formulas imply that animals living up to the end of the planned terminal sacrifice date will also be assigned with $w_{ij} = 1$ since $t_{ij} = t_{sacr}$.

Certain treatment groups of a study or the entire study may be terminated earlier than the planned (or intended) time of terminal sacrifice due to excessive mortalities. However, based on the principle of the Intention-to-treat (ITT) analysis in randomized trials, the t_{sacr} should not be affected by the unplanned early terminations. The t_{sacr} should always be equal to the planned (or intended) time of terminal sacrifice.

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 mouse and mouse studies, a value of k=3 is suggested in the literature (Portier, et al. (1986), Moon et al. (2003), Gebregziabher and Hoel (2009)). Hence, this reviewer used k=3 for the analysis of this data.

The p-values were calculated using the exact permutation method with used dose levels (0, 3, 10, and 30 for male rats, and 0, 5, 15, and 50 for female rats) as scores for the combined vehicle control, low, mid, and high dose groups, respectively. The tumor rates and the p-values of the tested tumor types are listed in Tables 2A and 2B in the appendix for male and female rats, respectively.

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%. 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 for 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 Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-k tests.

A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%, while the common tumor is defined as one with tumor rate greater than or equal to 1%, if the historical spontaneous tumor rate information is available. However, in the case of lack of background information for the common or rare tumor, the number of animals bearing tumors in the control group in the present study is used to determine the common or rare tumor status.

Reviewer's findings:

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

		Vehicle Control		Combined V Cont (C)	Low (L)	Mid (M)	High (H)
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Male							
Skin	#B Fibroma	0/(60)	0/(60)	0/78 (120)	1/39 (60)	3/39 (60)	1/33 (60)
				0.1966	0.3333	0.0351 $	0.2973
Soft Tissue- Abd	#B Lipoma	0/(60)	0/(58)	0/77 (118)	3/39 (60)	0/39 (60)	0/33 (60)
				0.7674	0.0361 $	NC	NC
Systemic Tumors	#M Lymphoma, Malignant	1/(60)	1/(60)	2/79 (120)	2/39 (60)	3/40 (60)	4/34 (60)
				0.0373	0.4023	0.2098	0.0658
Testes	#B Adenoma, Interstitial Cell	1/(60)	1/(60)	2/79 (120)	2/39 (60)	2/39 (60)	2/33 (60)
				0.2230	0.4023	0.4023	0.3379
	#B Adenoma, Interstitial Cell, Multiple	0/(60)	0/(60)	0/78 (120)	0/38 (60)	0/39 (60)	2/33 (60)
				0.0300	NC	NC	0.0865
	#B Adenoma, Interstitial Cell + Multiple	1/(60)	1/(60)	2/79 (120)	2/39 (60)	2/39 (60)	4/33 (60)
				0.0324	0.4023	0.4023	0.0610
	#M Carcinoma, Interstitial Cell	0/(60)	0/(60)	0/78 (120)	1/38 (60)	0/39 (60)	0/33 (60)
				0.3830	0.3276	NC	NC
	#B+M Interstitial Cell	1/(60)	1/(60)	2/79 (120)	3/39 (60)	2/39 (60)	4/33 (60)
				0.0488	0.2014	0.4023	0.0610
Female							
Cervix	#B Granular Cell Tumor, Benign	0/(60)	1/(60)	1/82 (120)	3/42 (60)	2/43 (60)	4/42 (60)
				0.0486	0.1123	0.2719	0.0445
Cervix/Vagina	#B Granular Cell Tumor, Benign	0/(60)	1/(60)	1/82 (120)	3/41 (59)	3/43 (60)	4/42 (60)
				0.0561	0.1074	0.1172	0.0445
Cervix/Vagina/Ovaries	#B Granular Cell Tumor, Benign	0/(60)	1/(60)	1/82 (120)	4/42 (60)	3/43 (60)	4/42 (60)
				0.0797	0.0445	0.1172	0.0445

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
$ = Statistically significant at 0.025 and 0.05 level in rare tumor for tests of dose response relationship and pairwise comparison, respectively;
NC = Not calculable.

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

Based on the criteria of adjustment for multiple testing discussed above, the reviewer's analysis showed that in males, the incidence rate of benign fibroma in skin for animals in mid dose group was significantly higher than incidence in the combined vehicle control group (p = 0.0351), if this tumor was considered as a rare tumor. Also in males, the incidence rate of benign lipoma in Soft Tissue-Abd for animals in the low dose group was significantly higher than incidence in the combined vehicle control group (p = 0.0361). In both of these two cases, because no significant trend was noted, and the high dose group did not indicate any significant increases, these increases in the low and mid-dose group were not considered to be test article-related.

No other observed tumor types were noted to be statistically significant for the dose response relationships or pairwise comparisons in both male and female rats.

3. Mouse Study

Two separate experiments, one in male and one in female mice, were conducted. As indicated in Table 3, in each of these two experiments there were three treated groups and two identical vehicle control groups. Three hundred male and 300 female Crl:CD1® (ICR) mice were assigned randomly to the treated and control groups in equal size of 60 mice per group. The dose levels for treated groups were 3, 7, and 15 mg/kg/day for males and 10, 25, and 50 mg/kg/day for females, respectively. In this review these dose groups were referred to as the low, mid, and high dose groups, respectively. The mice in the two identical vehicle control groups remained untreated and received the vehicle (deionized water) in the same manner as the treated groups.

Table 3. Experimental Design in Mouse Study

		Dose Level (mg/kg/day)		Number of Animals	
Group	Dose Level	Males	Females	Males	Females
1	Vehicle Control 1	0	0	60	60
2	Vehicle Control 2	0	0	60	60
3	Low	3	10	60	60
4	Medium	7	25	60	60
5	High	15	50	60	60

All animals in this study were dosed for a minimum of 734 consecutive days (105 weeks), while the dosing for the male mice in the high dose group was suspended on study day 710 (Week 102) because the number of surviving animals of this group was reaching 20 per group due to the increased mortality rate. All surviving animals including males in the high dose group remained on study until the scheduled necropsy during the study Week 104.

All animals were observed twice daily for mortality or morbidity. Clinical observations were recorded once daily at approximately 1 to 2 hours following dose administration and once daily on nondosing days (Group 5 males during study days 710-733). Detailed physical examinations and palpable masses were recorded approximately weekly. Body weights and food consumption were recorded at least weekly through study week 13 and once every 2 weeks thereafter. All surviving animals were euthanized during study week 104. Blood smears were collected from all animals euthanized *in extremis* or at the scheduled necropsy. Selected tissues were examined microscopically from all toxicology group animals.

3.1. Sponsor's analyses

3.1.1. Survival analysis

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

Sponsor's findings:

In the sponsor's analysis, the numbers of mice surviving to their terminal necropsy were 28, 24, 21, 22, and 18 for males, and 22, 31, 22, 23, and 26 for females in the vehicle control 1, vehicle control 2, low, mid, and high dose groups, respectively.

The sponsor's analysis showed a statistically significant dose-related decreasing trend in survival rates in male mice when compared with the combined vehicle control group and control group 1. In addition, there was a statistically significant decrease in the survival rate when making the pairwise comparison of the high-dose groups with both the combined vehicle control group and control group 1 alone. Among females there were no statistically significant findings with respect to survival rates.

3.1.2. Tumor data analysis

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

Adjustment for multiple testing:

The sponsor used similar test levels of significance as those used for rat study to adjust for multiple testing.

Sponsor's findings:

Sponsor's analysis showed a statistically significant increase in the incidence of systemic hemangiosarcoma when comparing both control group 2 and the low dose group with control group 1 in male mice. There were no other statistically significant tumor findings among male and female mice.

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 of the mouse study, this reviewer used similar methodologies that were used for the analyses of the survival and tumor data of the rat study.

It was noticed that in this mouse study, the males in the high dose group were dosed up to study day 710 (Week 102), and stayed in the study undosed until they were terminal sacrificed at week

105, while all males in the rest of groups were dosed up to Week 105. The three week period of stopping dosing to those animals was not taken into consideration in the determination of a weighted dose to be used for the group in the statistical analysis, because the weighted high dose level would be 14.6, which is only slightly different from the targeted dose level of 15.

3.2.1. Survival analysis

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

Reviewer's findings:

In the reviewer's analysis, the numbers of mice surviving to their terminal necropsy were 28, 24, 21, 22, and 18 for males, and 22, 31, 22, 23, and 26 for females in the vehicle control 1, vehicle control 2, low, mid, and high dose groups, respectively. There were a statistically significant dose response relationship across the combined vehicle control group and the three treated groups was noted (p= 0.0213), and a statistically significant increased mortality in the high dose group when compared to the combined vehicle control group (p=0.0188) in male mice. No significant finding in mortality was noted in female mice.

3.2.2. Tumor data analysis

The p-values were calculated using the exact permutation method with used dose levels as scores (0, 3, 7, and 15 for male rats, and 0, 10, 25, and 50 for female rats) for the combined vehicle control, low, mid, and high dose groups, respectively. The tumor rates and the p-values of the tested tumor types are given in Tables 4A and Table 4B in the appendix, for male and female mice, respectively.

In this mouse study, relatively large differences in tumor bearing animals between the two vehicle control groups were noted for some tumors such as systemic hemangiosarcoma in males (0 and 6 for control 1 and 2, respectively), systemic lymphoma in males (6 and 2 for control 1 and 2, respectively), and liver carcinoma hepatocellular in males (6 and 1 for control 1 and 2, respectively). Following the guidance recommendation indicated above, in the reviewer's analysis the two vehicle control groups were combined, without the separate analysis for each single control group.

Reviewer's findings:

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

Based on the criteria of adjustment for multiple testing discussed above, no dose response relationship or pairwise comparisons were noted in the reviewer's analysis for the mice study.

Table 4. . Summary Table of Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Combined Control Group in Mice

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	10 mg	25 mg	50 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Female Lungs	#B Adenoma, Bronchiolo-Alveolar	3/(60)	3/(60)	6/87 (120)	5/42 (60)	7/41 (60)	6/36 (60)
				0.0479#	0.2623	0.0746	0.0953
Ovaries	#B Cystadenoma	1/(60)	0/(60)	1/86 (120)	2/42 (60)	2/40 (60)	3/34 (59)
				0.0414#	0.2505	0.2364	0.0683
Pituitary	#B Adenoma, Pars Distalis+Intermedia	0/(60)	1/(60)	1/86 (120)	4/42 (60)	2/40 (60)	1/34 (59)
				0.3602	0.0396#	0.2364	0.4881

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
$ = Statistically significant at 0.025 and 0.05 level in rare tumor for tests of dose response relationship and pairwise comparison, respectively;
NA = Not calculable.

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 evaluate the potential carcinogenic effects of ACP-103 when administered orally by gavage to rats for 24 months.

Rat Study:

Two separate experiments, one in male and one in female rats, were conducted. In each of these two experiments there were three treated groups and two identical vehicle control groups. Three hundred male and 300 female Crl:CD(SD) rats were assigned randomly to the treated and control groups in equal size of 60 rats per group. The dose levels for treated groups were 3, 10, and 30 mg/kg/day for males and 5, 15, and 50 mg/kg/day for females, respectively.

All animals were dosed for a minimum of 728 consecutive days (104 weeks), while the vehicle control Group 2 males were dosed for a minimum of 723 non-consecutive days (103 weeks), and the high dose group males were dosed for 674 consecutive days (96 weeks) due to increased mortality rates. Because of the group size reaching 15 animals with an increased mortality rate, all surviving males in the high dose group were euthanized on study day 708 (Week 101); all surviving rats/sex in the rest groups were euthanized during study week 104.

In the reviewer's analysis, the numbers of rats surviving to their terminal necropsy were 18, 15, 18, 21, and 15 for male, and 19, 20, 21, 23, and 25 for females in the vehicle control 1, vehicle control 2, low, mid, and high dose groups, respectively. No statistically significant dose response relationship or pairwise group comparisons in mortality were noted in both male and female rats.

For the tumor data, based on the criteria of adjustment for multiple testing discussed above, the reviewer's analysis showed that in males, the incidence rate of benign fibroma in skin for animals in mid dose group was significantly higher than the incidence in the combined vehicle control group ($p = 0.0351$), if this tumor was considered as a rare tumor. Also in males, the incidence rate of benign lipoma in soft tissue- abd for animals in the low dose group was significantly higher than incidence in the combined vehicle control group ($p = 0.0361$). In both of these two cases, no significant trend was noted, and high dose group did not indicate any significant increases. Because of these reasons, these increases in the low and mid-dose group

was not considered test article-related. No other observed tumor types were noted to be statistically significant for the dose response relationships or pairwise comparisons in both male and female rats.

Mouse Study:

Two separate experiments, one in male and one in female mice, were conducted. In each of these two experiments there were three treated groups and two identical vehicle control groups. Three hundred male and 300 female Crl:CD1® (ICR) mice were assigned randomly to the treated and control groups in equal size of 60 mice per group. The dose levels for treated groups were 3, 7, and 15 mg/kg/day for males and 10, 25, and 50 mg/kg/day for females, respectively.

All animals in this study were dosed for a minimum of 734 consecutive days (105 weeks), while the dosing for the male mice in the high dose group was suspended on study day 710 (Week 102) because the number of surviving animals of this group was reaching 20 per group due to the increased mortality rate. All surviving animals including males in the high dose group remained on study until the scheduled necropsy during the study Week 104.

In the reviewer's analysis, the numbers of mice surviving to their terminal necropsy were 28, 24, 21, 22, and 18 for male, and 22, 31, 22, 23, and 26 for females in the vehicle control 1, vehicle control 2, low, mid, and high dose groups, respectively. There were a statistically significant dose response relationship across the combined vehicle control group and the three treated groups was noted (p= 0.0213), and a statistically significant increased mortality in the high dose group when compared to the combined vehicle control group (p=0.0188) in male mice. No significant finding in mortality was noted in female mice.

For the tumor data, based on the criteria of adjustment for multiple testing discussed above, no dose response relationship or pairwise comparisons were noted in the reviewer's analysis for the mice study.

Hepei Chen.
Mathematical Statistician

Concur: Karl Lin, Ph.D.,
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cc: Archival NDA 207-318

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5. Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

	0 mg/kg/day Control 1		0 mg/kg/day Control 2		3 mg/kg/day Low		10 mg/kg/day Mid		30 mg/kg/day High	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	6	10.00	6	10.00	4	6.67	7	11.67	11	18.33
53 - 78	5	18.33	13	31.67	11	25.00	13	33.33	10	35.00
79 - 91	12	38.33	11	50.00	13	46.67	7	45.00	14	58.33
92 - 105	19	70.00	15	75.00	12	66.67	12	65.00	10	75.00
Accidental Death					2	3.33				
Terminal sacrifice	18	30.00	15	25.00	18	30.00	21	35.00	15	25.00
Total	60		60		60		60		60	

Test	All Dose Groups	Low vs Vehicle Control 1+2	Mid vs Vehicle Control 1+2	High vs Vehicle Control 1+2
Dose-Response (Likelihood Ratio)	0.1464	0.6943	0.4413	0.1920
Homogeneity (Log-Rank)	0.2495	0.6919	0.4393	0.1802

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 1B: Intercurrent Mortality Rate in Female Rats

	0 mg/kg/day Control 1		0 mg/kg/day Control 2		5 mg/kg/day Low		15 mg/kg/day Mid		50 mg/kg/day High	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	2	3.33	1	1.67	3	5.00	1	1.67	3	5.00
53 - 78	16	30.00	11	20.00	11	23.33	12	21.67	13	26.67
79 - 91	11	48.33	19	51.67	11	41.67	13	43.33	7	38.33
92 - 105	12	68.33	9	66.67	14	65.00	10	60.00	11	56.67
Accidental Death							1	1.67	1	1.67
Terminal sacrifice	19	31.67	20	33.33	21	35.00	23	38.33	25	41.67
Total	60		60		60		60		60	

Test	All Dose Groups	Low vs Vehicle Control 1+2	Mid vs Vehicle Control 1+2	High vs Vehicle Control 1+2
Dose-Response (Likelihood Ratio)	0.2706	0.7631	0.3739	0.2924
Homogeneity (Log-Rank)	0.6703	0.7611	0.3726	0.2930

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	3 mg	10 mg	30 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Adipose Tissue	#B Lipoma	0/(60)	0/(60)	0/78 (120)	1/38 (60)	0/39 (60)	0/33 (60)
				0.3830	0.3276	NC	NC
Adrenal Cortex	#B Adenoma	0/(60)	0/(60)	0/78 (120)	1/38 (60)	0/39 (60)	0/33 (60)
				0.3830	0.3276	NC	NC
	#B Adenoma/#M Carcinoma	0/(60)	0/(60)	0/78 (120)	2/38 (60)	0/39 (60)	0/33 (60)
				0.6205	0.1054	NC	NC
	#M Carcinoma	0/(60)	0/(60)	0/78 (120)	1/38 (60)	0/39 (60)	0/33 (60)
				0.3830	0.3276	NC	NC
Adrenal Medulla	#B Pheochromocytoma, Benign	3/(60)	2/(60)	5/79 (120)	3/39 (60)	1/39 (59)	1/33 (60)
				0.7953	0.5282	0.6489	0.5729
	#B Pheochromocytoma, Benign, Multiple	0/(60)	0/(60)	0/78 (120)	1/39 (60)	0/39 (59)	0/33 (60)
				0.3810	0.3333	NC	NC
	#B Pheochromocytoma, Benign/ Multiple	3/(60)	2/(60)	5/79 (120)	4/39 (60)	1/39 (59)	1/33 (60)
				0.8332	0.3388	0.6489	0.5729
	#M Pheochromocytoma, Malignant	0/(60)	0/(60)	0/78 (120)	1/38 (60)	0/39 (59)	0/33 (60)
				0.3830	0.3276	NC	NC
	#B+M Pheochromocytoma	3/(60)	2/(60)	5/79 (120)	5/39 (60)	1/39 (59)	1/33 (60)
				0.8625	0.1981	0.6489	0.5729
Bone	#B Osteoma	0/(60)	0/(60)	0/78 (120)	0/38 (60)	1/40 (60)	0/33 (60)
				0.3862	NC	0.3390	NC
	#M Carcinoma, Squamous Cell_unknown	0/(60)	0/(60)	0/78 (120)	1/38 (60)	0/39 (60)	0/33 (60)
				0.3830	0.3276	NC	NC
	#M Osteosarcoma	0/(60)	1/(60)	1/78 (120)	0/38 (60)	1/40 (60)	0/33 (60)
				0.4489	0.3276	0.5650	0.2973
Brain	#B Granular Cell Tumor, Benign	1/(60)	0/(60)	1/78 (120)	0/38 (60)	0/39 (60)	0/33 (60)
				0.5851	0.3276	0.3333	0.2973
	#M Astrocytoma, Malignant	1/(60)	2/(60)	3/79 (120)	0/38 (60)	0/39 (60)	1/33 (60)
				0.4967	0.6960	0.7037	0.3379
Cecum	#B Fibroma	1/(58)	0/(57)	1/75 (115)	0/38 (58)	0/39 (60)	0/32 (58)
				0.5924	0.3363	0.3421	0.2991
Gingiva	#M Carcinoma, Squamous Cell	1/(60)	0/(60)	1/78 (120)	0/38 (60)	0/39 (60)	1/33 (60)
				0.3210	0.3276	0.3333	0.5081

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

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	3 mg	10 mg	30 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Harderian Glands	#M Sarcoma, Undifferentiated	0/(60)	0/(59)	0/78 (119)	0/38 (60)	0/39 (60)	1/33 (60)
				0.1755	NC	NC	0.2973
	#M Schwannoma, Malignant	0/(60)	0/(59)	0/78 (119)	0/38 (60)	0/39 (60)	1/33 (60)
				0.1755	NC	NC	0.2973
Jejunum	#M Adenocarcinoma	0/(52)	0/(51)	0/69 (103)	0/35 (52)	1/36 (50)	0/29 (51)
				0.3846	NC	0.3429	NC
Kidneys	#B Adenoma, Renal Tubule	0/(60)	0/(60)	0/78 (120)	0/38 (60)	0/39 (60)	1/33 (60)
				0.1755	NC	NC	0.2973
	#B Lipoma	1/(60)	0/(60)	1/78 (120)	0/38 (60)	0/39 (60)	1/33 (60)
				0.3210	0.3276	0.3333	0.5081
	#B Lipoma/#M Liposarcoma	1/(60)	1/(60)	2/79 (120)	0/38 (60)	0/39 (60)	1/33 (60)
				0.4478	0.5460	0.5537	0.6530
	#M Liposarcoma	0/(60)	1/(60)	1/78 (120)	0/38 (60)	0/39 (60)	0/33 (60)
				0.5851	0.3276	0.3333	0.2973
Liver	#B Adenoma, Hepatocellular	0/(60)	0/(60)	0/78 (120)	1/38 (60)	2/39 (60)	0/33 (60)
				0.4499	0.3276	0.1092	NC
	#M Carcinoma, Hepatocellular	1/(60)	0/(60)	1/79 (120)	0/38 (60)	0/39 (60)	1/33 (60)
				0.3195	0.3248	0.3305	0.5043
	#B+M Hepatocellular	1/(60)	0/(60)	1/79 (120)	1/38 (60)	2/39 (60)	1/33 (60)
				0.2776	0.5460	0.2536	0.5043
Lungs	#B Adenoma, Bronchiolo-Alveolar	1/(60)	0/(60)	1/78 (120)	0/38 (60)	0/39 (60)	0/33 (60)
				0.5851	0.3276	0.3333	0.2973
	#M Carcinoma, Bronchiolo-Alveolar	0/(60)	0/(60)	0/78 (120)	0/38 (60)	1/40 (60)	0/33 (60)
				0.3862	NC	0.3390	NC
	#B+M Bronchiolo-Alveolar	1/(60)	0/(60)	1/78 (120)	0/38 (60)	1/40 (60)	0/33 (60)
				0.4489	0.3276	0.5650	0.2973
Mammary Gland	#B Adenoma	0/(56)	0/(58)	0/74 (114)	1/36 (56)	0/36 (56)	0/30 (56)
				0.3750	0.3273	NC	NC
	#B Fibroadenoma	2/(56)	1/(58)	3/75 (114)	0/36 (56)	1/36 (56)	0/30 (56)
				0.7885	0.6956	0.3912	0.6398
	#M Adenocarcinoma	0/(56)	1/(58)	1/74 (114)	0/36 (56)	1/36 (56)	1/30 (56)
				0.2298	0.3273	0.5495	0.4957

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

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	3 mg	10 mg	30 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Pancreas	#B Adenoma, Acinar Cell	1/(60)	1/(60)	2/79 (120)	0/38 (60)	0/39 (60)	0/33 (60)
				0.8266	0.5460	0.5537	0.5043
	#M Carcinoma, Acinar Cell	0/(60)	2/(60)	2/79 (120)	0/38 (60)	0/39 (60)	0/33 (60)
				0.8266	0.5460	0.5537	0.5043
	#B+M Acinar Cell	1/(60)	3/(60)	4/79 (120)	0/38 (60)	0/39 (60)	0/33 (60)
				0.9708	0.7973	0.8042	0.7581
	#B Adenoma, Islet Cell	2/(60)	3/(60)	5/78 (120)	3/38 (60)	3/40 (60)	3/33 (60)
				0.3248	0.5208	0.5496	0.4423
	#M Carcinoma, Islet Cell	1/(60)	2/(60)	3/79 (120)	0/38 (60)	2/40 (60)	3/34 (60)
				0.0811	0.6960	0.5475	0.2531
	#B+M Islet Cell	3/(60)	5/(60)	8/79 (120)	3/38 (60)	5/40 (60)	6/34 (60)
				0.1060	0.5061	0.4570	0.2083
	#B Fibroma	0/(60)	0/(60)	0/78 (120)	0/38 (60)	1/39 (60)	0/33 (60)
				0.3830	NC	0.3333	NC
Parathyroids	#B Adenoma	3/(58)	1/(58)	4/75 (116)	0/36 (56)	1/39 (60)	3/32 (57)
				0.1353	0.7971	0.5595	0.3485
Pituitary	#B Adenoma, Pars Distalis	28/(60)	36/(60)	64/93 (120)	26/44 (60)	28/46 (60)	21/39 (60)
				0.9268	0.8233	0.7717	0.9241
	#M Carcinoma, Pars Distalis	0/(60)	0/(60)	0/78 (120)	0/38 (60)	1/39 (60)	1/33 (60)
				0.1033	NC	0.3333	0.2973
	#B+M Pars Distalis	28/(60)	36/(60)	64/93 (120)	26/44 (60)	29/46 (60)	22/39 (60)
				0.8761	0.8233	0.6895	0.8775
Prostate	#B Adenoma	0/(60)	0/(60)	0/78 (120)	1/38 (60)	1/40 (60)	0/33 (60)
				0.3634	0.3276	0.3390	NC
Sal. Gland Mand	#M Schwannoma, Malignant	0/(60)	0/(60)	0/78 (120)	0/38 (60)	1/39 (60)	0/33 (60)
				0.3830	NC	0.3333	NC
Seminal Vesicles	#B Adenoma	0/(60)	0/(60)	0/78 (120)	1/39 (60)	0/39 (60)	0/33 (60)
				0.3810	0.3333	NC	NC

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

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	3 mg	10 mg	30 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Skin	#B Adenoma, Sebaceous Cell	0/(60)	0/(60)	0/78 (120)	1/39 (60)	0/39 (60)	0/33 (60)
				0.3810	0.3333	NC	NC
	#B Basal Cell Tumor, Benign	0/(60)	2/(60)	2/78 (120)	1/38 (60)	0/39 (60)	1/33 (60)
				0.4998	0.6999	0.5575	0.6570
	#M Basal Cell Tumor, Malignant	1/(60)	0/(60)	1/78 (120)	0/38 (60)	0/39 (60)	0/33 (60)
				0.5851	0.3276	0.3333	0.2973
	#B+M Basal Cell Tumor	1/(60)	2/(60)	3/78 (120)	1/38 (60)	0/39 (60)	1/33 (60)
				0.5555	0.3970	0.7075	0.3426
	#B Fibroma	0/(60)	0/(60)	0/78 (120)	1/39 (60)	3/39 (60)	1/33 (60)
				0.1966	0.3333	0.0351 $	0.2973
	#M Fibrosarcoma	1/(60)	0/(60)	1/79 (120)	1/38 (60)	0/39 (60)	0/33 (60)
				0.6576	0.5460	0.3305	0.2946
	#B Fibroma/#M Fibrosarcoma	1/(60)	0/(60)	1/79 (120)	2/39 (60)	3/39 (60)	1/33 (60)
				0.3494	0.2536	0.1048	0.5043
	#B Keratoacanthoma, Benign	4/(60)	5/(60)	9/80 (120)	2/39 (60)	0/39 (60)	0/33 (60)
				0.9989	0.7662	0.9760	0.9612
	#B Lipoma	0/(60)	3/(60)	3/79 (120)	0/38 (60)	0/39 (60)	0/33 (60)
				0.9286	0.6960	0.7037	0.6530
	#M Liposarcoma	0/(60)	1/(60)	1/78 (120)	0/38 (60)	0/39 (60)	0/33 (60)
				0.5851	0.3276	0.3333	0.2973
	#B Lipoma/#M Liposarcoma	0/(60)	4/(60)	4/79 (120)	0/38 (60)	0/39 (60)	0/33 (60)
				0.9708	0.7973	0.8042	0.7581
	#B Papilloma, Squamous Cell	1/(60)	0/(60)	1/78 (120)	0/38 (60)	0/39 (60)	0/33 (60)
				0.5851	0.3276	0.3333	0.2973
	#M Carcinoma, Squamous Cell	2/(60)	0/(60)	2/78 (120)	0/38 (60)	0/39 (60)	0/33 (60)
				0.8292	0.5498	0.5575	0.5081
	#B+M Papilloma, Squamous Cell	3/(60)	0/(60)	3/78 (120)	0/38 (60)	0/39 (60)	0/33 (60)
				0.9302	0.6999	0.7075	0.6570
	#M Hibernoma, Malignant	0/(60)	0/(60)	0/78 (120)	0/38 (60)	0/39 (60)	1/33 (60)
				0.1755	NC	NC	0.2973
	#M Myxosarcoma	0/(60)	0/(60)	0/78 (120)	0/38 (60)	0/39 (60)	1/33 (60)
				0.1755	NC	NC	0.2973

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
$ = Statistically significant at 0.025 and 0.05 level in rare tumor for tests of dose response relationship and pairwise comparison, respectively;
NA = Not calculable.

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	3 mg	10 mg	30 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Soft Tissue- Abd	#B Hibernoma, Benign	0/(60)	0/(58)	0/77 (118)	0/38 (60)	1/39 (60)	0/33 (60)
				0.3850	NC	0.3362	NC
	#M Hibernoma, Malignant	0/(60)	0/(58)	0/77 (118)	0/38 (60)	0/39 (60)	1/34 (60)
				0.1809	NC	NC	0.3063
	#B+M Hibernoma	0/(60)	0/(58)	0/77 (118)	0/38 (60)	1/39 (60)	1/34 (60)
				0.1074	NC	0.3362	0.3063
	#B Lipoma	0/(60)	0/(58)	0/77 (118)	3/39 (60)	0/39 (60)	0/33 (60)
				0.7674	0.0361 $	NC	NC
Soft Tissue- Tho	#B Hibernoma, Benign	3/(60)	2/(60)	5/80 (120)	2/38 (59)	1/39 (60)	1/34 (60)
				0.7602	0.4026	0.6432	0.5808
	#M Hibernoma, Malignant	5/(60)	4/(60)	9/83 (120)	3/40 (59)	8/44 (60)	5/35 (60)
				0.2165	0.5907	0.1878	0.4024
	#M Hibernoma, Malignant, Multiple	0/(60)	0/(60)	0/78 (120)	0/37 (59)	0/39 (60)	1/33 (60)
				0.1765	NC	NC	0.2973
	#M Hibernoma, Malignant + Multiple	5/(60)	4/(60)	9/83 (120)	3/40 (59)	8/44 (60)	6/36 (60)
				0.1325	0.5907	0.1878	0.2752
	#B+M Hibernoma	8/(60)	6/(60)	14/85 (120)	5/41 (59)	9/44 (60)	7/36 (60)
				0.2682	0.6338	0.3699	0.4383
Stomach, Glan	#M Fibrosarcoma	0/(60)	0/(60)	0/78 (120)	0/38 (60)	1/40 (60)	0/33 (60)
				0.3862	NC	0.3390	NC
	#M Schwannoma, Malignant	0/(60)	1/(60)	1/79 (120)	0/38 (60)	0/39 (60)	0/33 (60)
				0.5820	0.3248	0.3305	0.2946
Stomach, Non	#B Papilloma, Squamous Cell	0/(60)	0/(60)	0/78 (120)	0/38 (60)	1/40 (60)	0/33 (60)
				0.3862	NC	0.3390	NC
	#M Leiomyosarcoma	1/(60)	0/(60)	1/78 (120)	0/38 (60)	0/39 (60)	0/33 (60)
				0.5851	0.3276	0.3333	0.2973

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
$ = Statistically significant at 0.025 and 0.05 level in rare tumor for tests of dose response relationship and pairwise comparison, respectively;
NA = Not calculable.

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	3 mg	10 mg	30 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Systemic Tumors	#B Hemangioma	0/(60)	0/(60)	0/78 (120)	0/38 (60)	0/39 (60)	1/33 (60)
				0.1755	NC	NC	0.2973
	#M Hemangiosarcoma	2/(60)	0/(60)	2/78 (120)	1/38 (60)	0/39 (60)	1/33 (60)
				0.4998	0.6999	0.5575	0.6570
	#B Hemangioma/#M Hemangiosarcoma	2/(60)	0/(60)	2/78 (120)	1/38 (60)	0/39 (60)	2/34 (60)
				0.2059	0.6999	0.5575	0.3539
	#M Leukemia, Granulocytic	0/(60)	1/(60)	1/79 (120)	0/38 (60)	0/39 (60)	0/33 (60)
				0.5820	0.3248	0.3305	0.2946
	#M Lymphoma, Malignant	1/(60)	1/(60)	2/79 (120)	2/39 (60)	3/40 (60)	4/34 (60)
				0.0373#	0.4023	0.2098	0.0658
	#M Sarcoma, Histiocytic	4/(60)	3/(60)	7/81 (120)	0/38 (60)	2/40 (60)	2/33 (60)
				0.5375	0.9379	0.6229	0.5127
Tail	#B Keratoacanthoma, Benign	0/(60)	0/(60)	0/78 (120)	1/38 (60)	0/39 (60)	0/33 (60)
				0.3830	0.3276	NC	NC
Testes	#B Adenoma, Interstitial Cell	1/(60)	1/(60)	2/79 (120)	2/39 (60)	2/39 (60)	2/33 (60)
				0.2230	0.4023	0.4023	0.3379
	#B Adenoma, Interstitial Cell, Multiple	0/(60)	0/(60)	0/78 (120)	0/38 (60)	0/39 (60)	2/33 (60)
				0.0300 $	NC	NC	0.0865
	#B Adenoma, Interstitial Cell + Multiple	1/(60)	1/(60)	2/79 (120)	2/39 (60)	2/39 (60)	4/33 (60)
				0.0324#	0.4023	0.4023	0.0610
	#M Carcinoma, Interstitial Cell	0/(60)	0/(60)	0/78 (120)	1/38 (60)	0/39 (60)	0/33 (60)
				0.3830	0.3276	NC	NC
	#B+M Interstitial Cell	1/(60)	1/(60)	2/79 (120)	3/39 (60)	2/39 (60)	4/33 (60)
				0.0488	0.2014	0.4023	0.0610
Thymus	#B Thymoma, Benign	0/(60)	0/(59)	0/78 (119)	0/38 (59)	0/37 (56)	1/32 (59)
				0.1730	NC	NC	0.2909

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
$ = Statistically significant at 0.025 and 0.05 level in rare tumor for tests of dose response relationship and pairwise comparison, respectively;
# = Statistically significant at 0.005 and 0.01 level in common tumor for tests of dose response relationship and pairwise comparison, respectively;
NA = Not calculable.

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	3 mg	10 mg	30 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Thyroid Glands	#B Adenoma, C-Cell	8/(60)	4/(60)	12/81 (120)	6/39 (60)	3/39 (60)	4/33 (60)
				0.6869	0.5667	0.7878	0.5187
	#B Adenoma, C-Cell, Multiple	1/(60)	0/(60)	1/78 (120)	1/38 (60)	0/39 (60)	1/33 (60)
				0.3506	0.5498	0.3333	0.5081
	#B Adenoma, C-Cell+ Multiple	9/(60)	4/(60)	13/81 (120)	7/39 (60)	3/39 (60)	5/34 (60)
				0.6343	0.4917	0.8347	0.4496
	#M Carcinoma, C-Cell	1/(60)	1/(60)	2/78 (120)	0/38 (60)	2/40 (60)	2/34 (60)
				0.1318	0.5498	0.4176	0.3539
	#B+M C-Cell	10/(60)	5/(60)	15/81 (120)	7/39 (60)	5/40 (60)	7/35 (60)
				0.4437	0.4230	0.7133	0.5196
	#B Adenoma, Follicular Cell	4/(60)	1/(60)	5/79 (120)	1/39 (60)	4/40 (60)	3/34 (60)
				0.2250	0.6489	0.3531	0.4517
	#B Adenoma, Follicular Cell, Multiple	0/(60)	0/(60)	0/78 (120)	0/38 (60)	0/39 (60)	1/33 (60)
				0.1755	NC	NC	0.2973
	#B Adenoma, Follicular Cell+multiple	4/(60)	1/(60)	5/79 (120)	1/39 (60)	4/40 (60)	4/35 (60)
				0.1156	0.6489	0.3531	0.2806
	#M Carcinoma, Follicular Cell	0/(60)	2/(60)	2/78 (120)	1/38 (60)	2/39 (60)	0/33 (60)
				0.6870	0.6999	0.4074	0.5081
	#B+M Follicular Cell	4/(60)	3/(60)	7/79 (120)	2/39 (60)	6/40 (60)	4/35 (60)
				0.2420	0.6229	0.2372	0.4519
Urinary Bladder	#B Papilloma, Transitional Cell	0/(60)	0/(59)	0/78 (119)	0/38 (60)	1/39 (59)	0/33 (60)
				0.3830	NC	0.3333	NC
	#M Carcinoma, Transitional Cell	0/(60)	1/(59)	1/78 (119)	0/38 (60)	0/39 (59)	0/33 (60)
				0.5851	0.3276	0.3333	0.2973
	#B+M Transitional Cell	0/(60)	1/(59)	1/78 (119)	0/38 (60)	1/39 (59)	0/33 (60)
				0.4475	0.3276	0.5575	0.2973

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

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	5 mg	15 mg	50 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Adipose Tissue	#B Lipoma	1/(60)	0/(60)	1/82 (120)	0/41 (60)	0/42 (60)	0/42 (60)
				0.6039	0.3333	0.3387	0.3387
Adrenal Cortex	#B Adenoma	3/(60)	2/(60)	5/83 (120)	4/41 (60)	3/43 (60)	2/42 (60)
				0.6516	0.3394	0.5551	0.4356
	#M Carcinoma	0/(60)	0/(60)	0/81 (120)	0/41 (60)	0/42 (60)	1/42 (60)
				0.2039	NC	NC	0.3415
	#B+M Adenoma+ Carcinoma	3/(60)	2/(60)	5/83 (120)	4/41 (60)	3/43 (60)	3/42 (60)
				0.4758	0.3394	0.5551	0.5419
Adrenal Medulla	#B Pheochromocytoma, Benign	1/(60)	1/(58)	2/81 (118)	3/40 (59)	1/42 (60)	0/41 (59)
				0.8570	0.2016	0.2684	0.5610
Bone	#B Osteoma	1/(60)	0/(60)	1/81 (120)	0/41 (60)	0/42 (60)	0/42 (60)
				0.6068	0.3361	0.3415	0.3415
	#M Schwannoma, Malignant	1/(60)	0/(60)	1/82 (120)	0/41 (60)	0/42 (60)	0/42 (60)
				0.6039	0.3333	0.3387	0.3387
Brain	#B Granular Cell Tumor, Benign	0/(60)	1/(60)	1/81 (120)	0/41 (60)	0/42 (60)	0/42 (60)
				0.6068	0.3361	0.3415	0.3415
	#M Astrocytoma, Malignant	1/(60)	2/(60)	3/82 (120)	0/41 (60)	1/43 (60)	1/42 (60)
				0.5068	0.7074	0.4266	0.4171
	#M Reticulosis, Malignant	1/(60)	0/(60)	1/82 (120)	0/41 (60)	0/42 (60)	0/42 (60)
				0.6039	0.3333	0.3387	0.3387
Cervix	#B Granular Cell Tumor, Benign	0/(60)	1/(60)	1/82 (120)	3/42 (60)	2/43 (60)	4/42 (60)
				0.0486#	0.1123	0.2719	0.0445#
	#B Leiomyoma	1/(60)	0/(60)	1/82 (120)	0/41 (60)	0/42 (60)	0/42 (60)
				0.6039	0.3333	0.3387	0.3387
	#M Leiomyosarcoma	0/(60)	0/(60)	0/81 (120)	0/41 (60)	0/42 (60)	1/42 (60)
				0.2039	NC	NC	0.3415
	#B Leiomyoma/#M Leiomyosarcoma	1/(60)	0/(60)	1/82 (120)	0/41 (60)	0/42 (60)	1/42 (60)
				0.3654	0.3333	0.3387	0.5645
	#M Carcinoma, Squamous Cell	0/(60)	1/(60)	1/82 (120)	0/41 (60)	0/42 (60)	0/42 (60)
				0.6039	0.3333	0.3387	0.3387
	#M Fibrosarcoma	0/(60)	0/(60)	0/81 (120)	1/41 (60)	0/42 (60)	0/42 (60)
				0.4078	0.3361	NC	NC
	#M Schwannoma, Malignant	0/(60)	1/(60)	1/82 (120)	1/41 (60)	0/42 (60)	0/42 (60)
				0.6866	0.5574	0.3387	0.3387

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
# = Statistically significant at 0.005 and 0.01 level in common tumor for tests of dose response relationship and pairwise comparison, respectively;
NA = Not calculable.

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	5 mg	15 mg	50 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Cervix/Vagina	#B Granular Cell Tumor, Benign	0/(60)	1/(60)	1/82 (120)	3/41 (59)	3/43 (60)	4/42 (60)
				0.0561	0.1074	0.1172	0.0445
Cervix/Vagina/Ovaries	#B Granular Cell Tumor, Benign	0/(60)	1/(60)	1/82 (120)	4/42 (60)	3/43 (60)	4/42 (60)
				0.0797	0.0445	0.1172	0.0445
Clitoral Gl	#B Papilloma, Squamous Cell	0/(58)	0/(57)	0/78 (115)	0/40 (58)	0/42 (59)	1/41 (59)
				0.2040	NC	NC	0.3445
Colon	#B Lipoma	0/(60)	0/(60)	0/81 (120)	0/41 (60)	1/42 (60)	0/42 (60)
				0.4078	NC	0.3415	NC
Duodenum	#M Fibrosarcoma	1/(59)	0/(58)	1/80 (117)	0/41 (59)	0/42 (59)	0/41 (59)
				0.6078	0.3388	0.3443	0.3388
Jejunum	#M Leiomyosarcoma	1/(52)	0/(54)	1/74 (106)	0/36 (52)	1/40 (55)	0/36 (49)
				0.4795	0.3273	0.5807	0.3273
Kidneys	#M Liposarcoma	0/(60)	0/(60)	0/81 (120)	0/41 (60)	1/43 (60)	0/42 (60)
				0.4106	NC	0.3468	NC
Liver	#M Carcinoma, Hepatocellular	0/(60)	0/(60)	0/81 (120)	1/41 (60)	0/42 (60)	0/42 (60)
				0.4078	0.3361	NC	NC
Lungs	#M Carcinoma, Squamous Cell	0/(60)	0/(60)	0/81 (120)	0/41 (60)	0/42 (60)	1/42 (60)
				0.2039	NC	NC	0.3415
	#M Carcinoma_unknown	1/(60)	0/(60)	1/82 (120)	0/41 (60)	0/42 (60)	0/42 (60)
				0.6039	0.3333	0.3387	0.3387

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

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	5 mg	15 mg	50 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Mammary Gland	#B Adenolipoma	1/(60)	1/(60)	2/81 (120)	0/41 (60)	0/42 (60)	0/42 (60)
				0.8466	0.5610	0.5682	0.5682
	#B Adenoma	1/(60)	1/(60)	2/82 (120)	1/41 (60)	4/42 (60)	1/42 (60)
				0.4924	NC	0.1000	0.2647
	#B Fibroadenoma	12/(60)	16/(60)	28/87 (120)	16/44 (60)	16/46 (60)	6/42 (60)
				0.9899	0.3864	0.4539	0.9770
	#B Fibroadenoma, Multiple	9/(60)	9/(60)	18/85 (120)	7/41 (60)	7/43 (60)	1/42 (60)
				0.9985	0.6127	0.6590	0.9971
	#B Fibroadenoma+Multiple	21/(60)	25/(60)	46/91 (120)	23/44 (60)	23/47 (60)	7/42 (60)
				1.0000	0.4986	0.5000	0.9999
	#B Lipoma	0/(60)	0/(60)	0/81 (120)	1/41 (60)	0/42 (60)	0/42 (60)
				0.4078	0.3361	NC	NC
	#M Adenocarcinoma	7/(60)	12/(60)	19/86 (120)	14/43 (60)	11/46 (60)	8/44 (60)
				0.7974	0.1425	0.4872	0.6093
	#M Adenocarcinoma, Multiple	3/(60)	12/(60)	15/86 (120)	6/42 (60)	8/44 (60)	3/42 (60)
				0.9306	0.5708	0.5481	0.9073
	#M Adenocarcinoma +Multiple	10/(60)	24/(60)	34/90 (120)	20/44 (60)	19/48 (60)	11/44 (60)
				0.9562	0.2529	0.4887	0.9000
	#M Mixed Tumor, Malignant	0/(60)	1/(60)	1/82 (120)	0/41 (60)	1/43 (60)	0/42 (60)
				0.4877	0.3333	0.5715	0.3387
	#M Mixed Tumor, Malignant, Multiple	0/(60)	0/(60)	0/81 (120)	0/41 (60)	1/43 (60)	1/42 (60)
				0.1251	NC	0.3468	0.3415
	#M Mixed Tumor, Malignant+Multiple	0/(60)	1/(60)	1/82 (120)	0/41 (60)	2/43 (60)	1/42 (60)
				0.2507	0.3333	0.2719	0.5645
Mesentery	#M Leiomyosarcoma	0/(60)	0/(60)	0/81 (120)	0/41 (60)	0/42 (60)	1/42 (60)
				0.2039	NC	NC	0.3415

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

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	5 mg	15 mg	50 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Ovaries	#B Adenoma, Sex Cord Stromal	1/(60)	0/(60)	1/81 (120)	0/41 (60)	0/42 (60)	0/42 (60)
				0.6068	0.3361	0.3415	0.3415
	#B Adenoma, Sex Cord Stromal, Multiple	1/(60)	0/(60)	1/82 (120)	0/41 (60)	0/42 (60)	0/42 (60)
				0.6039	0.3333	0.3387	0.3387
	#B Adenoma, Sex Cord Stromal+Multiple	2/(60)	0/(60)	2/82 (120)	0/41 (60)	0/42 (60)	0/42 (60)
				0.8442	0.5574	0.5645	0.5645
	#B Granulosa Cell Tumor, Benign	0/(60)	0/(60)	0/81 (120)	1/41 (60)	0/42 (60)	0/42 (60)
				0.4078	0.3361	NC	NC
	#M Schwannoma, Malignant	1/(60)	0/(60)	1/81 (120)	0/41 (60)	0/42 (60)	0/42 (60)
				0.6068	0.3361	0.3415	0.3415
Pancreas	#B Adenoma, Islet Cell	0/(60)	1/(60)	1/81 (120)	1/41 (60)	1/42 (60)	1/42 (60)
				0.3527	0.5610	0.5682	0.5682
	#M Carcinoma, Islet Cell	2/(60)	1/(60)	3/82 (120)	0/41 (60)	0/42 (60)	1/42 (60)
				0.5508	0.7074	0.7144	0.4171
	#B+M Islet Cell	2/(60)	2/(60)	4/82 (120)	1/41 (60)	1/42 (60)	2/42 (60)
				0.4583	0.5418	0.5525	0.3277
Parathyroids	#B Adenoma	0/(58)	0/(54)	0/76 (112)	1/38 (56)	1/41 (58)	1/41 (59)
				0.1904	0.3333	0.3504	0.3504
Pituitary	#B Adenoma, Pars Distalis	52/(60)	56/(60)	108/113 (120)	48/53 (60)	49/57 (60)	44/51 (60)
				0.9578	0.8215	0.9697	0.9596
	#M Carcinoma, Pars Distalis	0/(60)	1/(60)	1/82 (120)	1/41 (60)	0/42 (60)	0/42 (60)
				0.6866	0.5574	0.3387	0.3387
	#B+M Pars Distalis	52/(60)	57/(60)	109/114 (120)	49/53 (60)	49/57 (60)	44/51 (60)
				0.9682	0.6925	0.9708	0.9609
Sal Gland, Gen	#M Schwannoma, Malignant	0/(60)	0/(60)	0/81 (120)	1/41 (60)	0/42 (60)	0/42 (60)
				0.4078	0.3361	NC	NC

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

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	5 mg	15 mg	50 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Skin	#B Basal Cell Tumor, Benign	0/(60)	0/(59)	0/81 (119)	0/41 (60)	0/42 (60)	1/42 (60)
				0.2039	NC	NC	0.3415
	#B Fibroma	3/(60)	0/(59)	3/82 (119)	1/41 (60)	0/42 (60)	1/42 (60)
				0.6122	0.4074	0.7144	0.4171
	#B Lipoma	1/(60)	0/(59)	1/82 (119)	0/41 (60)	0/42 (60)	0/42 (60)
				0.6039	0.3333	0.3387	0.3387
	#B Papilloma, Squamous Cell	0/(60)	0/(59)	0/81 (119)	0/41 (60)	1/42 (60)	0/42 (60)
				0.4078	NC	0.3415	NC
	#M Hibernoma, Malignant	0/(60)	0/(59)	0/81 (119)	1/41 (60)	0/42 (60)	0/42 (60)
				0.4078	0.3361	NC	NC
	#M Sarcoma, Undifferentiated	0/(60)	0/(59)	0/81 (119)	1/42 (60)	0/42 (60)	0/42 (60)
				0.4058	0.3415	NC	NC
	#M Schwannoma, Malignant	1/(60)	0/(59)	1/81 (119)	0/41 (60)	0/42 (60)	0/42 (60)
				0.6068	0.3361	0.3415	0.3415
Soft Tissue- Abd	#B Hibernoma, Benign	0/(60)	0/(60)	0/81 (120)	0/41 (60)	1/42 (59)	1/42 (60)
				0.1243	NC	0.3415	0.3415
	#M Hibernoma, Malignant	0/(60)	1/(60)	1/82 (120)	0/41 (60)	0/41 (59)	1/43 (60)
				0.3731	0.3333	0.3333	0.5715
	#B+M Hibernoma	0/(60)	1/(60)	1/82 (120)	0/41 (60)	1/42 (59)	2/43 (60)
				0.1003	0.3333	0.5645	0.2719
Soft Tissue- Tho	#B Hibernoma, Benign	0/(60)	3/(60)	3/83 (120)	1/41 (60)	1/43 (60)	1/43 (60)
				0.5724	0.4026	0.4217	0.4217
	#M Hibernoma, Malignant	7/(60)	3/(60)	10/87 (120)	5/44 (60)	2/43 (60)	4/44 (60)
				0.6640	0.3857	0.8267	0.5374
	#B+M Hibernoma	7/(60)	5/(60)	12/88 (120)	6/44 (60)	3/44 (60)	5/45 (60)
				0.6622	NC	0.8064	0.5459

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

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	5 mg	15 mg	50 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Systemic Tumors	#B Lymphangioma	0/(60)	0/(60)	0/81 (120)	0/41 (60)	1/42 (60)	1/42 (60)
				0.1243	NC	0.3415	0.3415
	#M Lymphoma, Malignant	1/(60)	2/(60)	3/83 (120)	3/43 (60)	1/43 (60)	1/42 (60)
				0.6897	0.3330	0.4217	0.4122
	#M Fibrous Histiocytoma, Malignant	0/(60)	0/(60)	0/81 (120)	0/41 (60)	1/43 (60)	0/42 (60)
				0.4106	NC	0.3468	NC
	#M Hemangiosarcoma	0/(60)	0/(60)	0/81 (120)	0/41 (60)	1/43 (60)	1/42 (60)
				0.1251	NC	0.3468	0.3415
	#M Mesothelioma, Malignant	0/(60)	0/(60)	0/81 (120)	0/41 (60)	0/42 (60)	1/42 (60)
				0.2039	NC	NC	0.3415
	#M Sarcoma, Histiocytic	2/(60)	2/(60)	4/83 (120)	2/41 (60)	2/43 (60)	0/42 (60)
				0.9100	0.6489	0.3330	0.8104
Thymus	#B Thymoma, Benign	0/(59)	0/(59)	0/81 (118)	0/40 (58)	1/40 (57)	1/41 (59)
				0.1212	NC	0.3306	0.3361
Thyroid Glands	#B Adenoma, C-Cell	2/(60)	7/(60)	9/84 (120)	4/42 (60)	5/43 (60)	5/43 (60)
				0.4115	0.4479	0.5467	0.5467
	#B Adenoma, C-Cell, Multiple	0/(60)	0/(60)	0/81 (120)	1/41 (60)	1/42 (60)	0/42 (60)
				0.4078	0.3361	0.3415	NC
	#B Adenoma, C-Cell+Multiple	2/(60)	7/(60)	9/84 (120)	5/42 (60)	6/43 (60)	5/43 (60)
				0.4511	0.5290	0.3948	0.5467
	#M Carcinoma, C-Cell	1/(60)	0/(60)	1/82 (120)	3/41 (60)	0/42 (60)	0/42 (60)
				0.8291	0.1074	0.3387	0.3387
	#B+M C-Cell	3/(60)	7/(60)	10/84 (120)	8/43 (60)	6/43 (60)	5/43 (60)
				0.6023	0.2225	0.4721	0.3948
	#B Adenoma, Follicular Cell	1/(60)	0/(60)	1/82 (120)	1/42 (60)	0/42 (60)	0/42 (60)
				0.6858	0.5645	0.3387	0.3387
	#M Carcinoma, Follicular Cell	1/(60)	0/(60)	1/81 (120)	0/41 (60)	0/42 (60)	0/42 (60)
				0.6068	0.3361	0.3415	0.3415
	#B+M Follicular Cell	2/(60)	0/(60)	2/82 (120)	1/42 (60)	0/42 (60)	0/42 (60)
				0.8457	0.2647	0.5645	0.5645

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

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	5 mg	15 mg	50 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Uterus	#B Fibroma	0/(60)	0/(60)	0/81 (120)	0/41 (60)	0/42 (60)	1/42 (60)
				0.2039	NC	NC	0.3415
	#B Polyp, Endometrial Stromal	4/(60)	3/(60)	7/82 (120)	3/41 (60)	5/42 (60)	7/43 (60)
				0.0801	0.4407	0.3804	0.1572
	#B Polyp, Endometrial Stromal, Multiple	0/(60)	0/(60)	0/81 (120)	1/41 (60)	0/42 (60)	0/42 (60)
				0.4078	0.3361	NC	NC
	#B Polyp, Endometrial Stromal+Multiple	4/(60)	3/(60)	7/82 (120)	4/41 (60)	5/42 (60)	7/43 (60)
				0.1004	0.5315	0.3804	0.1572
	#M Sarcoma, Endometrial Stromal	0/(60)	1/(60)	1/82 (120)	0/41 (60)	0/42 (60)	0/42 (60)
				0.6039	0.3333	0.3387	0.3387
	#B+M Endometrial Stromal	4/(60)	4/(60)	8/83 (120)	4/41 (60)	5/42 (60)	7/43 (60)
				0.1307	0.6071	0.4566	0.2093
	#M Adenocarcinoma	0/(60)	0/(60)	0/81 (120)	1/41 (60)	0/42 (60)	0/42 (60)
				0.4078	0.3361	NC	NC
	#M Carcinoma, Squamous Cell	0/(60)	0/(60)	0/81 (120)	0/41 (60)	1/42 (60)	0/42 (60)
				0.4078	NC	0.3415	NC
	#M Leiomyosarcoma	1/(60)	0/(60)	1/81 (120)	0/41 (60)	0/42 (60)	0/42 (60)
				0.6068	0.3361	0.3415	0.3415
Vagina	#B Granular Cell Tumor, Benign	0/(60)	1/(60)	1/82 (120)	0/40 (59)	1/42 (60)	0/42 (60)
				0.4873	0.3279	0.5645	0.3387
	#B Polyp	0/(60)	0/(60)	0/81 (120)	1/40 (59)	0/42 (60)	0/42 (60)
				0.4098	0.3306	NC	NC
	#M Fibrosarcoma	0/(60)	0/(60)	0/81 (120)	0/40 (59)	1/42 (60)	0/42 (60)
				0.4098	NC	0.3415	NC
Zymbal_s Glands	#B Adenoma	0/(60)	0/(60)	0/81 (120)	1/41 (60)	0/42 (60)	0/42 (60)
				0.4078	0.3361	NC	NC

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

Table 3A: Intercurrent Mortality Rate in Male Mice

	0 mg/kg/day Control 1		0 mg/kg/day Control 2		3 mg/kg/day Low		7 mg/kg/day Mid		15 mg/kg/day High	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	2	3.33	3	5.00	1	1.69	4	6.67	11	18.33
53 - 78	7	15.00	13	26.67	13	23.73	14	30.00	11	36.67
79 - 91	11	33.33	10	43.33	9	38.98	2	33.33	8	50.00
92 - 105	9	48.33	9	58.33	14	62.71	15	58.33	11	68.33
Accidental Death	3	5.00	1	1.67	1	1.69	3	5.00	1	1.67
Terminal sacrifice	28	46.67	24	40.00	21	35.59	22	36.67	18	30.00
Total	60		60		59		60		60	

Test	All Dose Groups	Low vs Vehicle Control 1+2	Mid vs Vehicle Control 1+2	High vs Vehicle Control 1+2
Dose-Response (Likelihood Ratio)	0.0213*	0.3352	0.4172	0.0188*
Homogeneity (Log-Rank)	0.1041	0.3261	0.4094	0.0147*

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 3B: Intercurrent Mortality Rate in Female Mice

	0 mg/kg/day Control 1		0 mg/kg/day Control 2		10 mg/kg/day Low		25 mg/kg/day Mid		50 mg/kg/day High	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	5	8.33	3	5.00	4	6.67	7	11.67	15	25.00
53 - 78	9	23.33	4	11.67	10	23.33	6	21.67	6	35.00
79 - 91	11	41.67	13	33.33	7	35.00	10	38.33	5	43.33
92 - 105	11	60.00	7	45.00	15	60.00	11	56.67	5	51.67
Accidental Death	2	3.33	2	3.33	2	3.33	3	5.00	3	5.00
Terminal sacrifice	22	36.67	31	51.67	22	36.67	23	38.33	26	43.33
Total	60		60		60		60		60	

Test	All Dose Groups	Low vs Vehicle Control 1+2	Mid vs Vehicle Control 1+2	High vs Vehicle Control 1+2
Dose-Response (Likelihood Ratio)	0.4681	0.4197	0.5252	0.4318
Homogeneity (Log-Rank)	0.8046	0.4117	0.5187	0.4239

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	3 mg	7 mg	15 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Adrenal Cortex	#B Adenoma	1/(60)	1/(60)	2/85 (120)	1/41 (59)	1/40 (60)	0/34 (60)
				0.6952	0.6966	0.6892	0.4915
	#B Adenoma, Subcapsular	0/(60)	2/(60)	2/85 (120)	1/41 (59)	0/40 (60)	1/34 (60)
				0.4301	0.6966	0.5394	0.6393
Epididymides	#M Sarcoma, Undifferentiated	1/(60)	0/(60)	1/85 (120)	0/41 (59)	0/40 (60)	0/33 (59)
				0.5729	0.3254	0.3200	0.2797
Gallbladder	#B Adenoma	1/(54)	2/(48)	3/77 (102)	1/33 (45)	1/32 (44)	1/24 (35)
				0.4858	0.3475	0.3360	0.6686
Harderian Glands	#B Adenoma	9/(60)	5/(60)	14/87 (120)	4/42 (59)	8/40 (60)	3/35 (60)
				0.7514	0.7658	0.3797	0.7830
	#M Carcinoma	2/(60)	0/(60)	2/85 (120)	2/41 (59)	0/40 (60)	0/34 (60)
				0.8608	0.3931	0.5394	0.4915
	#B+M Adenoma	11/(60)	5/(60)	16/87 (120)	6/42 (59)	8/40 (60)	3/35 (60)
				0.8623	0.6227	0.5038	0.8605
Jejunum	#M Adenocarcinoma, Mucinous	0/(48)	1/(54)	1/76 (102)	0/37 (52)	0/34 (48)	0/28 (48)
				0.5657	0.3274	0.3091	0.2692
Kidneys	#B Adenoma, Renal Tubule	1/(60)	0/(59)	1/85 (119)	2/41 (59)	1/40 (60)	1/34 (60)
				0.3493	0.2469	0.5394	0.4915
	#M Carcinoma, Renal Tubule	0/(60)	1/(59)	1/85 (119)	0/41 (59)	0/40 (60)	0/34 (60)
				0.5750	0.3254	0.3200	0.2857
	#B+M Renal Tubule	1/(60)	1/(59)	2/85 (119)	2/41 (59)	1/40 (60)	1/34 (60)
				0.4885	0.3931	0.6892	0.6393
Lac. Gland Exor	#M Schwannoma, Malignant	0/(60)	1/(60)	1/85 (120)	0/41 (59)	0/40 (60)	0/34 (60)
				0.5750	0.3254	0.3200	0.2857

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
$ = Statistically significant at 0.025 and 0.05 level in rare tumor for tests of dose response relationship and pairwise comparison, respectively;
# = Statistically significant at 0.005 and 0.01 level in common tumor for tests of dose response relationship and pairwise comparison, respectively;
NA = Not calculable.

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	3 mg	7 mg	15 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Liver	#B Adenoma, Hepatocellular	6/(60)	4/(60)	10/88 (120)	7/42 (59)	4/41 (60)	3/34 (60)
				0.7006	0.2823	0.4759	0.5161
	#B Adenoma, Hepatocellular, Multiple	0/(60)	1/(60)	1/86 (120)	1/41 (59)	0/40 (60)	0/34 (60)
				0.6427	0.5432	0.3175	0.2833
	#B Adenoma, Hepatocellular+Multiple	6/(60)	5/(60)	11/88 (120)	8/42 (59)	4/41 (60)	3/34 (60)
				0.7734	0.2319	0.5513	0.5860
	#M Carcinoma, Hepatocellular	6/(60)	1/(60)	7/87 (120)	5/42 (59)	2/40 (60)	2/35 (60)
				0.7334	0.3415	0.5820	0.5052
	#M Carcinoma, Hepatocellular, Multiple	1/(60)	1/(60)	2/86 (120)	0/41 (59)	0/40 (60)	0/34 (60)
				0.8182	0.5432	0.5359	0.4881
	#M Carcinoma, Hepatocellular+Multiple	7/(60)	2/(60)	9/88 (120)	5/42 (59)	2/40 (60)	2/35 (60)
				0.8426	0.4939	0.7295	0.6561
	#B+M Hepatocellular	10/(60)	6/(60)	16/90 (120)	13/43 (59)	6/41 (60)	5/35 (60)
				0.7760	0.0820	0.5687	0.5698
Lungs	#B Adenoma, Bronchial, Multiple	0/(60)	1/(60)	1/85 (120)	0/41 (59)	0/40 (60)	0/34 (60)
				0.5750	0.3254	0.3200	0.2857
	#B Papilloma, Bronchial	1/(60)	0/(60)	1/85 (120)	0/41 (59)	0/40 (60)	0/34 (60)
				0.5750	0.3254	0.3200	0.2857
	#B Adenoma+Papilloma, Bronchial	1/(60)	1/(60)	2/85 (120)	0/41 (59)	0/40 (60)	0/34 (60)
				0.8206	0.5467	0.5394	0.4915
	#B Adenoma, Bronchiolo-Alveolar	5/(60)	3/(60)	8/87 (120)	3/41 (59)	2/40 (60)	5/35 (60)
				0.2397	0.4923	0.6648	0.2995
	#B Adenoma, Bronchiolo-Alveolar, Multiple	1/(60)	0/(60)	1/85 (120)	1/41 (59)	0/40 (60)	0/34 (60)
				0.6455	0.5467	0.3200	0.2857
	#B Adenoma, Bronchiolo-Alveolar+Multiple	6/(60)	3/(60)	9/87 (120)	4/41 (59)	2/40 (60)	5/35 (60)
				0.3379	0.4055	0.7356	0.3691
	#M Carcinoma, Bronchiolo-Alveolar	3/(60)	2/(60)	5/86 (120)	5/42 (59)	4/40 (60)	1/34 (60)
				0.6709	0.1940	0.3066	0.5471
	#M Carcinoma, Bronchiolo-Alveolar, Multiple	4/(60)	1/(60)	5/86 (120)	2/42 (59)	4/41 (60)	0/34 (60)
				0.8104	0.4170	0.3199	0.8173
	#M Carcinoma, Bronchiolo-Alveolar+Multiple	7/(60)	3/(60)	10/87 (120)	7/43 (59)	8/42 (60)	1/34 (60)
				0.8373	0.3080	0.1857	0.8715
	#B+M Bronchiolo-Alveolar	13/(60)	6/(60)	19/89 (120)	11/43 (59)	10/43 (60)	5/35 (60)
				0.7911	0.3690	0.4846	0.7351

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
$ = Statistically significant at 0.025 and 0.05 level in rare tumor for tests of dose response relationship and pairwise comparison, respectively;
# = Statistically significant at 0.005 and 0.01 level in common tumor for tests of dose response relationship and pairwise comparison, respectively;
NA = Not calculable.

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	3 mg	7 mg	15 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Lymph Node, Mand	#M Mast Cell Tumor, Malignant	1/(58)	0/(59)	1/84 (117)	0/41 (59)	0/40 (60)	0/34 (59)
				0.5779	0.3280	0.3226	0.2881
Pancreas	#B Adenoma, Islet Cell	0/(60)	0/(58)	0/85 (118)	0/40 (58)	0/40 (60)	1/34 (60)
				0.1709	NC	NC	0.2857
Prostate	#M Carcinoma	0/(60)	0/(60)	0/85 (120)	0/40 (58)	1/40 (60)	0/34 (60)
				0.3719	NC	0.3200	NC
Skin	#B Papilloma, Squamous Cell	1/(60)	0/(60)	1/86 (120)	0/41 (59)	0/40 (60)	0/34 (60)
				0.5721	0.3228	0.3175	0.2833
	#M Fibrosarcoma	2/(60)	2/(60)	4/86 (120)	2/42 (59)	3/41 (60)	1/34 (60)
				0.5504	0.6436	0.4046	0.4384
Systemic Tumors	#B Hemangioma	2/(60)	0/(60)	2/85 (120)	0/41 (59)	0/40 (60)	0/34 (60)
				0.8206	0.5467	0.5394	0.4915
	#M Hemangiosarcoma	0/(60)	6/(60)	6/87 (120)	6/42 (59)	4/41 (60)	0/34 (60)
				0.8978	0.1514	0.4038	0.8686
	#B Hemangioma/#M Hemangiosarcoma	2/(60)	6/(60)	8/87 (120)	6/42 (59)	4/41 (60)	0/34 (60)
				0.9525	0.2789	0.5754	0.9351
	#M Leukemia	0/(60)	0/(60)	0/85 (120)	0/41 (59)	1/40 (60)	0/34 (60)
				0.3700	NC	0.3200	NC
	#M Leukemia, Granulocytic	0/(60)	0/(60)	0/85 (120)	0/41 (59)	1/40 (60)	0/34 (60)
				0.3700	NC	0.3200	NC
	#M Leukemia, Myeloid	1/(60)	0/(60)	1/86 (120)	0/41 (59)	0/40 (60)	0/34 (60)
				0.5721	0.3228	0.3175	0.2833
	#M Leukemia+Granulocytic + Myeloid	1/(60)	0/(60)	1/86 (120)	0/41 (59)	2/41 (60)	0/34 (60)
				0.5113	0.3228	0.2435	0.2833
	#M Lymphoma, Malignant	6/(60)	2/(60)	8/88 (120)	3/42 (59)	2/41 (60)	2/35 (60)
				0.7572	0.5006	0.6720	0.5817
	#M Mesothelioma, Malignant	1/(60)	0/(60)	1/86 (120)	0/41 (59)	0/40 (60)	0/34 (60)
				0.5721	0.3228	0.3175	0.2833
	#M Sarcoma, Histiocytic	0/(60)	0/(60)	0/85 (120)	1/41 (59)	2/41 (60)	1/34 (60)
				0.1261	0.3254	0.1041	0.2857
Testes	#B Adenoma, Interstitial Cell	2/(60)	2/(60)	4/86 (120)	2/41 (59)	1/40 (60)	1/34 (60)
				0.6689	0.6328	0.5096	0.4384
Thymus	#M Thymoma, Malignant	0/(60)	0/(52)	0/82 (112)	0/36 (52)	1/39 (59)	0/29 (49)
				0.3656	NC	0.3223	NC
Thyroid Glands	#B Adenoma, Follicular Cell	2/(60)	0/(60)	2/86 (120)	1/41 (59)	0/40 (59)	1/34 (59)
				0.4266	0.6930	0.5359	0.6356

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
$ = Statistically significant at 0.025 and 0.05 level in rare tumor for tests of dose response relationship and pairwise comparison, respectively;
# = Statistically significant at 0.005 and 0.01 level in common tumor for tests of dose response relationship and pairwise comparison, respectively;
NA = Not calculable.

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	10 mg	25 mg	50 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Adrenal Cortex	#B Adenoma, Subcapsular	0/(60)	1/(60)	1/86 (120)	0/42 (60)	0/40 (60)	1/35 (60)
				0.3539	0.3281	0.3175	0.4966
Adrenal Medulla	#B Pheochromocytoma, Benign	1/(59)	1/(60)	2/86 (119)	0/41 (59)	0/40 (60)	0/35 (59)
				0.8200	0.5432	0.5359	0.4966
Bone	#B Fibroma, Ossifying	0/(60)	0/(60)	0/86 (120)	0/42 (60)	1/41 (60)	0/35 (60)
				0.3725	NC	0.3228	NC
Brain	#B Meningioma, Benign	0/(60)	1/(60)	1/87 (120)	0/42 (60)	0/40 (60)	0/35 (60)
				0.5735	0.3256	0.3150	0.2869
Cervix	#B Fibroma	0/(60)	1/(58)	1/85 (118)	0/42 (60)	0/40 (60)	0/35 (60)
				0.5792	0.3307	0.3200	0.2917
	#B Granular Cell Tumor, Benign	0/(60)	1/(58)	1/85 (118)	0/42 (60)	0/40 (60)	0/35 (60)
				0.5792	0.3307	0.3200	0.2917
	#B Leiomyoma	0/(60)	1/(58)	1/85 (118)	1/42 (60)	0/40 (60)	0/35 (60)
				0.6483	0.5538	0.3200	0.2917
	#M Leiomyosarcoma	1/(60)	0/(58)	1/85 (118)	0/42 (60)	0/40 (60)	1/35 (60)
				0.3556	0.3307	0.3200	0.5000
	#B Leiomyoma/ #M Leiomyosarcoma	1/(60)	1/(58)	2/85 (118)	1/42 (60)	0/40 (60)	1/35 (60)
				0.4365	0.7037	0.5394	0.6483
	#B Polyp, Endometrial Stromal	0/(60)	1/(58)	1/85 (118)	1/42 (60)	0/40 (60)	0/35 (60)
				0.6483	0.5538	0.3200	0.2917
	#M Adenocarcinoma	0/(60)	1/(58)	1/85 (118)	0/42 (60)	0/40 (60)	0/35 (60)
				0.5792	0.3307	0.3200	0.2917
Duodenum	#M Adenocarcinoma	0/(55)	0/(57)	0/80 (112)	1/38 (53)	0/37 (55)	0/32 (53)
				0.3690	0.3220	NC	NC
Ears	#B Mast Cell Tumor, Benign	0/(60)	0/(60)	0/86 (120)	0/42 (60)	1/40 (60)	0/35 (60)
				0.3695	NC	0.3175	NC
Harderian Glands	#B Adenoma	3/(60)	2/(60)	5/87 (120)	0/42 (60)	3/41 (60)	2/35 (60)
				0.3613	0.8658	0.5019	0.3207
	#M Carcinoma	0/(60)	1/(60)	1/86 (120)	0/42 (60)	0/40 (60)	0/35 (60)
				0.5764	0.3281	0.3175	0.2893
	#B Adenoma/#M Carcinoma	3/(60)	3/(60)	6/87 (120)	0/42 (60)	3/41 (60)	2/35 (60)
				0.4670	0.9112	0.5961	0.4149
Kidneys	#M Renal Mesenchymal Tumor, Malignant	1/(60)	0/(60)	1/86 (120)	0/42 (60)	0/40 (60)	0/35 (60)
				0.5764	0.3281	0.3175	0.2893

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

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	10 mg	25 mg	50 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Liver	#B Adenoma, Hepatocellular	1/(60)	0/(60)	1/86 (120)	3/42 (60)	0/40 (60)	0/35 (60)
				0.7867	0.1030	0.3175	0.2893
Lungs	#B Adenoma, Bronchiolo-Alveolar	3/(60)	3/(60)	6/87 (120)	5/42 (60)	7/41 (60)	6/36 (60)
				0.0479#	0.2623	0.0746	0.0953
	#M Carcinoma, Bronchiolo-Alveolar	1/(60)	3/(60)	4/86 (120)	2/42 (60)	3/40 (60)	2/36 (60)
				0.3709	0.6436	0.3919	0.5735
	#M Carcinoma, Bronchiolo-Alveolar, Multiple	2/(60)	1/(60)	3/87 (120)	1/42 (60)	1/41 (60)	0/35 (60)
				0.8126	0.3935	0.3840	0.6410
	#B+M Bronchiolo-Alveolar	5/(60)	6/(60)	11/87 (120)	7/42 (60)	10/42 (60)	8/37 (60)
				0.0802	0.3572	0.0896	0.1590
Mammary Gland	#B Adenoma	0/(60)	0/(60)	0/86 (120)	0/42 (60)	1/41 (60)	0/34 (57)
				0.3695	NC	0.3228	NC
	#M Adenocarcinoma	1/(60)	0/(60)	1/86 (120)	1/42 (60)	1/41 (60)	0/34 (57)
				0.5346	0.5503	0.5432	0.2833
	#B Adenoma/#M Adenoacanthoma, Malignant	1/(60)	0/(60)	1/86 (120)	1/42 (60)	2/41 (60)	0/34 (57)
				0.4275	0.5503	0.2435	0.2833
	#M Adenoacanthoma, Malignant	0/(60)	0/(60)	0/86 (120)	2/42 (60)	0/40 (60)	0/34 (57)
				0.5996	0.1059	NC	NC
Nerve, Trigemin	#M Schwannoma, Malignant	0/(60)	1/(60)	1/86 (120)	0/42 (60)	0/40 (60)	0/35 (60)
				0.5764	0.3281	0.3175	0.2893

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
$ = Statistically significant at 0.025 and 0.05 level in rare tumor for tests of dose response relationship and pairwise comparison, respectively;
# = Statistically significant at 0.005 and 0.01 level in common tumor for tests of dose response relationship and pairwise comparison, respectively;
NA = Not calculable.

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	10 mg	25 mg	50 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Ovaries	#B Adenoma, Tubulostromal	0/(60)	0/(60)	0/86 (120)	0/42 (60)	1/40 (60)	0/34 (59)
				0.3663	NC	0.3175	NC
	#B Cystadenoma	1/(60)	0/(60)	1/86 (120)	2/42 (60)	2/40 (60)	3/34 (59)
				0.0414#	0.2505	0.2364	0.0683
	#B Cystadenoma, Multiple	0/(60)	1/(60)	1/86 (120)	0/42 (60)	0/40 (60)	0/34 (59)
				0.5743	0.3281	0.3175	0.2833
	#B Cystadenoma+Multiple	1/(60)	1/(60)	2/86 (120)	2/42 (60)	2/40 (60)	3/34 (59)
				0.0823	0.3980	0.3789	0.1372
	#B Granulosa Cell Tumor, Benign	0/(60)	0/(60)	0/86 (120)	0/42 (60)	1/41 (60)	0/34 (59)
				0.3695	NC	0.3228	NC
	#M Granulosa Cell Tumor, Malignant	1/(60)	0/(60)	1/86 (120)	0/42 (60)	0/40 (60)	0/34 (59)
				0.5743	0.3281	0.3175	0.2833
	#B+M Granulosa Cell	1/(60)	0/(60)	1/86 (120)	0/42 (60)	1/41 (60)	0/34 (59)
				0.4316	0.3281	0.5432	0.2833
	#B Luteoma	1/(60)	0/(60)	1/86 (120)	1/42 (60)	1/40 (60)	0/34 (59)
				0.5330	0.5503	0.5359	0.2833
	#B Luteoma, Multiple	0/(60)	1/(60)	1/86 (120)	0/42 (60)	0/40 (60)	0/34 (59)
				0.5743	0.3281	0.3175	0.2833
	#B Luteoma+Multiple	1/(60)	1/(60)	2/86 (120)	1/42 (60)	1/40 (60)	0/34 (59)
				0.6912	0.7002	0.6856	0.4881
	#B Sex Cord Stromal Tumor, Mixed, Benign	0/(60)	0/(60)	0/86 (120)	0/42 (60)	1/40 (60)	1/34 (59)
				0.0946	NC	0.3175	0.2833
Pituitary	#B Adenoma, Pars Distalis	0/(60)	1/(60)	1/86 (120)	3/42 (60)	1/40 (60)	1/34 (59)
				0.3851	0.1030	0.5359	0.4881
	#B Adenoma, Pars Intermedia	0/(60)	0/(60)	0/86 (120)	1/42 (60)	1/40 (60)	0/34 (59)
				0.4302	0.3281	0.3175	NC
	#B Adenoma, Pars Distalis+Intermedia	0/(60)	1/(60)	1/86 (120)	4/42 (60)	2/40 (60)	1/34 (59)
				0.3602	0.0396#	0.2364	0.4881
Rectum	#M Adenocarcinoma	0/(59)	0/(59)	0/84 (118)	0/41 (59)	0/38 (57)	1/34 (59)
				0.1726	NC	NC	0.2881

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
$ = Statistically significant at 0.025 and 0.05 level in rare tumor for tests of dose response relationship and pairwise comparison, respectively;
# = Statistically significant at 0.005 and 0.01 level in common tumor for tests of dose response relationship and pairwise comparison, respectively;
NA = Not calculable.

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	10 mg	25 mg	50 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Skin	#B Fibroma	0/(60)	0/(60)	0/86 (120)	1/42 (60)	0/40 (60)	0/35 (60)
				0.3695	0.3281	NC	NC
	#M Fibrosarcoma	0/(60)	1/(60)	1/86 (120)	1/42 (60)	1/40 (60)	1/35 (60)
				0.2927	0.5503	0.5359	0.4966
	#B Fibroma/#M Fibrosarcoma	0/(60)	1/(60)	1/86 (120)	2/42 (60)	1/40 (60)	1/35 (60)
				0.3558	0.2505	0.5359	0.4966
	#M Basal Cell Tumor, Malignant	1/(60)	0/(60)	1/86 (120)	0/42 (60)	0/40 (60)	0/35 (60)
				0.5764	0.3281	0.3175	0.2893
	#M Carcinoma, Squamous Cell	0/(60)	0/(60)	0/86 (120)	1/42 (60)	0/40 (60)	0/35 (60)
				0.3695	0.3281	NC	NC
	#M Sarcoma, Undifferentiated	0/(60)	1/(60)	1/86 (120)	0/42 (60)	0/40 (60)	0/35 (60)
				0.5764	0.3281	0.3175	0.2893
Systemic Tumors	#B Hemangioma	1/(60)	1/(60)	2/86 (120)	0/42 (60)	1/40 (60)	0/35 (60)
				0.6534	0.5503	0.6856	0.4966
	#M Hemangiosarcoma	2/(60)	4/(60)	6/88 (120)	3/42 (60)	2/41 (60)	3/36 (60)
				0.4439	0.6032	0.4955	0.5148
	#B Hemangioma/#M Hemangiosarcoma	3/(60)	5/(60)	8/88 (120)	3/42 (60)	3/41 (60)	3/36 (60)
				0.5325	0.5006	0.4847	0.4008
	#M Leukemia, Granulocytic	1/(60)	1/(60)	2/86 (120)	0/42 (60)	1/40 (60)	0/35 (60)
				0.6534	0.5503	0.6856	0.4966
	#M Lymphoma, Malignant	9/(60)	15/(60)	24/91 (120)	15/47 (60)	13/46 (60)	5/36 (60)
				0.9148	0.3113	0.4834	0.9016
	#M Mesothelioma, Malignant	0/(60)	0/(60)	0/86 (120)	0/42 (60)	0/40 (60)	1/36 (60)
				0.1765	NC	NC	0.2951
	#M Sarcoma, Histiocytic	5/(60)	3/(60)	8/88 (120)	5/43 (60)	4/42 (60)	0/35 (60)
				0.9470	0.4313	0.5838	0.9376
Thymus	#M Thymoma, Malignant	0/(57)	1/(60)	1/85 (117)	0/42 (60)	0/40 (60)	0/34 (57)
				0.5771	0.3307	0.3200	0.2857
Thyroid Glands	#B Adenoma, Follicular Cell	1/(60)	0/(60)	1/86 (120)	0/42 (60)	1/40 (60)	0/35 (59)
				0.4358	0.3281	0.5359	0.2893
Tongue	#M Carcinoma, Squamous Cell	1/(60)	0/(60)	1/86 (120)	0/42 (60)	0/40 (60)	0/35 (60)
				0.5764	0.3281	0.3175	0.2893
Urinary Bladder	#B Submucosal Mesenchymal Tumor	0/(60)	0/(59)	0/85 (119)	0/40 (58)	0/40 (58)	1/35 (60)
				0.1750	NC	NC	0.2917

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
$ = Statistically significant at 0.025 and 0.05 level in rare tumor for tests of dose response relationship and pairwise comparison, respectively;
# = Statistically significant at 0.005 and 0.01 level in common tumor for tests of dose response relationship and pairwise comparison, respectively;
NA = Not calculable.

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

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	10 mg	25 mg	50 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Uterus	#B Granular Cell Tumor, Benign, Multiple	0/(60)	1/(60)	1/86 (120)	0/42 (60)	0/40 (60)	0/35 (60)
				0.5764	0.3281	0.3175	0.2893
	#B Leiomyoma	0/(60)	0/(60)	0/86 (120)	2/42 (60)	1/40 (60)	0/35 (60)
				0.5148	0.1059	0.3175	NC
	#M Leiomyosarcoma	1/(60)	1/(60)	2/86 (120)	1/42 (60)	2/40 (60)	0/35 (60)
				0.5935	0.7002	0.3789	0.4966
	#B Leiomyoma /#M Leiomyosarcoma	1/(60)	1/(60)	2/86 (120)	3/43 (60)	3/40 (60)	0/35 (60)
				0.6189	0.2059	0.1827	0.4966
	#B Polyp, Endometrial Stromal	3/(60)	6/(60)	9/87 (120)	3/42 (60)	3/40 (60)	2/35 (60)
				0.7757	0.5915	0.5588	0.6628
	#B Polyp, Endometrial Stromal, Multiple	1/(60)	0/(60)	1/86 (120)	0/42 (60)	0/40 (60)	0/35 (60)
				0.5764	0.3281	0.3175	0.2893
	#B Polyp, Endometrial Stromal+ Multiple	4/(60)	6/(60)	10/87 (120)	3/42 (60)	3/40 (60)	2/35 (60)
				0.8319	0.6665	0.6347	0.7274
	#M Sarcoma, Endometrial Stromal	2/(60)	1/(60)	3/86 (120)	0/42 (60)	0/40 (60)	1/35 (60)
				0.5589	0.7002	0.6856	0.3284
	#B+M Endometrial Stromal	5/(60)	6/(60)	11/87 (120)	3/42 (60)	3/40 (60)	3/35 (60)
				0.7461	0.7321	0.7021	0.6140
	#M Adenocarcinoma	0/(60)	0/(60)	0/86 (120)	2/42 (60)	0/40 (60)	1/36 (60)
				0.2627	0.1059	NC	0.2951
Vagina	#B Granular Cell Tumor, Benign	1/(60)	0/(60)	1/86 (120)	0/42 (60)	0/40 (60)	0/35 (60)
				0.5764	0.3281	0.3175	0.2893
Vagina/Uterus	#B Granular Cell Tumor, Benign	1/(60)	1/(60)	2/86 (120)	0/42 (60)	0/40 (60)	0/35 (60)
				0.8217	0.5503	0.5359	0.4966

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
$ = Statistically significant at 0.025 and 0.05 level in rare tumor for tests of dose response relationship and pairwise comparison, respectively;
# = Statistically significant at 0.005 and 0.01 level in common tumor for tests of dose response relationship and pairwise comparison, respectively;
NA = Not calculable.

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

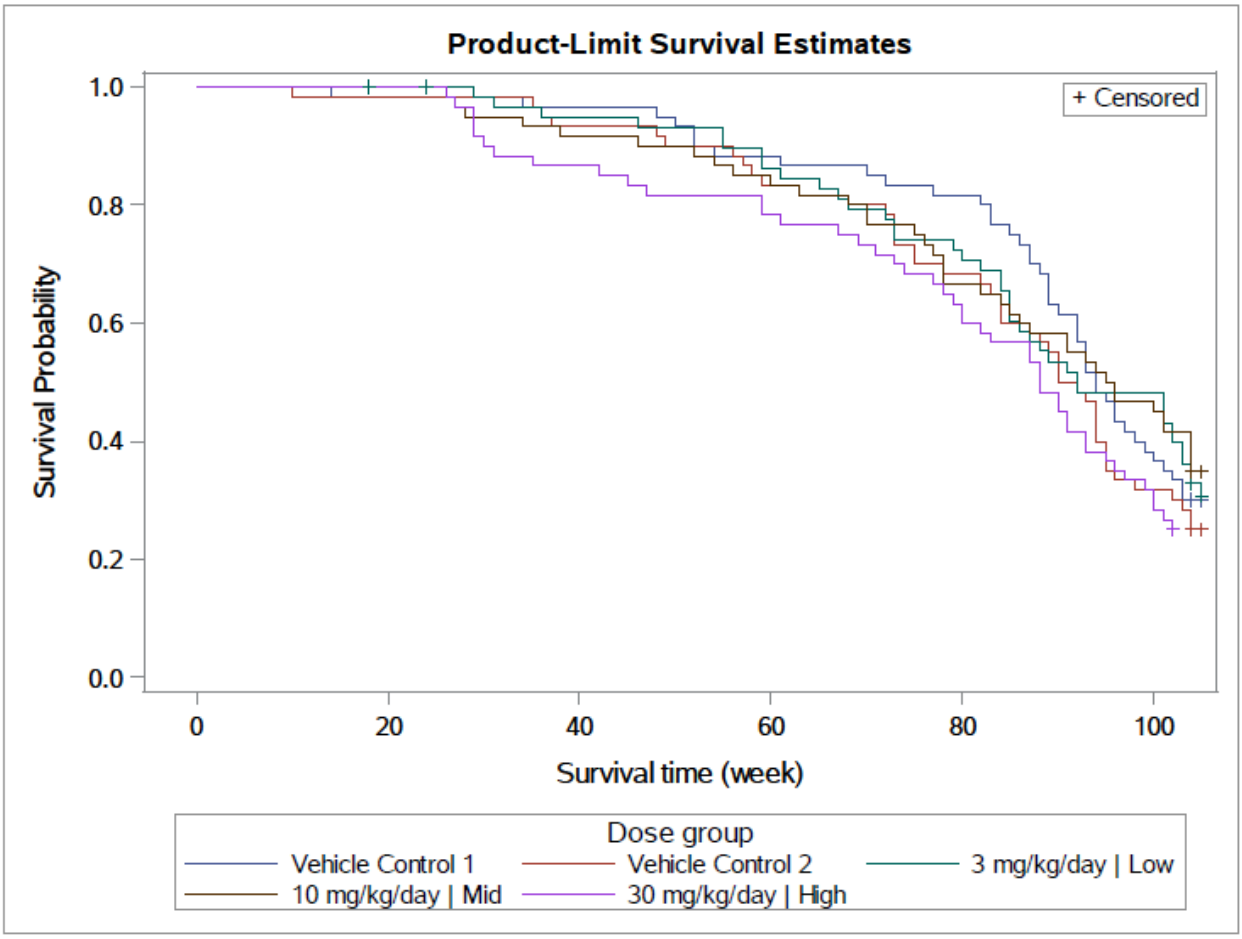


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

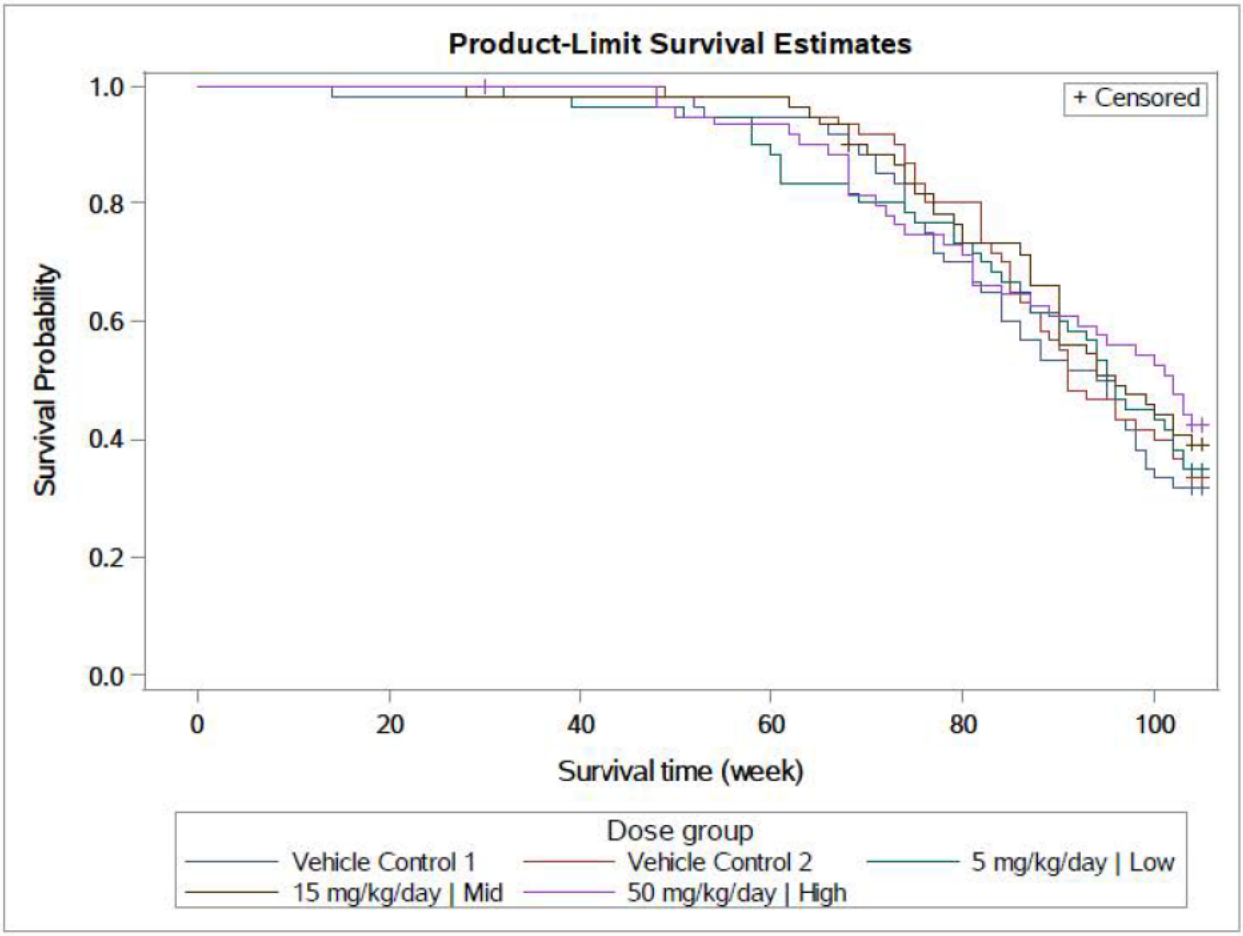


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

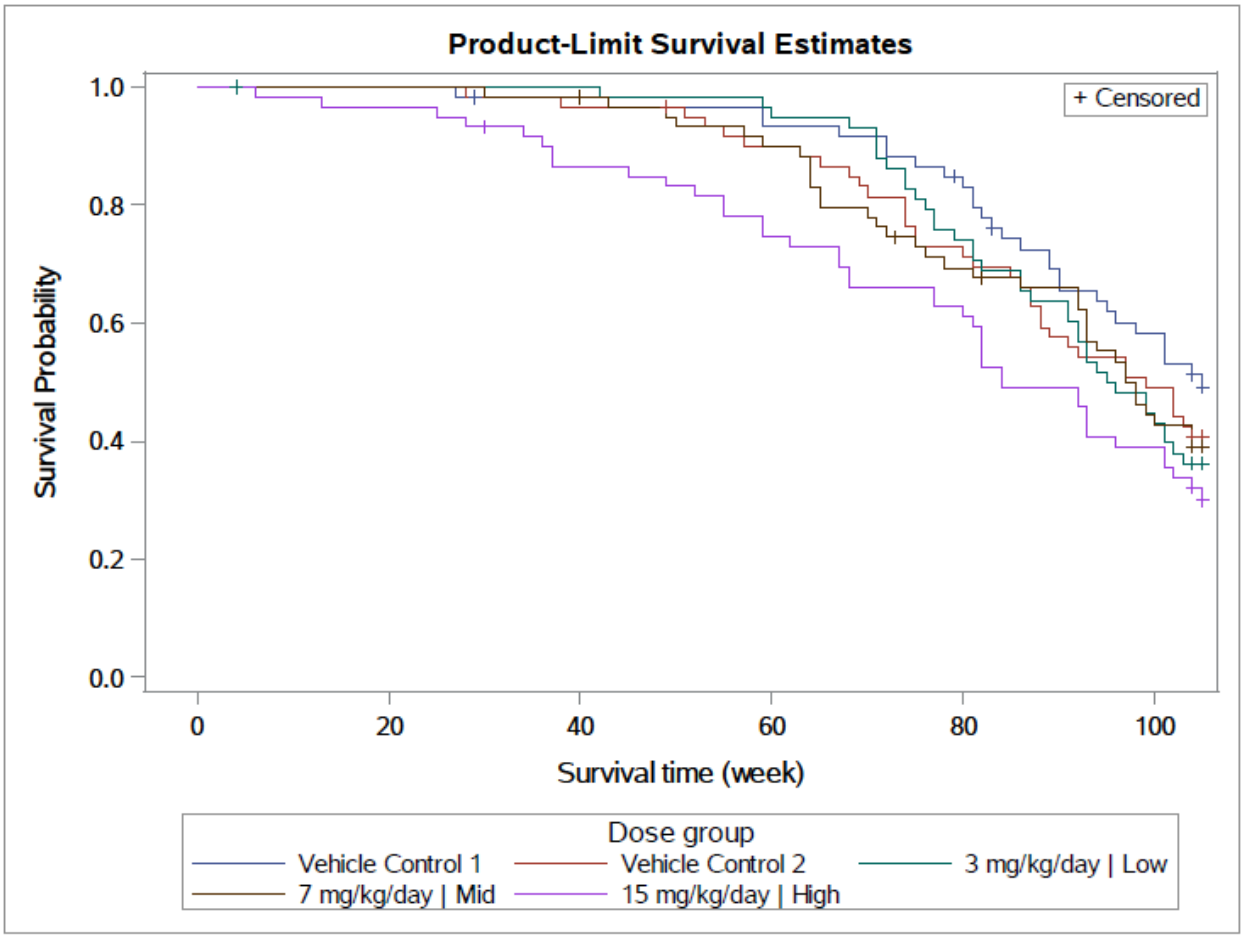
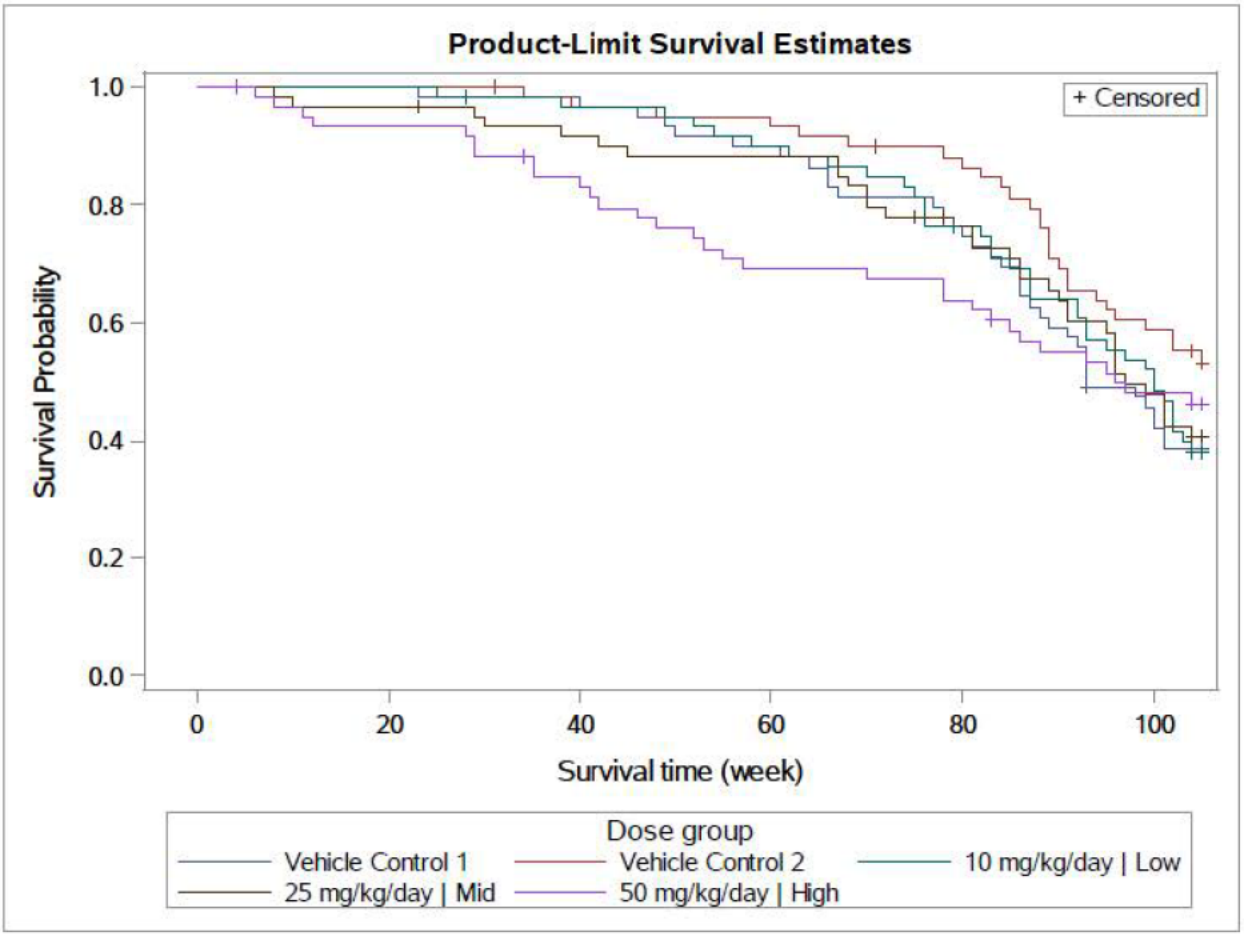


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



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/s/

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12/08/2015

KARL K LIN
12/10/2015
Concur with review