CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211230Orig1s000
211230Orig2s000

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA 211230/0001
Supplement Number:	NA
Drug Name:	Solriamfetol (JZP-110)
Indication(s):	Treatment of excessive sleepiness in adult patients with narcolepsy or obstructive sleep apnea; (b) (4)
Applicant:	Jazz Pharmaceuticals
Date(s):	12/13/2018
Review Priority:	P
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Wei Liu, Ph.D., Mathematical Statistician, QT-CSS/DBVI/OB/OTS
Concurring Reviewers:	Qianyu Dang, Ph.D., Team Leader, DBVI/OB/OTS Yi Tsong, Ph.D., Division Director, DBVI/OB/OTS
Medical Division:	Controlled Substance Staff
The CSS Team:	Shalini Bansil, MD., OD/CSS Silvia Calderon, Ph.D., Senior Pharmacologist, OD/CSS
Project Manager:	Sandra Saltz, OD/CSS
Keywords: NDA review, clinical studies, Crossover design; Clinical abuse potential study; Self-reported endpoint; Multiple endpoints, stimulant	

Supplementary Results

Per meeting discussion with Dr. Shalini Bansil and Dr. Silvia Calderon in CSS on 11/29/2018, this reviewer provided the following tables and figure as NDA 211230 stat review Supplementary:

Table 1- Descriptive stats for Primary Endpoint Drug liking Emax (N=37)

Treatment	Mean	SD	Min	Q1	Med	Q3	Max
PTN 45 mg	74.9	16.6	50	62	76	86	100
PTN 90 mg	86.3	11.9	60	78	87	99	100
JZP-110 300 mg	65.3	17.0	50	50	57	78	97
JZP-110 600 mg	70.9	14.7	50	58	68	84	98
JZP -110 1200 mg	79.6	15.9	50	69	79	94	100
Placebo	52.7	6.1	50	50	50	53	81

Figure 1. Distribution of the Primary Endpoint Drug Liking VAS Emax Across Treatments (N=37)

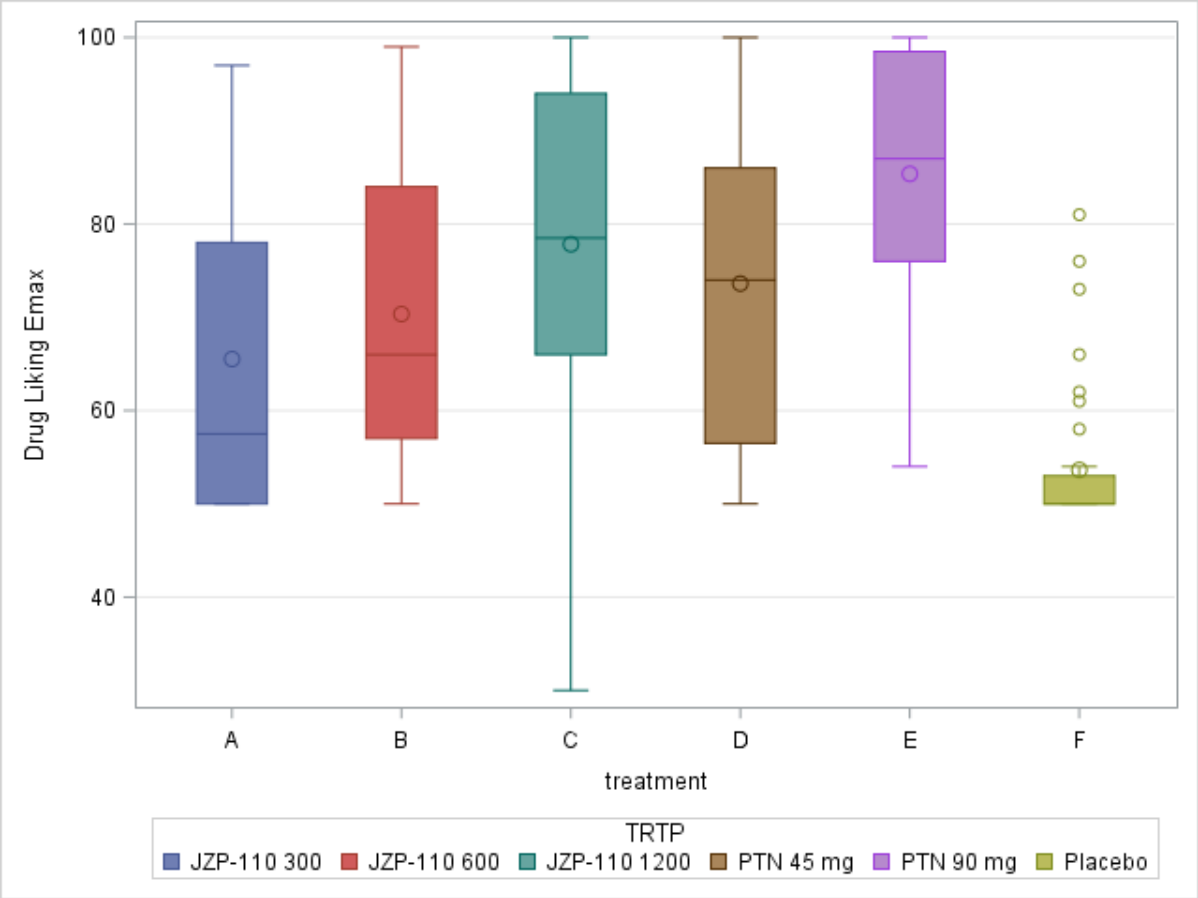

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Table 2- Adjusted Lease Square Mean Emax for Primary and Secondary Endpoints of Controls (PTN 45mg and PTN 90 mg), Treatment (JZP-110 300 mg, JZP-110 600mg and JZP-110 1,200 mg) and Placebo (Mean ± SD) (N=37)

Measure	Placebo	Control Low Dose PTN 45 mg	Control High Dose PTN 90 mg	Treatment Low Dose JZP-110 300 mg	Treatment Mid Dose JZP-110 600mg	Treatment High/Dose JZP-110 1,200 mg
Drug Liking (bipolar)	50.7±2.0	73.4±26.2	87.3±18.9	62.4±26.3	68.9±26.7	77.4±27.6
High Vas (Unipolar)	6.1±29.3	51.2±45.3	84.0±23.8	34.5±48.2	67.9±36.0	64.3±53.4
Overall Drug Liking (bipolar)	46.4±19.8	54.1±31.7	65.9±41.8	49.1±40.2	46.9±31.8	40.8±46.8
Take Drug Again (unipolar)	11.2±32.3	34.5±57.3	52.6±68.8	20.0±38.6	20.0±46.1	25.6±61.0

Table 3- Adjusted Mean Difference Between Treatments for Primary Endpoint of Controls (PTN 45mg and PTN 90 mg), Treatment (JZP-110 300 mg, JZP-110 600mg and JZP-110 1,200 mg) and Placebo (N=37)

Measure	mean	SD	95% Confidence Interval		p-value
			Lower limit	Upper limit	
PTN 45 mg - Placebo	22.7	26.3	15.0	infinity	0.0499
PTN 90 mg - Placebo	36.6	19.0	31.0	infinity	<0.0001
PTN 45 mg - JZP-110 300 mg	11.0	37.1	0.6	infinity	0.0420
PTN 45 mg - JZP-110 600 mg	4.5	37.3	-6.0	infinity	0.2355
PTN 45 mg - JZP-110 1200 mg	-4.0	38.0	-14.7	infinity	0.7348
PTN 90 mg - JZP-110 300 mg	24.9	32.3	15.8	infinity	<0.0001
PTN 90 mg - JZP-110 600 mg	18.4	32.5	9.1	infinity	0.0014
PTN 90 mg - JZP-110 1200 mg	9.9	33.3	0.5	infinity	0.0419
JZP-110 300 mg - Placebo	11.7	26.4	infinity	19.4	0.5622
JZP-110 600 mg - Placebo	18.2	26.7	infinity	26.1	0.9352
JZP-110 1200 mg - Placebo	26.7	27.6	infinity	34.8	0.9978

Note: The mixed-effects model included treatment, sequence, and period as fixed effects, and subject nested within treatment sequence as a random effect. The Kenward-Roger approximation was used to estimate denominator degrees of freedom.

Reference ID: 4362957

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

/s/

WEI LIU
12/13/2018

QIANYU DANG
12/13/2018

YI TSONG
12/13/2018

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 211230
Supplement #:	NA
Drug Name:	Solriamfetol (JZP-110) 37.5 mg, 75 mg, 150 mg, and 300 mg tablets
Indication(s):	To improve wakefulness and reduce excessive sleepiness in adult patients with narcolepsy or obstructive sleep apnea (OSA)
Applicant:	Jazz Pharmaceuticals
Date(s):	Initial submission date: December 20, 2017
	PDUFA due date: December 20, 2018
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Jinglin Zhong, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D.
Medical Division:	Division of Psychiatry Products
Clinical Team:	David H. Millis, M.D.
Project Manager:	Sarah H. Seung, PharmD

Keywords: Clinical studies, NDA review, MMRM

Link to keywords:

http://intranetapps.fda.gov/scripts/ob_apps/ob/eWork/uploads/eWork/2009/Keywords-in-DFS.htm

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1 EXECUTIVE SUMMARY

This review describes statistical findings about Sponsor's studies (ADX-N05 202, 14-002, 14-003, 14-004, and 14-005), supporting the request for approval of JZP-110 to improve wakefulness and reduce excessive sleepiness in adult patients with narcolepsy or obstructive sleep apnea (OSA). The open label phase of Study 14-005 is still on-going. As of the interim cutoff date of April 21, 2017, all randomized subjects have efficacy assessment at the end of the double-blind randomized withdrawal phase. Therefore, the efficacy dataset for Study 14-005 is complete.

Three studies, ADX-N05 202 (doses titration from 150 mg during the first 4 weeks to 300 mg during the last 8 weeks), 14-002 (fixed doses at 75 mg, 150 mg, and 300 mg), and 14-005 (flexible doses at 75 mg, 150 mg, and 300 mg), were conducted in subjects with narcolepsy. This review confirms the Sponsor's finding in subjects with narcolepsy. Based on the results from the Phase 2 Study ADX-N05 202, the difference between treatment groups for the Maintenance of Wakefulness Test (MWT) at the last post-baseline assessment and Clinical Global Impression of change (CGIc) at the last post-baseline assessment were statistically significant, favoring JZP-110. Based on the results from Study 14-002, JZP-110 of 150 mg and 300 mg were statistically better than the placebo group in terms of Change from Baseline (CFB) in MWT at Week 12, CFB in Epworth Sleepiness Scale (ESS) at Week 12, and percentage of subjects reported improved at Week 12 by Patient Global Impression of change (PGIc). JZP-110 of 75 mg failed one of the co-primary endpoint. Based on the results from Study 14-005, JZP-110 were statistically better than the placebo group in terms of CFB in ESS at Week 12, and percentage of subjects reported improved at Week 12 by PGIc and Clinical Global Impression of change (CGIc).

Three studies, 14-003 (fixed doses at 37.5 mg, 75 mg, 150 mg, and 300 mg), 14-004 (flexible doses at 75 mg, 150 mg, and 300 mg), and 14-005 (flexible doses at 75 mg, 150 mg, and 300 mg), were conducted in subjects with OSA. This review confirms the Sponsor's finding in subjects with OSA. Based on the results from 14-003, JZP-110 doses of 75 mg, 150 mg, and 300 mg were statistically better than the placebo group in terms of CFB in MWT at Week 12, CFB in ESS at Week 12, and percentage of subjects reported improved at Week 12 by PGIc. JZP-110 dose of 37.5 mg was statistically better than the placebo group in terms of CFB in MWT at Week 12 and CFB in ESS at Week 12, but not in terms of percentage of subjects reported improved at Week 12 by PGIc. Based on the results from 14-004, JZP-110 was statistically better than the placebo group in terms of change from Week 4 to Week 6 in MWT and change from Week 4 to Week 6 in ESS, and percentage of subjects reported improved at Week 6 by PGIc. Based on the results from Study 14-005, JZP-110 were statistically better than the placebo group in terms of CFB in ESS at Week 12, and percentage of subjects reported improved at Week 12 by PGIc and CGIc.

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The primary endpoints of the Phase 2 Study ADX-N05 202 are CFB in MWT at the last post-baseline assessment and CGIc at the last post-baseline assessment. Before Division of Psychiatry Products (DPP) took over the review of applications for this class of indications, the submitted protocol and the SAP of this trial were not reviewed by the statistical team then. The design of the study is appropriate for the objectives of the study. However, the choices of primary endpoints are not appropriate because we would not accept CGI-C as a primary endpoint, and additionally the duration for measuring improvement should have been a fixed duration instead of varying durations depending on the time when subject dropped out. For the other Phase 3 trials with similar designs included in the NDA, the co-primary endpoints FDA agreed upon are the CFB in MWT at Week 12 and CFB in ESS at Week 12. The Sponsor did not pre-specify the multiplicity adjustment for the primary endpoints and secondary endpoints in the protocol and SAP. CFB in ESS and PGIc are considered as exploratory endpoints in this study.

2 INTRODUCTION

2.1 Overview

The Sponsor submits this New Drug Application (NDA) seeking approval of JZP-110. The indication sought for JZP-110 is to improve wakefulness and reduce excessive sleepiness in adult patients with narcolepsy or OSA. This submission is based on one Phase 2 12-week trial, ADX-N05-202, two Phase 3 short-term pivotal trials, 14-002, 14-003, and one Phase 3 6-week randomized withdrawal trial 14-004, and one 40- or 52- week randomized withdrawal trial, 14-005.

Table 1: List of All Studies Included in Analyses

Protocol Number	Phase and Design	Treatment Period	Follow-up Period	# of randomized Subjects	Study Population
ADX-N05 202 (TONES 1	Phase 2, double blind, placebo-controlled, parallel, randomized trial	12-week double blind treatment	1 week	Placebo 49 JZP-110 44	Adult subjects with narcolepsy
14-002 (TONES 2)	Phase 3, double blind, placebo-controlled, parallel, randomized trial	12-week double blind treatment	2 weeks	Placebo 60 JZP-110 75 mg 59 150 mg 60 300 mg 60	Adult subjects with narcolepsy
14-003 (TONES 3)	Phase 3, double blind, placebo-controlled, parallel, randomized trial	12-week double blind treatment	2 weeks	Placebo 119 JZP-110 37.5 mg 58 75 mg 62 150 mg 117 300 mg 118	Adult subjects with OSA

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14-004 (TONE S 4)	Phase 3, double blind, placebo-controlled, parallel, randomized-withdrawal trial	4-week open label, 2-week double blind randomized withdrawal treatment	2 weeks	Placebo 62 JZP-110 62	Adult subjects with OSA
14-005 (TONE S 5)	Long-term double blind, placebo-controlled, parallel, randomized-withdrawal trial	40- or 52-week open label, 2-week double blind randomized withdrawal treatment	2 weeks	Placebo 142 JZP-110 140	Adult subjects with narcolepsy or OSA

2.2 Data Sources

The Sponsor submitted study reports, analysis datasets, raw datasets, and programs for all five studies. The analysis datasets and raw datasets are in the following directories of the CDER electronic document room (EDR): \\Cdsesub1\evsprod\NDA211230\0001.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

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

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 ADX-N05 202

This was a Phase 2, 12-week, double-blind, placebo-controlled, randomized, parallel-group, multi-center study of the safety and efficacy of ADX-N05 in the treatment of excessive daytime sleepiness in subjects with narcolepsy. The study was conducted at 28 study centers in the United States. ADX-N05 is an alternative research name for JZP-110.

This study had 3 phases:

- Screening and baseline phase (up to 28 days screening and washout)
- Double blind treatment phase (12 weeks)
- Follow up phase (1 week)

Subjects randomized to the ADX-N05 group initially received 150 mg from Week 1 through Week 4, and received 300 mg starting on Week 5.

A total of 93 subjects were randomized (44 subjects in the ADX-N05 and 49 in the placebo treatment groups). Among them, 74 subjects completed the study.

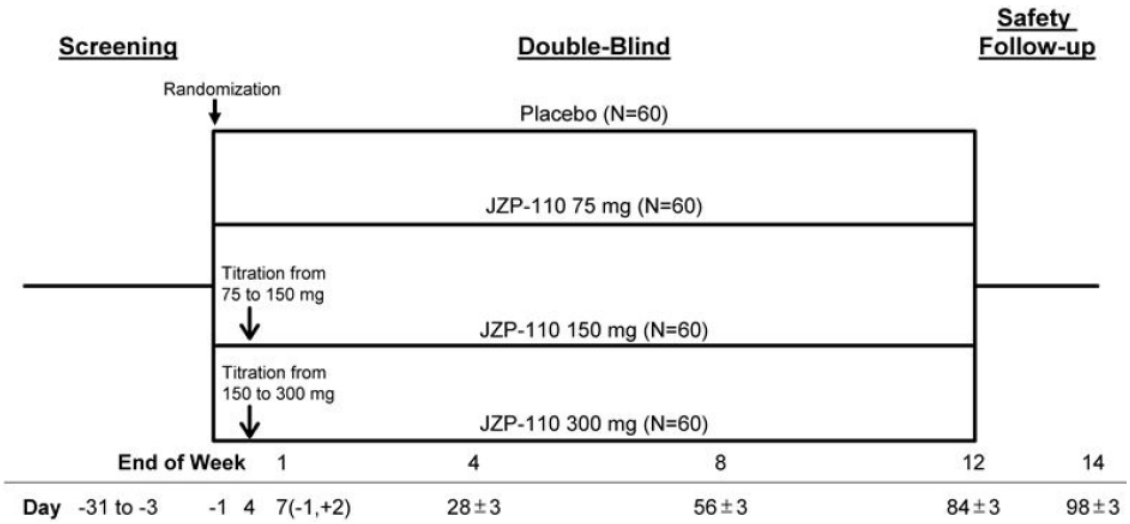
There are two primary endpoints. One is CFB in MWT at the last post-baseline assessment. The other is CGI-c scores at the last post-baseline assessment. There are four secondary endpoints. In the final protocol, SAP, and clinical study report, these 4 secondary endpoints were listed as secondary endpoints without any multiplicity adjustment. However, in Table 1 on Page 13 of Summary of Clinical Efficacy of this NDA submission, the Sponsor listed the 4 secondary endpoints as key secondary endpoints (b) (4) .

Before DPP took over the review of applications for this class of indications, the submitted protocol and the SAP of this trial were not reviewed by the statistical team then. The design of the study is appropriate for the objectives of the study. However, the choices of primary endpoints are not appropriate because we would not accept CGI-C as a primary endpoint, and additionally the duration for measuring improvement should have been a fixed duration instead of varying durations depending on the time when subject dropped out. For the other Phase 3 trials with similar designs included in the NDA, the co-primary endpoints FDA agreed upon are the CFB in MWT at Week 12 and CFB in ESS at Week 12. The Sponsor did not pre-specify the multiplicity adjustment for the primary endpoints and secondary endpoints in the protocol and SAP. CFB in ESS and PGIc are considered as exploratory endpoints in this study.

3.2.1.2 14-002

This was a 12-week, randomized, double-blind, placebo-controlled, multicenter, 4-arm, parallel group study of safety and efficacy of JZP-110 in the treatment of excessive sleepiness in adult subjects with narcolepsy. The study has three phases. The study design is graphically presented in Figure 1.

Figure 1: Study Schema – 14-002



Source: Sponsor's Figure 1 in Protocol 14-002.

Subjects randomized to the 150 mg dose initially received 75 mg from Day 1 through Day 3 of the first week of the Treatment Phase and received 150 mg starting on Day 4. Subjects randomized to the 300 mg dose initially received 150 mg from Day 1 through Day 3 of the first week of the Treatment Phase and received 300 mg starting on Day 4. Subjects randomized to the 75 mg group did not require titration.

A total of 239 subjects were randomized and 195 subjects completed the study.

There are two co-primary endpoints. One is CFB in MWT at Week 12. The other is CFB in ESS score at Week 12. The key secondary endpoint is percentage of subjects reported as improved (minimally, much, or very much) at Week 12 by PGIc.

The design of the study is appropriate for the objectives of the study. The choice of the co-primary endpoints and the key secondary endpoint is appropriate for the study design.

3.2.1.3 14-003

This trial was a 12-week, randomized, double-blind, placebo-controlled, multicenter, 5-arm parallel group study of safety and efficacy of JZP-110 in the treatment of excessive sleepiness in adult subjects with OSA.

The study has three phases. The study design is graphically presented in Figure 2.

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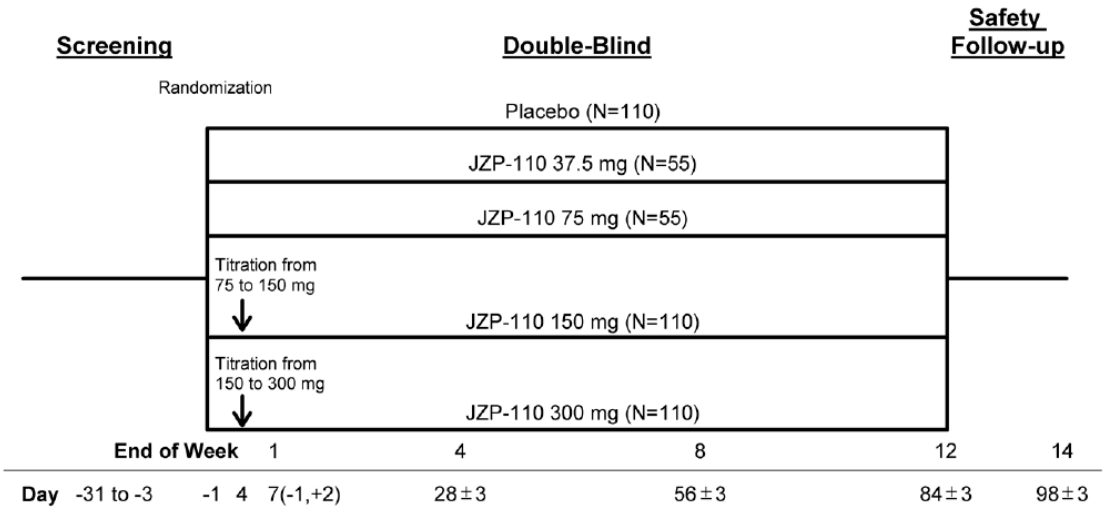
Figure 2: Study Schema – 14-003



Source: Sponsor's Figure 1 in Protocol 14-003.

Subjects randomized to the 150 mg dose initially received 75 mg from Day 1 through Day 3 of the first week of the Treatment Phase and received 150 mg starting on Day 4. Subjects randomized to the 300 mg dose initially received 150 mg from Day 1 through Day 3 of the first week of the Treatment Phase and received 300 mg starting on Day 4. Subjects randomized to the other treatment groups did not require titration.

A total of 476 subjects were randomized and 404 subjects completed the study.

There are two co-primary endpoints. One is CFB in MWT at Week 12. The other is CFB in ESS score at Week 12. The key secondary endpoint is percentage of subjects reported as improved (minimally, much, or very much) at Week 12 by PGIc.

The design of the study is appropriate for the objectives of the study. The choice of the co-primary endpoints and the key secondary endpoint is appropriate for the study design.

3.2.1.3 14-004

This trial is a 6-week, double-blind, placebo-controlled, randomized-withdrawal, multicenter study of safety and efficacy of JZP-110 in the treatment of excessive sleepiness in adult subjects with OSA. The study design is graphically presented in Figure 3.

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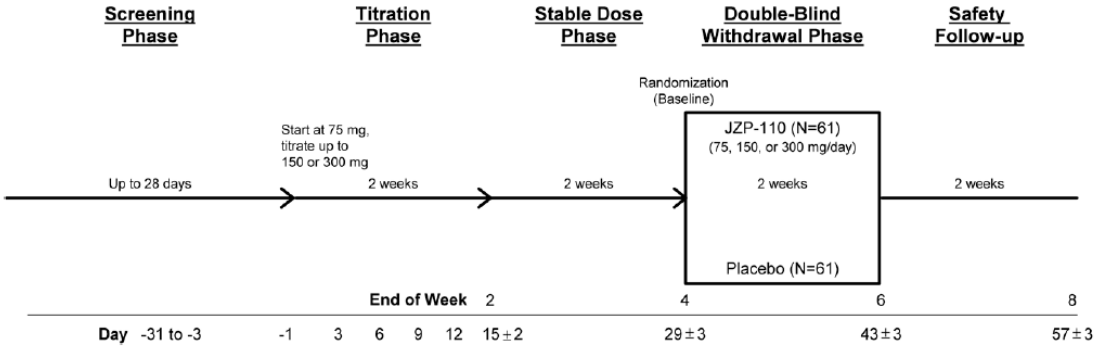
Figure 3: Study Schema – 14-004



Source: Sponsor's Figure 1 in Protocol 14-004.

During the 2-week Titration Phase, subjects were titrated to the maximal dose that is tolerated. Subjects started at a once-daily dose of 75 mg JZP-110 and could titrate up one dose level (to 150 mg/day or a maximum dose of 300 mg/day) once every 3 days following a telephone consultation with investigative site staff. Subjects could titrate down to 75 mg or 150 mg at any time following a telephone consultation with investigative site staff. Following completion of the Titration Phase, subjects who had been titrated to an efficacious and tolerable dose remained on that dose for the subsequent 2 weeks during an open-label Stable Dose Phase. During the 2-week Stable Dose Phase, subjects received a once daily dose of JZP-110 equal to the dose that they received at the end of the Titration Phase.

At the end of the Stable Dose Phase (Week 4), subjects who reported much or very much improvement on the PGIc scale as compared to the beginning of the Titration Phase (after discontinuation of prior medications and before receiving JZP-110) underwent additional assessments, which included an overnight stay at the investigational site for nocturnal polysomnography (PSG) followed by a MWT as well as safety assessments. Subjects who completed the Week 4 Visit and who reported much or very much improvement on the PGIc scale and whose mean sleep latency on the MWT and ESS scores also improved were randomized in the Double-blind Withdrawal Phase. Stratified randomization on the basis of subjects' compliant or non-compliant use of their primary OSA therapy were used to assign subjects in a 1:1 ratio to continue to receive JZP-110 at the dose that was received in the Stable Dose Phase or to receive placebo for 2 weeks in the Double-blind Withdrawal Phase. Subjects who did not report being much or very much improved on the PGIc scale or who did not improve on the MWT and ESS from the beginning of the Titration Phase to Week 4 were discontinued from the study.

There are two co-primary endpoints. One is change in MWT from the end of the Stable Dose Phase (Week 4) to the end of the Double-blind Withdrawal Phase (Week 6). The other is change in ESS score from the end of the Stable Dose Phase (Week 4) to the end of the Double-blind Withdrawal Phase (Week 6). The key secondary endpoint is PGIc:

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percentage of subjects reported as worse (minimally, much, or very much) at the end of the Double-blind Withdrawal Phase (Week 6).

There was a concern about the duration of the study. It is too short, which may hamper its ability to provide evidence of sustained efficacy over time. The choice of primary endpoints and key secondary endpoint is appropriate for the study design.

3.2.1.3 14-005

This is a Phase 3 study to assess the long-term safety, open-label maintenance of efficacy, and double-blind, placebo-controlled maintenance of efficacy of JZP-110 in subjects who had completed Study 14-002, 14-003, 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202. The study consists of a 2-week Titration Phase for all subjects, a 38-week Maintenance Phase for subjects who completed Study 14-002 or 14-003 or a 50-week Maintenance Phase for subjects who completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202, and a 2-week Safety Follow-up period. The study design is graphically presented in Figure 4.

During the 2-week Titration Phase, subjects began with a once-daily dose of 75 mg JZP-110 and could titrate up one dose level (to 150 mg/day or a maximum dose of 300 mg/day) once every 3 days following a telephone consultation with investigative site staff. Subjects could titrate down to 75 or 150 mg at any time following a telephone consultation with investigative site staff to achieve a maximal dose that is tolerable. After the 2-week Titration Phase, subjects entered the Maintenance Phase at the stable dose that was reached at the end of the Titration Phase. After entering the Maintenance Phase, only three dose adjustments (to doses of 75 mg, 150 mg or 300 mg daily) were allowed during the first 12 weeks of the Maintenance Phase. If the dose could not be successfully adjusted within these parameters, the subject was discontinued from the study.

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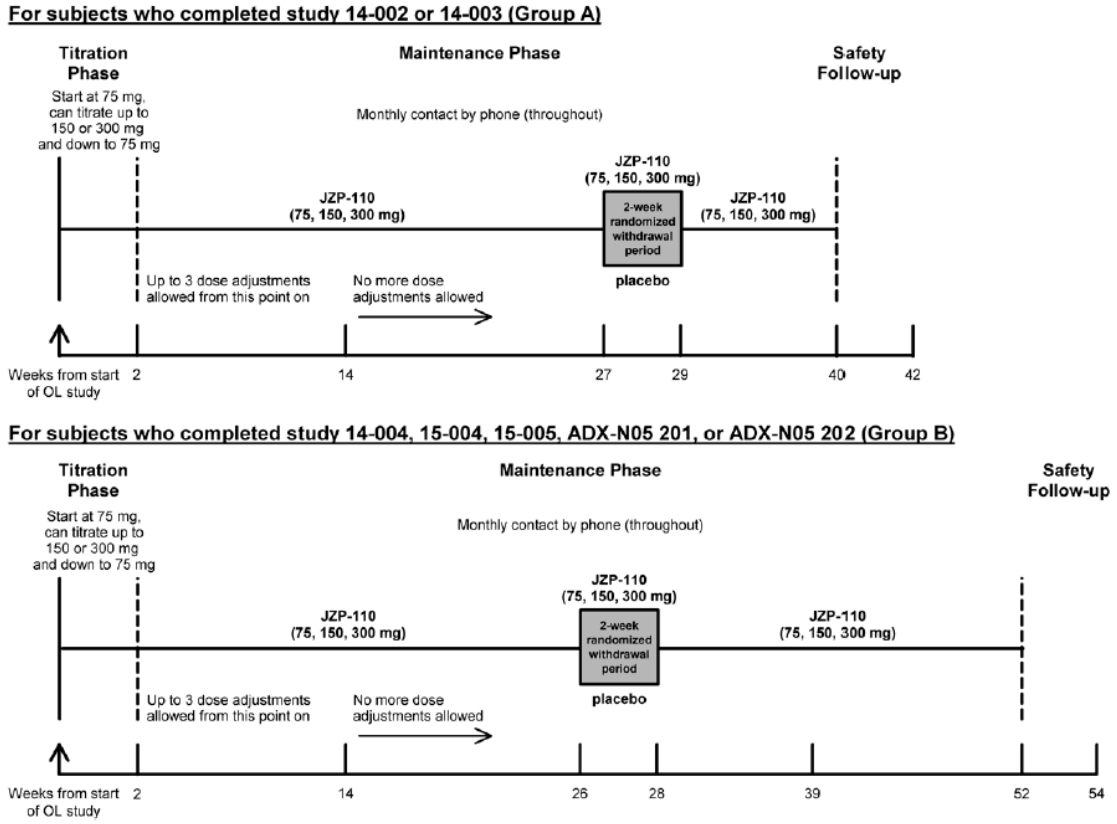
Figure 4: Study Schema – 14-005



Source: Sponsor's Figure 1 in Protocol 14-005.

The primary endpoint is the change in ESS score form the beginning to the end of the 2-week RW phase. There are two key secondary endpoints, PGIc and CGIc, percentage of subjects reported as worse at the end of the 2-week RW phase.

The design of the study is appropriate for the objectives of the study. The choice of primary endpoints is appropriate for the study design. PGIc and CGIc provides redundant information with each other. (b) (4)

Statistical Methodologies

3.2.2.1 ADX-N05 202

The intent-to-treat (ITT) population was the basis for the primary and secondary efficacy analyses. The ITT population consisted of all randomized subjects who received at least 1 dose of double-blind study drug and had at least 1 post-baseline efficacy evaluation.

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When comparison between groups were performed, two-sided tests at a 0.05 significance level were used. No adjustment of multiplicity was made for endpoints.

The primary analysis on CFB in MWT at the last post-baseline assessment used a two-sample test. Two sensitivity analyses were planned by the Sponsor: analysis of covariance (ANCOVA) and per-protocol analysis. The primary analysis on CGI-C at the last post-baseline assessment used Fisher's exact test. An additional sensitivity analysis was performed using logistic regression.

The Sponsor's primary endpoints were assessed at the last post-baseline assessment. The varying endpoint visit is different from FDA agreed primary endpoints, which were assessed at Week 12 for the Phase 3 trials with a similar design. This reviewer performed analyses on the primary endpoints assessed at Week 12. To deal with missing data at Week 12, this reviewer performed the same analyses agreed for those Phase 3 trials: a mixed effect repeated measures model (MMRM) for MWT, Chi-square with last observation carried forward (LOCF) for CGIc.

3.2.2.1 14-002

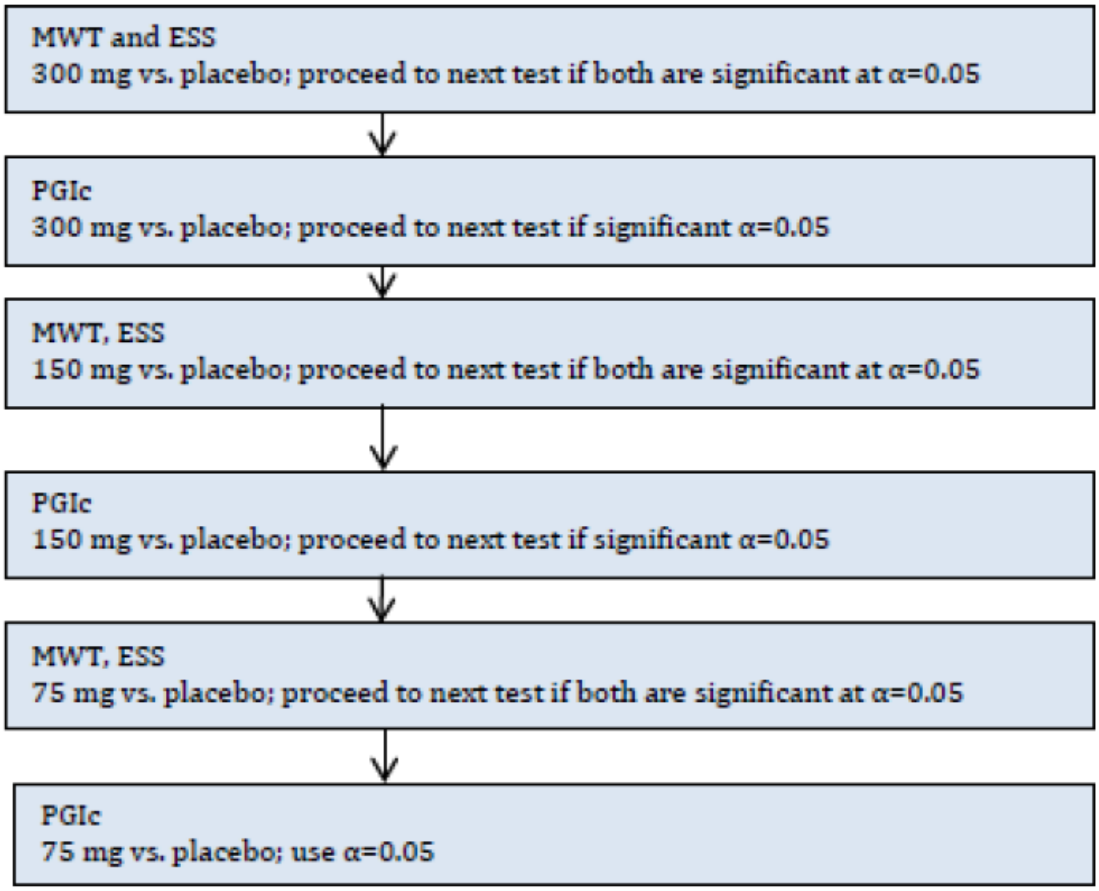
The analysis population for the efficacy analyses of the study is the modified intent-to-treat (mITT) population, defined as subjects who received at least 1 dose of study medication and had baseline and at least 1 post-baseline evaluation of MWT or ESS.

The primary endpoint of MWT or ESS was analyzed using MMRM, with treatment, time, treatment by time interaction, and randomization stratification factor (presence or absence of cataplexy at Screening) as the fixed effects and baseline value of the efficacy endpoint as the covariate. An unstructured covariance matrix was used to model the correlations among repeated measurements. Should the model fail to converge, an auto-regressive (AR1) covariance structure would be used. It the model still failed to converge, a compound symmetric covariance structure would be used.

The key secondary endpoint of PGIc was analyzed using chi-squared tests with LOCF method for missing data. A gatekeeping testing procedure was utilized to control the overall type I error rate at 0.05. The sequence of testing multiple endpoints and doses is displayed in the following figure.

Reference ID: 4324053

Figure 5: Multiple Testing Procedure – 14-002



Source: Sponsor's Figure 2 on Page 27 of SAP.

The sensitivity analyses for the co-primary endpoints relied on ANCOVA models with single imputation approaches (LOCF and mean imputation) and multiple imputation approaches based on Markov Chain Monte Carlo (MCMC) method and regression method. For the sensitivity analyses for the key secondary endpoint, chi-square tests with worst case carried forward and imputation based on early termination reason were used.

3.2.2.1 14-003

The analysis population for the efficacy analyses of the study is the mITT population, defined as subjects who received at least 1 dose of study medication and had baseline and at least 1 post-baseline evaluation of MWT or ESS.

The primary endpoint of MWT or ESS was analyzed using MMRM, with treatment, time, treatment by time interaction, and randomization stratification factor (compliant or non-compliant use of a primary OSA therapy at Screening) as the fixed effects and baseline value of the efficacy endpoint as the covariate. An unstructured covariance matrix was used

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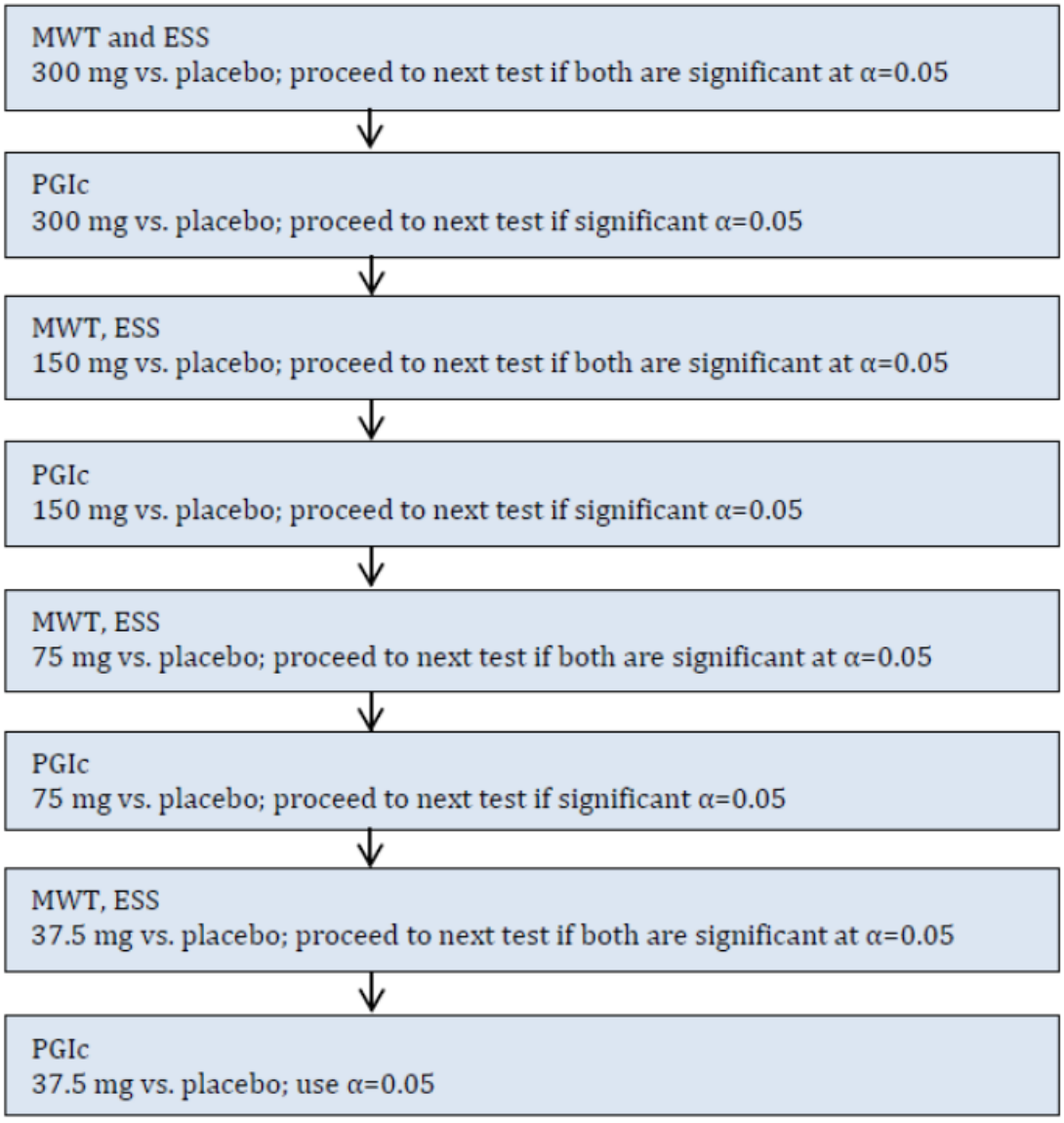
to model the correlations among repeated measurements. Should the model fail to converge, an auto-regressive (AR1) covariance structure would be used. It the model still failed to converge, a compound symmetric covariance structure would be used.

The key secondary endpoint of PGIc was analyzed using chi-squared tests with LOCF method for missing data. A gatekeeping testing procedure was utilized to control the overall type I error rate at 0.05. The sequence of testing multiple endpoints and doses is displayed in the following figure.

Figure 6: Multiple Testing Procedure – 14-003



Source: Sponsor's Figure 2 on Page 26 of SAP.

Reference ID: 4324053

The sensitivity analyses for the co-primary endpoints relied on ANCOVA models with single imputation approaches (LOCF and mean imputation) and multiple imputation approaches based on MCMC method and regression method. For the sensitivity analyses for the key secondary endpoint, chi-square tests with worst case carried forward and imputation based on early termination reason were used.

3.2.2.1 14-004

The analysis population for the primary and secondary analyses of the study is the mITT population, defined as subjects who were randomized in the Double-blind Withdrawal Phase, who received at least one dose of study medication in the Double-blind Withdrawal Phase, and who have a Week 4 (end of Stable Dose Phase) and at least one post-Week 4 assessment of MWT or ESS.

The primary endpoint of MWT or ESS was analyzed using an ANCOVA model, with treatment and randomization stratification factor (compliant or non-compliant use of a primary OSA therapy at the end of the Stable Dose Phase) as the fixed effects and end of the Stable Dose Phase (Week 4) value of the efficacy endpoint as the covariate. The LOCF method is used for subjects who discontinued early in the Double-Blind Withdrawal Phase. The key secondary endpoint of PGIc was analyzed using chi-squared test with the LOCF method for missing data.

The sensitivity analyses for the co-primary endpoints were planned. They relied on the ANCOVA model with mean imputation approach. For the sensitivity analyses for the key secondary endpoint, chi-square tests with worst case carried forward and imputation based on early termination reason were planned.

3.2.2.1 14-005

The analysis population for the primary and secondary analyses of the study is the mITT population, defined as subjects who were randomized in the Double-blind Withdrawal Phase, who received at least one dose of study medication in the Double-blind Withdrawal Phase, and who have evaluable efficacy data at Week 29 (Group A) or Week 28 (Group B).

For the primary analysis of the ESS score, an ANCOVA model were used. The response variable was the change from the beginning to the end of Randomized Withdrawal Period. The model included the following fixed effects: Treatment group, Randomization stratification factor (narcolepsy vs. OSA) and efficacy baseline. The LOCF approach were planned for subjects who discontinued early in the Randomized Withdrawal Period. The key secondary endpoints of PGIc and CGIc were analyzed using chi-squared test with the LOCF method for missing data.

Reference ID: 4324053

To address multiplicity issues in the analysis of the primary and secondary efficacy endpoints, a fixed hierarchical testing sequence (ESS, PGIc and CGIc) were used.

ANCOVA with single imputation based on mean imputation and ANCOVA with multiple imputations based on MNAR were planned as sensitivity analyses for the primary endpoint. For the sensitivity analyses for the key secondary endpoint, chi-square tests with worst case carried forward and imputation based on early termination reason were planned.

Interim analyses were planned in the protocol and SAP. However, no details about how to perform the interim analyses and how to adjust the alpha level were provided in the protocol and SAP. The following two paragraphs are all the details provided in the protocol and SAP.

"*Interim analyses are planned when the study has approximately 50 subjects with narcolepsy and 50 subjects with OSA with an exposure to JZP-110 of 52 weeks and 100 subjects with narcolepsy and 200 subjects with OSA with an exposure to JZP-110 of 26 weeks.*

An interim analysis of the double-blind, placebo-controlled efficacy data from the Randomized Withdrawal Period of the Maintenance Phase may be conducted as well."

A sample size of 300 subjects was planned for the RW period. The randomized withdrawal period is either Week 27 to 29 or Week 26 to Week 28. Therefore, the planned time of the interim analysis is essentially the time when the efficacy data from the RW is complete and the open-label part of the study is still going on. The interim efficacy analysis is the final efficacy analysis.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 ADX-N05 202

A total of 93 subjects were randomized in the study. All 93 subjects were included in the Safety Population. Three subjects (subjects (b) (6) and (b) (6) in the placebo group and subject (b) (6) of the JZP-110 group) received at least one dose of study drug but had no post-baseline efficacy measurements. The remaining 90 subjects were included in the ITT population. Of the 90 subjects in the ITT population, 32 had cataplexy (Cataplexy Population), and 74 completed 12 weeks of dosing with study drug and completed their last MWT assessment. A summary of subject disposition of all screened subjects is presented in Table 2.

Reference ID: 4324053

Table 2: Subject Disposition (All Screened Subjects) – ADX-N05-202

	ADX-N05 N (%)	Placebo N (%)	Total N (%)
Subjects Screened			213
Screen Failures			120
Subjects Randomized	44	49	93
Subjects Completed Study	36 (81.8)	38 (77.6)	74 (79.6)
Subjects Discontinued Prematurely	8 (18.2)	11 (22.4)	19 (20.4)
Reason for Discontinuation			
Withdrawal by Subject	3 (6.8)	5 (10.2)	8 (8.6)
Protocol Violation	1 (2.3)	0	1 (1.1)
Lack of Efficacy	0	3 (6.1)	3 (3.2)
Adverse Event	3 (6.8)	2 (4.1)	5 (5.4)
Withdrawn by Investigator	0	0	0
Lost to Follow-Up	0	1 (2.0)	1 (1.1)
Other	1 (2.3)	0	1 (1.1)
Safety Population	44	49	93
ITT Population	43	47	90
Per Protocol Population	36	38	74
Cataplexy Population	17	15	32

Note: ADX-N05 is an alternative research name for JZP-110.
Source: Sponsor's Table 6 on Page 57 of Clinical Study Report of ADX-N05-202.

Summary of the demographic and baseline physical characteristics is presented in Table 3. The majority of subjects were female (64.5%) and White (74.2%). Mean (SD) age was 38.7 (12.13) years and the range was 18 to 70 years. Mean (SD) body weight was 76.1 (16.44) kg. Mean (SD) body mass index was 26.6 (4.46) kg/m^2. The majority of the subjects had a diagnosis of narcolepsy without cataplexy (64.5%). The demographic and baseline characteristics of the JZP-110 and placebo groups of the safety population were generally comparable with a few exceptions. Compared with the placebo group, the JZP-110 group had slightly older subjects (median age 39.5 versus 32.0).

Reference ID: 4324053

Table 3: Summary of Demographic Characteristics (Safety Population) – ADX-N05-202

Summary	ADX-N05 N=44	Placebo N=49	Overall N=93	P-value [1]
AGE (YEARS)				
N	44	49	93	0.0812
MEAN (SD)	41.0 (12.33)	36.7 (11.71)	38.7 (12.13)	
MEDIAN	39.5	32.0	36.0	
MIN, MAX	19, 70	18, 66	18, 70	
GENDER				
FEMALE	30 (68.2%)	30 (61.2%)	60 (64.5%)	0.5214
MALE	14 (31.8%)	19 (38.8%)	33 (35.5%)	
RACE				
AMERICAN INDIAN OR ALASKA NATIVE	0	0	0	0.3577
BLACK OR AFRICAN AMERICAN	12 (27.3%)	10 (20.4%)	22 (23.7%)	
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (2.3%)	0	1 (1.1%)	
ASIAN	1 (2.3%)	0	1 (1.1%)	
WHITE	30 (68.2%)	39 (79.6%)	69 (74.2%)	
ETHNICITY				
HISPANIC OR LATINO	1 (2.3%)	3 (6.1%)	4 (4.3%)	0.6190
NOT HISPANIC OR LATINO	43 (97.7%)	46 (93.9%)	89 (95.7%)	
HEIGHT (cm)				
N	44	49	93	0.5470
MEAN (SD)	168.7 (7.94)	168.3 (10.25)	168.5 (9.18)	
MEDIAN	168.8	167.6	167.6	
MIN, MAX	154.9, 185.4	149.8, 197.0	149.8, 197.0	
WEIGHT (kg)				
N	44	49	93	0.6481
MEAN (SD)	76.8 (16.05)	75.4 (16.92)	76.1 (16.44)	
MEDIAN	77.7	78.0	78.0	
MIN, MAX	37.4, 112.5	47.4, 114.3	37.4, 114.3	

Summary	ADX-N05 N=44	Placebo N=49	Overall N=93	P-value [1]
BMI (kg/m^2)				
N	44	49	93	0.7070
MEAN (SD)	26.8 (4.52)	26.4 (4.44)	26.6 (4.46)	
MEDIAN	26.9	26.8	26.8	
MIN, MAX	15.6, 33.6	17.8, 33.5	15.6, 33.6	
DIAGNOSIS				
NARCOLEPSY WITH CATAPLEXY	17 (38.6%)	16 (32.7%)	33 (35.5%)	0.6649
NARCOLEPSY WITHOUT CATAPLEXY	27 (61.4%)	33 (67.3%)	60 (64.5%)	

Source: Sponsor's Table 14.1.2 on Page 97 of Clinical Study Report ADX-N05-202.

3.2.3.2 14-002

A total of 239 subjects were randomized. Of these, 236 subjects received at least 1 dose of study medication and comprised the Safety Population. There are 5 subjects (subjects (b) (6)) excluded from the mITT population (231 subjects) because of missing a baseline evaluation or at least 1 post-baseline evaluation of MWT and ESS. There are 195 subjects completed the study. A summary of subject disposition of the safety population is presented in Table 4.

Reference ID: 4324053

Table 4: Subject Disposition (Safety Population) – 14-002

Category	Placebo N = 59	75 mg JZP-110 N = 59	150 mg JZP-110 N = 59	300 mg JZP-110 N = 59	Combined JZP-110 N = 177
Completed; n (%)					
Yes	52 (88.1)	49 (83.1)	51 (86.4)	43 (72.9)	143 (80.8)
No	7 (11.9)	10 (16.9)	8 (13.6)	16 (27.1)	34 (19.2)
If No, Primary Reason, n (%)					
Lack of Efficacy	1 (1.7)	4 (6.8)	1 (1.7)	6 (10.2)	11 (6.2)
Protocol Violation	0	0	1 (1.7)	1 (1.7)	2 (1.1)
Adverse Event	1 (1.7)	2 (3.4)	4 (6.8)	5 (8.5)	11 (6.2)
Withdrawal of Consent	1 (1.7)	1 (1.7)	1 (1.7)	2 (3.4)	4 (2.3)
Lost to Follow-up	1 (1.7)	1 (1.7)	0	0	1 (0.6)
Treatment Non-compliant	0	0	0	0	0
Diary Non-compliant	0	0	0	0	0
Sponsor Decision	1 (1.7)	0	0	0	0
Investigator Decision	0	0	0	0	0
Other[a]	2 (3.4)	2 (3.4)	1 (1.7)	2 (3.4)	5 (2.8)

Source: Sponsor's Table 3 on Page 79 of the Clinical Study Report of 14-002.

Summary of the demographic and baseline physical characteristics is presented in Table 5 and Table 6. The majority of subjects were white, not Hispanic or Latino, females, and the majority of subjects in each treatment group were enrolled at sites in North America. Subject age ranged from 18 to 70 years, with a mean age of approximately 36 years and a mean BMI of approximately 28 kg/m^2. Demographic characteristics were balanced across treatment groups with the exception of a higher percentage of black or African American subjects in the placebo and 75 mg JZP-110 groups compared with the 150 mg and 300 mg JZP-110 groups. In addition, a higher percentage of subjects in the 75 mg treatment group were from Europe compared with the other treatment groups. Baseline CGIs evaluation categorized most subjects in each treatment group as markedly ill, with a similar percentage of subjects across all groups classified as moderately or severely ill. Overall, the percentage of subjects with the presence or absence of cataplexy was similar across all treatment groups. Baseline MWT sleep latency times and baseline ESS scores were similar across treatment groups.

Reference ID: 4324053

Table 5: Demographic and Baseline Characteristics (Safety Population) – 14-002

Characteristic	Placebo N = 59	75 mg JZP-110 N = 59	150 mg JZP-110 N = 59	300 mg JZP-110 N = 59	Combined JZP-110 N = 177
Age (years)					
n	59	59	59	59	177
Mean (SD)	36.0 (15.17)	36.5 (12.78)	38.1 (13.00)	34.3 (11.51)	36.3 (12.47)
Median	32.0	36.0	38.0	32.0	35.0
Range	18,70	18,68	20,68	18,64	18,68
Sex, n (%)					
Male	24 (40.7)	22 (37.3)	17 (28.8)	19 (32.2)	58 (32.8)
Female	35 (59.3)	37 (62.7)	42 (71.2)	40 (67.8)	119 (67.2)
Race, n (%)					
American Indian or Alaska Native	0	0	1 (1.7)	1 (1.7)	2 (1.1)
Asian	0	0	3 (5.1)	3 (5.1)	6 (3.4)
Black or African American	10 (16.9)	12 (20.3)	6 (10.2)	5 (8.5)	23 (13.0)
Native Hawaiian or Other Pacific Islander	0	0	0	1 (1.7)	1 (0.6)
White	47 (79.7)	46 (78.0)	48 (81.4)	48 (81.4)	142 (80.2)
Multiple	2 (3.4)	1 (1.7)	1 (1.7)	1 (1.7)	3 (1.7)
Ethnicity, n (%)					
Hispanic or Latino	1 (1.7)	4 (6.8)	7 (11.9)	1 (1.7)	12 (6.8)
Not Hispanic or Latino	58 (98.3)	55 (93.2)	52 (88.1)	58 (98.3)	165 (93.2)
Region, n (%)					
North America	52 (88.1)	43 (72.9)	49 (83.1)	48 (81.4)	140 (79.1)
Europe	7 (11.9)	16 (27.1)	10 (16.9)	11 (18.6)	37 (20.9)
Body Mass Index (kg/m^2)					
n	59	59	59	59	177
Mean (SD)	29.12 (5.952)	27.94 (5.355)	27.94 (5.829)	28.12 (6.296)	28.00 (5.807)
Median	28.40	26.59	28.31	26.89	27.27
Range	18.9,43.4	18.4,40.0	18.0,40.4	18.0,44.6	18.0,44.6

Source: Sponsor's Table 7 in Clinical Study Report of 14-002.

Reference ID: 4324053

Table 6: Baseline Disease Characteristics (Safety Population) – 14-002

Characteristic	Placebo N = 59	75 mg JZP-110 N = 59	150mg JZP-110 N = 59	300 mg JZP-110 N = 59	Combined JZP-110 N = 177
Baseline Mean Sleep Latency Time (min), n	58	58	57	59	174
Mean (SD)	6.14 (5.628)	7.50 (5.386)	7.70 (5.574)	8.73 (6.153)	7.98 (5.710)
Median	4.63	6.13	6.00	6.75	6.44
Range	0.3, 25.4	0.3, 21.9	0.0, 22.4	0.3, 22.6	0.0, 22.6
Baseline ESS Total Score, n	59	59	59	59	177
Mean (SD)	17.3 (2.83)	17.3 (3.53)	16.9 (3.66)	17.2 (2.81)	17.1 (3.34)
Median	17.0	18.0	17.0	17.0	17.0
Range	11, 24	10, 24	10, 24	11, 24	10, 24
Randomization Stratification Factor, n (%)					
Presence of Cataplexy	29 (49.2)	31 (52.5)	30 (50.8)	30 (50.8)	91 (51.4)
Absence of Cataplexy	30 (50.8)	28 (47.5)	29 (49.2)	29 (49.2)	86 (48.6)
Baseline CGIs, n (%)					
1=Normal, not at all ill	0	0	0	0	0
2=Borderline ill	0	0	0	0	0
3=Mildly ill	1 (1.7)	3 (5.1)	3 (5.1)	1 (1.7)	7 (4.0)
4=Moderately ill	14 (23.7)	14 (23.7)	16 (27.1)	17 (28.8)	47 (26.6)
5=Markedly ill	26 (44.1)	20 (33.9)	24 (40.7)	21 (35.6)	65 (36.7)
6=Severely ill	13 (22.0)	17 (28.8)	13 (22.0)	12 (20.3)	42 (23.7)
7=Among the most extremely ill patients	4 (6.8)	5 (8.5)	3 (5.1)	8 (13.6)	16 (9.0)
Missing	1 (1.7)	0	0	0	0

Source: Sponsor's Table 8 in Clinical Study Report of 14-002.

3.2.3.2 14-003

A total of 476 subjects were randomized. Of these, 474 subjects received at least 1 dose of study medication and comprised the Safety Population. There are 15 subjects excluded from the mITT population resulting in a total of 459 subjects. The reason for exclusion was lack of baseline or at least 1 postbaseline evaluation of MWT and ESS. There are 404 subjects completed the study.

Summary of the demographic and baseline physical characteristics is presented in Table 7 and Table 8. The majority of subjects were white, not Hispanic or Latino, females, and the majority of subjects in each treatment group were enrolled at sites in North America. Subject age ranged from 20 to 75 years, with a mean age of approximately 54 years and a mean BMI of approximately 33 kg/m^2. Demographic characteristics were balanced across treatment groups. Baseline CGIs evaluation categorized most subjects in each treatment

Reference ID: 4324053

group as moderate (~40%) or markedly ill (~30%). Across treatment groups, compliance with use of primary OSA therapy ranged from 68.4% to 72.9%. The Baseline MWT mean (SD) sleep latency (minutes) for subjects randomized to placebo or a dose of JZP-110 was 12.4 (7.19) and 12.6 (7.38) minutes, respectively; Baseline mean ESS scores for subjects randomized to placebo or a dose of JZP-110 were 15.6 (3.30) and 15.1 (3.33), respectively. Overall, baseline disease characteristics were well balanced between placebo and JZP-110 dose groups.

Reference ID: 4324053

Table 7: Demographic and Baseline Characteristics (Safety Population) – 14-003

Characteristic	Placebo N = 119	37.5 mg JZP-110 N = 58	75 mg JZP-110 N = 62	150 mg JZP-110 N = 117	300 mg JZP-110 N = 118	Combined JZP-110 N = 355
Age (years)						
n	119	58	62	117	118	355
Mean (SD)	54.1 (11.41)	57.1 (10.19)	54.4 (11.46)	52.7 (10.57)	53.2 (10.62)	53.9 (10.75)
Median	55.0	59.5	56.5	53.0	54.0	55.0
Range	20,74	33,72	29,74	21,75	24,72	21,75
Sex, n (%)						
Male	77 (64.7)	39 (67.2)	35 (56.5)	72 (61.5)	74 (62.7)	220 (62.0)
Female	42 (35.3)	19 (32.8)	27 (43.5)	45 (38.5)	44 (37.3)	135 (38.0)
Race, n (%)						
American Indian or Alaska Native	1 (0.8)	0	0	0	0	0
Asian	4 (3.4)	3 (5.2)	1 (1.6)	3 (2.6)	6 (5.1)	13 (3.7)
Black or African American	26 (21.8)	10 (17.2)	14 (22.6)	18 (15.4)	21 (17.8)	63 (17.7)
Native Hawaiian or Other Pacific Islander	1 (0.8)	0	0	1 (0.9)	0	1 (0.3)
White	87 (73.1)	45 (77.6)	46 (74.2)	93 (79.5)	90 (76.3)	274 (77.2)
Multiple	0	0	1 (1.6)	2 (1.7)	1 (0.8)	4 (1.1)
Ethnicity, n (%)						
Hispanic or Latino	13 (10.9)	6 (10.3)	5 (8.1)	11 (9.4)	11 (9.3)	33 (9.3)
Not Hispanic or Latino	106 (89.1)	52 (89.7)	57 (91.9)	106 (90.6)	107 (90.7)	322 (90.7)
Region, n (%)						
North America	115 (96.6)	55 (94.8)	62 (100)	115 (98.3)	111 (94.1)	343 (96.6)
Europe	4 (3.4)	3 (5.2)	0	2 (1.7)	7 (5.9)	12 (3.4)
Body Mass Index (kg/m^2)						
n	119	58	62	117	118	355
Mean (SD)	33.10 (5.224)	34.07 (5.323)	33.41 (5.668)	33.27 (4.758)	32.92 (5.602)	33.31 (5.295)
Median	33.50	34.54	33.16	33.16	33.18	33.28
Range	13.6[a],44.4	20.5,45.0	21.8,44.3	23.8,45.4	21.4,45.2	20.5,45.4

Source: Sponsor's Table 7 in Clinical Study Report of 14-003.

Reference ID: 4324053

Table 8: Baseline Disease Characteristics (Safety Population) – 14-003

Characteristic	Placebo N = 119	37.5 mg JZP-110 N = 58	75 mg JZP-110 N = 62	150 mg JZP-110 N = 117	300 mg JZP-110 N = 118	Combined JZP-110 N = 355
Baseline Mean MWT Sleep Latency Time (min), n	114	55	61	116	116	348
Mean (SD)	12.40 (7.193)	13.64 (8.085)	13.08 (7.240)	12.50 (7.165)	12.00 (7.347)	12.61 (7.381)
Median	10.81	12.88	12.25	11.63	10.63	11.50
Range	0.6, 29.5	1.4, 40.0	1.9, 29.4	1.1, 37.0	1.0, 29.6	1.0, 40.0
Baseline ESS Total Score, n	119	58	62	117	118	355
Mean (SD)	15.6 (3.30)	15.1 (3.48)	14.8 (3.53)	15.1 (3.37)	15.2 (3.13)	15.1 (3.33)
Median	15.0	15.0	14.0	15.0	15.0	15.0
Range	10, 24	10, 24	10, 23	10, 24	10, 23	10, 24
Primary OSA Therapy Use, n%						
Compliant	83 (69.7)	40 (69.0)	45 (72.6)	80 (68.4)	86 (72.9)	251 (70.7)
Noncompliant	36 (30.3)	18 (31.0)	17 (27.4)	37 (31.6)	32 (27.1)	104 (29.3)
Baseline CGIs, n (%)						
1 = Normal, not at all ill	0	0	0	0	0	0
2 = Borderline ill	3 (2.5)	1 (1.7)	1 (1.6)	2 (1.7)	1 (0.8)	5 (1.4)
3 = Mildly ill	8 (6.7)	5 (8.6)	4 (6.5)	7 (6.0)	10 (8.5)	26 (7.3)
4 = Moderately ill	48 (40.3)	28 (48.3)	31 (50.0)	53 (45.3)	44 (37.3)	156 (43.9)
5 = Markedly ill	39 (32.8)	14 (24.1)	15 (24.2)	41 (35.0)	44 (37.3)	114 (32.1)
6 = Severely ill	15 (12.6)	9 (15.5)	7 (11.3)	14 (12.0)	17 (14.4)	47 (13.2)
7 = Among the most extremely ill patients	4 (3.4)	1 (1.7)	3 (4.8)	0	2 (1.7)	6 (1.7)
Missing	2 (1.7)	0	1 (1.6)	0	0	1 (0.3)

Source: Sponsor's Table 8 in Clinical Study Report of 14-003.

3.2.3.2 14-004

A total of 174 subjects were enrolled at 34 study centers (25 in the United States and 9 in Europe). All of the 174 enrolled subjects received at least 1 dose of study medication and comprised the Safety population in the Titration phase. Of the initial 174 subjects enrolled, 157 (90.2%) entered the Stable-Dose phase. A total of 124 subjects were randomized into the Double-Blind Withdrawal phase, 62 to receive placebo and 62 to receive JZP-110 at the dose level taken in the Stable-Dose phase: 9 at 75 mg, 26 at 150 mg, and 27 at 300 mg. Of the 124 randomized subjects, 122 completed the Double-Blind Withdrawal Phase. The mITT population consists of the 122 subjects. The two subjects ([redacted] (b) (6)) were excluded from the mITT because of early discontinuation and lack of post efficacy baseline assessment.

Reference ID: 4324053

Summary of the demographic and baseline physical characteristics is presented in Table 9 and Table 10. In the overall Safety population and randomized population, the majority of subjects were white, male, and located in North America. Subjects were approximately 55 years of age, and had a mean BMI of approximately 33 kg/m2. Baseline demographics were similar between the Placebo and JZP-110 groups in the Double-Blind Withdrawal phase. For both treatment groups in the Double-Blind Withdrawal phase, most subjects were compliant users of a primary OSA therapy: 77.4% and 80.0% for the Placebo and JZP-110 groups, respectively. Efficacy baseline (Week 4) disease characteristics for the Double-Blind Withdrawal phase were similar between the Placebo and JZP-110 groups.

Table 9: Demographics and Baseline Characteristics – 14-004

Characteristic	Titration Phase Combined JZP-110 N=174	Stable-Dose Phase Combined JZP-110 N=157	Double-Blind Withdrawal Phase Placebo N=62	Double-Blind Withdrawal Phase Combined JZP-110 N=62
Age (years)				
n	174	157	62	62
Mean (SD)	54.8 (10.50)	55.4 (10.15)	56.2 (9.75)	56.3 (11.36)
Median	56.0	56.0	59.0	58.0
Range	24,74	30,74	30,72	30,74
Sex, n (%)				
Male	107 (61.5)	97 (61.8)	41 (66.1)	36 (58.1)
Female	67 (38.5)	60 (38.2)	21 (33.9)	26 (41.9)
Race, n (%)				
American Indian or Alaska Native	0	0	0	0
Asian	2 (1.1)	2 (1.3)	2 (3.2)	0
Black or African American	34 (19.5)	34 (21.7)	15 (24.2)	12 (19.4)
Native Hawaiian or Other Pacific Islander	0	0	0	0
White	137 (78.7)	121 (77.1)	45 (72.6)	50 (80.6)
Other	0	0	0	0
Multiple	1 (0.6)	0	0	0
Ethnicity, n (%)				
Hispanic/Latino	18 (10.3)	17 (10.8)	4 (6.5)	9 (14.5)
Not Hispanic/ Latino	156 (89.7)	140 (89.2)	58 (93.5)	53 (85.5)
Region, n (%)				
North America	141 (81.0)	131 (83.4)	51 (82.3)	50 (80.6)
Europe	33 (19.0)	26 (16.6)	11 (17.7)	12 (19.4)
Height (cm)				
n	173	156	62	62
Mean (SD)	173.47 (10.242)	172.96 (9.921)	173.34 (10.272)	173.04 (10.115)
Median	175.00	174.00	173.00	175.15
Range	151.0,198.0	151.0,198.0	156.0,198.0	151.0,193.0
Weight (kg)				
n	174	157	62	62
Mean (SD)	100.72 (20.432)	99.93 (19.762)	100.64 (21.537)	99.13 (20.158)
Median	99.10	98.80	97.55	100.85
Range	57.6,155.0	57.6,149.7	59.9, 149.1	57.6,149.7
Body mass index (kg/m^2)				
n	173	156	62	62
Mean (SD)	33.34 (5.370)	33.27 (5.237)	33.32 (5.502)	32.91 (5.027)
Median	33.35	32.93	32.73	33.07
Range	21.1,44.4	22.0,44.4	22.0,44.4	23.2,43.1

Source: Sponsor's Table 6 in Clinical Study Report of 14-004.

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Table 10: Efficacy Baseline (week 4) Disease Characteristics (RW Period, mITT) – 14-004

Characteristic	Placebo N=62	Combined JZP-110 N=60
Week 4 Mean Sleep Latency (min)		
n	60	59
Mean (SD)	28.95 (9.871)	31.71 (9.218)
Median	32.13	34.13
Range	6.3, 40.0	3.9, 40.0
Week 4 ESS Total Score		
n	62	60
Mean (SD)	5.9 (3.82)	6.4 (4.42)
Median	5.5	6.0
Range	0, 19	0, 22
Randomization Stratification Factor, n (%)		
Compliant Use of Primary OSA Therapy	48 (77.4)	48 (80.0)
Non-Compliant Use of Primary OSA	14 (22.6)	12 (20.0)
Week 4 CGIc, n (%)		
1=Very much improved	24 (38.7)	19 (31.7)
2=Much improved	34 (54.8)	38 (63.3)
3=Minimally improved	3 (4.8)	1 (1.7)
4=No change	1 (1.6)	1 (1.7)
5=Minimally worse	0	0
6=Much worse	0	0
7=Very much worse	0	0
Missing	0	1 (1.7)
Week 4 PGIc, n (%)		
1=Very much improved	19 (30.6)	22 (36.7)
2=Much improved	41 (66.1)	36 (60.0)
3=Minimally improved	2 (3.2)	1 (1.7)
4=No change	0	0
5=Minimally worse	0	0
6=Much worse	0	0
7=Very much worse	0	0
Missing	0	1 (1.7)

Source: Sponsor's Table 8 in Clinical Study Report of 14-004.

3.2.3.2 14-005

Approximately 600 subjects were planned for enrollment of the study with 300 subjects planned for the randomized withdrawal period. At the interim analysis cutoff date of 4/21/2017, a total of 640 subjects were enrolled at 79 study centers (63 in the United States and 16 in Europe). Of the 640 enrolled subjects, 2 of them did not receive any study drug. Therefore, a total of 638 subjects (226 with narcolepsy and 412 with OSA) received at least 1 dose of study medication and comprised the Safety population in the Titration phase. Of these, 282 subjects were randomized and received at least 1 dose of blinded study medication in the randomized withdrawal period (ie, the Safety Population of the randomized withdrawal period). The randomization was stratified on the basis of subjects' diagnosis of narcolepsy or OSA. Two of the subjects ((b) (6) and (b) (6)) who were treated in the randomized withdrawal period did not have evaluable efficacy data post-randomization, and therefore, the mITT Population was comprised of 280 subjects, 141 who received placebo and 139 who received JZP-110. A total of 203 patients with OSA

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participated in the randomized withdrawal period. A total of 79 subjects with narcolepsy participated in the randomized withdrawal period. Of the 280 subjects in the mITT population, 278 subjects completed the double-blind RW phase (141 in the placebo group, 137 in the JZP-110 group). The other ongoing 2 subjects in the double-blind RW phase, (b) (6) and (b) (6), have efficacy assessments at the end of the RW phase. Therefore, there is no missing efficacy data in the mITT population.

Summary of the demographic and baseline physical characteristics is presented in Table 11 and Table 12. In the overall Safety population and randomized population, the majority of subjects were white, not Hispanic or Latino, and located in North America. Subjects were approximately 50 years of age, and had a mean BMI of approximately 32 kg/m2. Baseline demographics were similar between the Placebo and JZP-110 groups in the Double-Blind Withdrawal phase. Efficacy baseline (Week 4) disease characteristics for the Double-Blind Withdrawal phase were similar between the Placebo and JZP-110 groups.

Table 11: Demographic and Baseline Characteristics (RW Period, mITT) – 14-005

	Randomized Withdrawal Period				
Characteristic	Placebo (N=141)	75 mg (N=13)	150 mg (N=46)	300 mg (N=80)	Combined JZP-110 (N=139)
Age (years)					
n	141	13	46	80	139
Mean (SD)	50.77 (12.149)	56.38 (11.464)	49.00 (13.592)	49.96 (13.135)	50.24 (13.212)
Median	51.00	59.00	50.50	53.00	53.00
Range	22.0, 74.0	34.0, 72.0	24.0, 71.0	20.0, 74.0	20.0, 74.0
Sex, n (%)					
Male	85 (60.3)	7 (53.8)	24 (52.2)	44 (55.0)	75 (54.0)
Female	56 (39.7)	6 (46.2)	22 (47.8)	36 (45.0)	64 (46.0)
Race, n (%)					
American Indian or Alaska Native	0	0	0	0	0
Asian	5 (3.5)	1 (7.7)	1 (2.2)	1 (1.3)	3 (2.2)
Black or African American	25 (17.7)	4 (30.8)	7 (15.2)	14 (17.5)	25 (18.0)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
White	110 (78.0)	8 (61.5)	38 (82.6)	65 (81.3)	111 (79.9)
Multiple	1 (0.7)	0	0	0	0
Ethnicity, n (%)					
Hispanic or Latino	7 (5.0)	1 (7.7)	1 (2.2)	2 (2.5)	4 (2.9)
Not Hispanic or Latino	134 (95.0)	12 (92.3)	45 (97.8)	78 (97.5)	135 (97.1)

Source: Sponsor's Table 14.1.5.2b in Clinical Study Report of 14-005.

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Table 12: Baseline Disease Characteristics (RW Period, mITT) – 14-005

Characteristic	Overall		OSA		Narcolepsy	
	Placebo (N=141)	Combined JZP-110 (N=139)	Placebo N=101	Combined JZP-110 N=101	Placebo N=40	Combined JZP-110 (N=38)
Condition						
Narcolepsy	40 (28.4)	38 (27.3)	NA	NA	40 (100.0)	38 (100.0)
OSA	101 (71.6)	101 (72.7)	101 (100.0)	101 (100.0)	0	0
Presence of cataplexy						
Yes	20 (14.2)	20 (14.4)	NA	NA	20 (50.0)	20 (52.6)
No	20 (14.2)	18 (12.9)	NA	NA	20 (50.0)	18 (47.4)
Primary OSA Therapy use						
Compliant	83 (58.9)	80 (57.6)	83 (82.2)	80 (79.2)	NA	NA
Non-compliant	18 (12.8)	21 (15.1)	18 (17.8)	21 (20.8)	NA	NA
Efficacy Baseline [3] Total ESS Score						
n	141	139	101	101	40	38
Mean (SD)	7.82 (4.975)	7.25 (5.307)	6.54 (4.344)	5.87 (4.298)	11.03 (5.071)	10.92 (6.006)
Median	7.00	6.00	6.00	5.00	11.00	11.00
Range	0.0, 22.0	0.0, 23.0	0.0, 18.0	0.0, 23.0	2.0, 22.0	1.0, 22.0
Efficacy Baseline [3] CGIc, n(%)						
1 = Very much improved	46 (32.6)	54 (38.8)	39 (38.6)	45 (44.6)	7 (17.5)	9 (23.7)
2 = Much improved	70 (49.6)	60 (43.2)	49 (48.5)	41 (40.6)	21 (52.5)	19 (50.0)
3 = Minimally improved	20 (14.2)	19 (13.7)	10 (9.9)	12 (11.9)	10 (25.0)	7 (18.4)
4 = No change	2 (1.4)	4 (2.0)	1 (1.0)	3 (3.0)	1 (2.5)	1 (2.6)
5 = Minimally worse	1 (0.7)	0	1 (1.0)	0	0	0
6 = Much worse	1 (0.7)	0	0	0	1 (2.5)	0
7 = Very much worse	0	0	0	0	0	0
Missing	1 (0.7)	2 (1.4)	1 (1.0)	0	0	2 (5.3)
Efficacy Baseline [3] PGIc, n(%)						
1 = Very much improved	46 (32.6)	47 (33.8)	38 (37.6)	39 (38.6)	8 (20.0)	8 (21.1)
2 = Much improved	65 (46.1)	66 (47.5)	44 (43.6)	47 (46.5)	21 (52.5)	19 (50.0)
3 = Minimally improved	25 (17.7)	22 (15.8)	16 (15.8)	12 (11.9)	9 (22.5)	10 (26.3)
4 = No change	4 (2.8)	3 (2.2)	2 (2.0)	2 (2.0)	2 (5.0)	1 (2.6)
5 = Minimally worse	0	1 (0.7)	0	1 (1.0)	0	0
6 = Much worse	1 (0.7)	0	1 (1.0)	0	0	0
7 = Very much worse	0	0	0	0	0	0
Missing	0	0	0		0	0

Source: Sponsor's Table 13 in Clinical Study Report of 14-005.

Three subjects were each enrolled and treated twice in Study 14-005, which resulted duplicate subject information for this study. None of the subjects has more than 1 entry of the RW phase. Therefore, there is no duplicate subject information in the efficacy analysis data set.

3.2.3 Results and Conclusions

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3.2.4.1 ADX-N05-202

Sponsor's Results and Conclusions:

Based on the primary analysis results (Table 13) for the pre-specified primary endpoint, the Sponsor concluded that the differences between treatment groups for MWT at the last post-baseline assessment and CGIc at the last post-baseline assessment were statistically significant, favoring JZP-110.

Table 13: Summary of CFB MWT at the Last Post-Baseline Assessment Results – ADX-N05-202

	Observed Values Mean (SD)	Calculated Change from Baseline Mean (SD)	P-Value[2]
Baseline		-	-
ADX-N05 (N=43)	5.66 (5.89)		
Placebo (N=47)	5.70 (2.83)		
Week 12/Last Assessment[1]			
ADX-N05 (N=40)	17.6 (11.42)	12.8 (10.28)	<0.0001[1]
Placebo (N=45)	7.9 (8.63)	2.1 (7.88)	

[1] Week 12/Last Assessment is an end-point analysis representing last post-Baseline observation carried forward.
[2] Two-sample t-test.
SD=standard deviation

Source: Sponsor's Table 7 on Page 60 of Clinical Study Report of ADX-N05-202.

Table 14: Summary of CGIc at the Last Post-Baseline Assessment Results – ADX-N05-202

	Observed Values Mean (SD)	Proportion of Subjects Experiencing Improvement[2] N (%)	P-Value[3]
Baseline			
ADX-N05 (N=43)	5.00 (0.79)		
Placebo (N=47)	5.04 (1.02)		
Week 12/Last Assessment[1]			
ADX-N05 (N=43)	2.2 (1.16)	37 (86.0)	<0.0001
Placebo (N=47)	3.5 (1.10)	18 (38.3)	

Note: Observed values for the Baseline visit are derived from the CGI-S assessment. Observed values for Week 12/Last Assessment are derived from the CGI-C assessment.
[1] Week 12/Last Assessment is an end-point analysis representing last post-Baseline observation carried forward.
[2] Improvement is any score of a 1 (very much improved), 2 (much improved), or 3 (minimally improved).
[3] Fisher's Exact test
SD=standard deviation

Source: Sponsor's Table 8 on Page 61 of the Clinical Study Report of ADX-N05-202.

The Sponsor pre-specified two sensitivity analyses. The first one is ANCOVA with treatment, site, treatment*site as factors and baseline values as a covariate. The Estimate of

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treatment difference is 11.08 with p-value <0.0001. The second sensitivity analysis is per-protocol analysis, which is not a sensible sensitivity analysis. Therefore, the results from per-protocol analysis is not reported in the review.

There are four secondary endpoints. In the final protocol, SAP, and clinical study report, these 4 secondary endpoints were listed as secondary endpoints without any multiplicity adjustment. However, in Table 1 on Page 13 of Summary of Clinical Efficacy of this NDA submission, the Sponsor listed the 4 secondary endpoints as key secondary endpoints and [redacted]. The Sponsor did not pre-specify the multiple adjustment for the primary endpoints and secondary endpoints in the protocol and SAP. Therefore, in principle, the results of these secondary endpoints are exploratory. The results on CFB in ESS and PGIc are summarize in Table 15 and Table 16.

Table 15: Summary of CFB in ESS Total Scores at the Last Post-Baseline Assessment Results – ADX-N05-202

	Observed Values Mean (SD)	Calculated Change from Baseline Mean (SD)	P-Value[2]
Baseline			
ADX-N05 (N=43)	17.3 (3.72)		
Placebo (N=47)	17.4 (2.94)		
Week 12/Last Assessment[1]			
ADX-N05 (N=43)	8.8 (5.66)	-8.5 (5.75)	<0.0001
Placebo (N=47)	14.9 (5.36)	-2.5 (5.13)	

[1] Week 12/Last Assessment is an end-point analysis representing last post-Baseline observation carried forward.
[2] Two-sample t-test.
SD=standard deviation

Source: Sponsor's Table 11 on Page 66 of the Clinical Study Report of ADX-N05-202.

Table 16: Summary of PGIc at the Last Post-Baseline Assessment Results – ADX-N05-202

	Observed Values Mean (SD)	Subjects Experiencing Improvement[2] N (%)	P-Value[3]
Week 1			
ADX-N05 (N=43)	2.6 (0.93)	36 (83.7)	0.0030
Placebo (N=47)	3.4 (1.01)	25 (53.2)	
Week 12/Last Assessment			
ADX-N05 (N=43)	2.2 (0.87)	40 (93.0)	<0.0001
Placebo (N=47)	3.7 (1.42)	18 (38.3)	

[1] Week 12/Last Assessment is an end-point analysis representing last post-Baseline observation carried forward.
[2] Improvement is any score of a 1 (very much improved), 2 (much improved), or 3 (minimally improved).
[3] Fisher's Exact test
SD=standard deviation

Source: Sponsor's Table 12 on Page 67 of the Clinical Study Report of ADX-N05-202.

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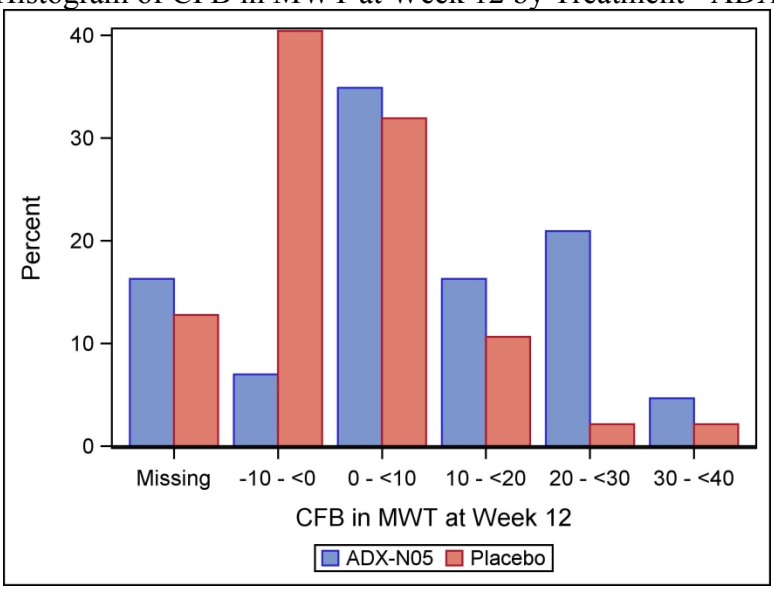
Reviewer's Results and Conclusions:

This reviewer repeated the pre-specified primary analysis on the CFB in MWT at the last post-baseline assessment and CGIc at the last post-baseline assessment, and obtained the same results.

Before DPP took over the review of applications for this class of indications, the submitted protocol and the SAP of this trial were not reviewed by the statistical team then. The design of the study is appropriate for the objectives of the study. However, the choices of primary endpoints are not appropriate because we would not accept CGI-C as a primary endpoint, and additionally the duration for measuring improvement should have been a fixed duration instead of varying durations depending on the time when subject dropped out. For the other Phase 3 trials with similar designs included in the NDA, the co-primary endpoints FDA agreed upon are the CFB in MWT at Week 12 and CFB in ESS at Week 12. CFB in ESS at Week 12 is one of the secondary endpoint in this study.

Figure 7 to Figure 8 display the histograms of the CFB in MWT at week 12 and CGIc at week 12 by treatment, respectively.

Figure 7: Histogram of CFB in MWT at Week 12 by Treatment - ADX-N05-202



Source: This reviewer.

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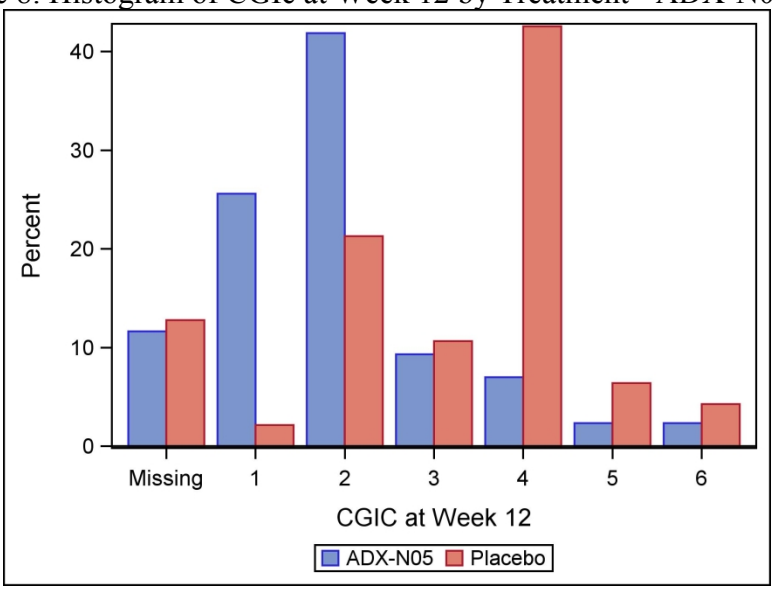
Figure 8: Histogram of CGIc at Week 12 by Treatment - ADX-N05-202



Source: This reviewer.

For CFB in MWT at Week 12, this reviewer performed analysis based on MMRM, which is agreed upon by FDA for the other Phase 3 trials with the same design. In the MMRM model, the response variable is the change from baseline to each post-baseline visit, and the following are fixed effects: treatment, visit (as a discrete and repeated factor), treatment-by-visit interaction, baseline value as a continuous covariate. An unstructured covariance matrix was used to model the correlation among repeated measurements. The estimate of treatment difference and the 95% confidence intervals is 11.4 (7.2, 15.5). The corresponding p-value is <0.0001.

To assess the impact of the dropouts on the primary analysis results, this reviewer conducted sensitivity analyses on CFB in MWT at Week 12 using two different imputing methods on those discontinued in treatment period: 1). missing data are imputed by the worst observed score among all subjects at Week 12. 2). missing data are imputed by the mean score at Week 12 from the placebo arm. Both imputations give the similar results to the primary analysis. The results are summarized in Table 17.

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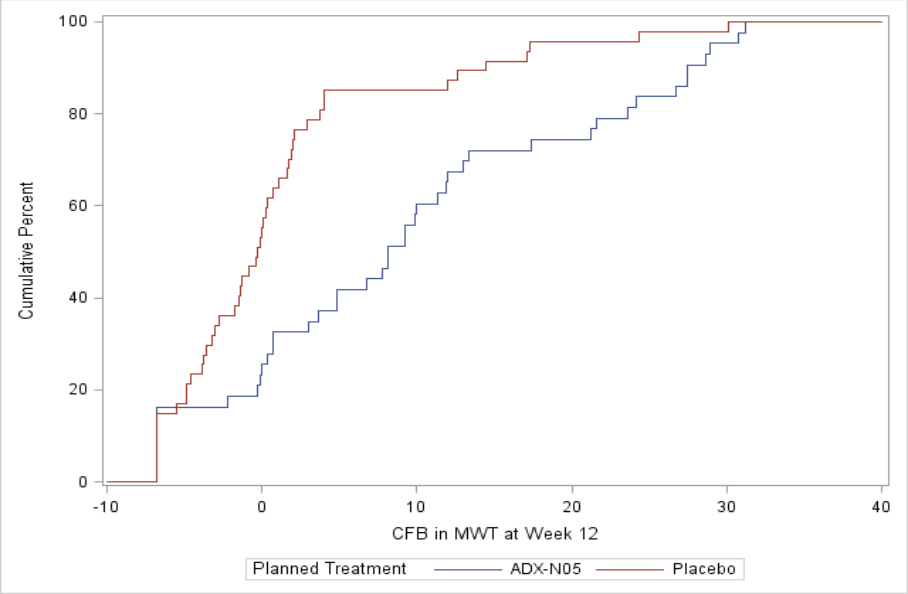
Table 17: Summary of Sensitivity Analysis Results on CFB in MWT at Week 12 - ADX-N05-202

Imputation Method	JZP-110 LS Mean (SE)	Placebo LS Mean (SE)	LS Mean Diff (SE) (JZP-110 - Placebo)
the Worst Score	9.5 (1.57)	1.3 (1.50)	8.2 (2.17) (p=0.0003)
Placebo Mean	11.0 (1.38)	2.4 (1.32)	8.6 (1.91) (p<0.0001)

Source: This reviewer.

This reviewer also plotted the CDF of the CFB in MWT at Week 12 with the above two imputation methods in Figure 9 to Figure 10.

Figure 9: CDF of CFB in MWT at Week 12 by Treatment (Imputed by the Worst Score) – ADX-N05-202



Source: This reviewer.

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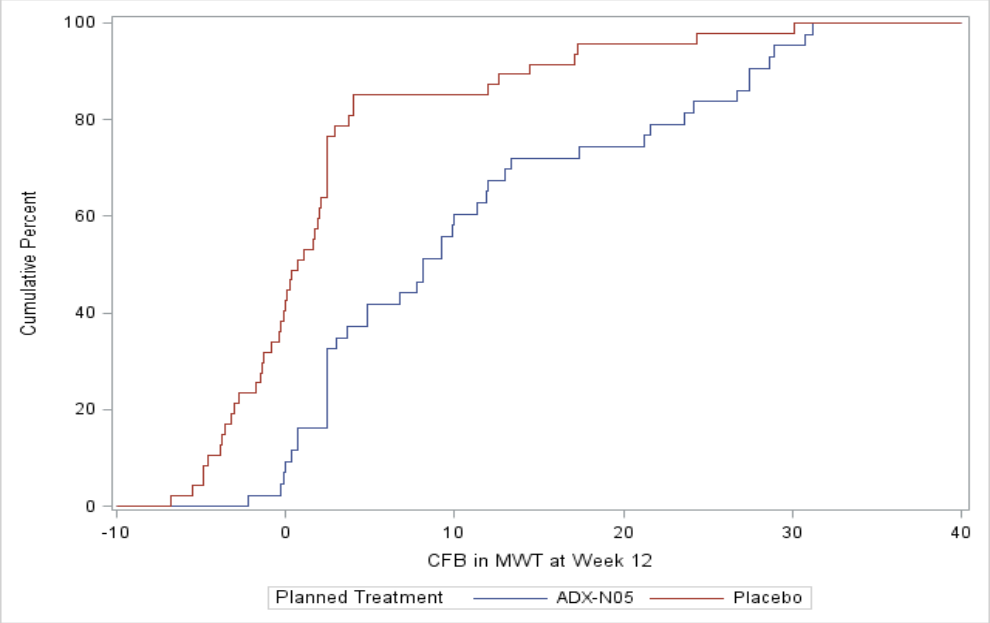
Figure 10: CDF of CFB in MWT at Week 12 by Treatment (Imputed by Placebo Mean) – ADX-N05-202



Source: This reviewer.

For CGIc at Week 12, this reviewer performed chi-square test with LOCF, which is agreed upon by FDA for the other Phase 3 trials with the same design. The p-value is < 0.001, favoring JZP-110.

The placebo group has more missing data in CGIc than the JZP-110 group. Therefore, imputation by worst score will over-estimate the treatment effect. This reviewer performed a sensitivity analysis based on imputing missing data by the placebo median. The increase in the percentage of subjects reporting improvement on the CGIc relative to placebo was 42.7% ($p < 0.0001$). This reviewer plotted the CDF of CGIc at Week 12 with missing data imputed by placebo median in Figure 11.

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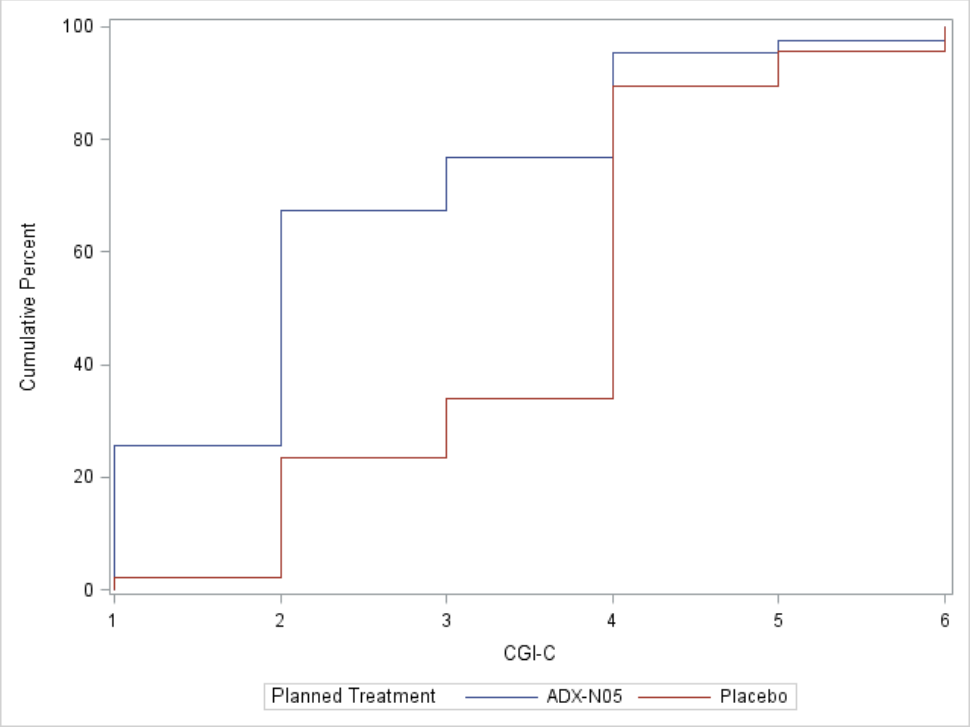
Figure 11: CDF of CGIc at Week 12 by Treatment (Imputed by Placebo Median) – ADX-N05-202



Source: This reviewer.

3.2.4.2 14-002

Sponsor's Results and Conclusions:

The Sponsor performed the pre-specified primary analyses on co-primary and key secondary endpoints. However, the Sponsor excluded few data assessed at unscheduled visits to enable the program to converge. Based on the fixed hierarchical testing sequence, JZP-110 doses of 150 and 300 mg won on co-primary and key secondary endpoints (Table 18), and were considered efficacious.

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Table 18: Primary Analysis Results on Co-Primary and Key Secondary Efficacy Endpoints – 14-002

Co-Primary and Key Secondary Endpoints	Placebo N = 58	75 mg JZP-110 N = 59	150 mg JZP-110 N = 55	300 mg JZP-110 N = 59
Co-Primary Endpoints				
Change in MWT from Baseline to Week 12				
LS Mean (SE)	2.12 (1.289)	4.74 (1.335)	9.77 (1.327)	12.27 (1.389)
LS Mean Difference	NA	2.62	7.65	10.14
95% CI	NA	(-1.04, 6.28)	(3.99, 11.31)	(6.39, 13.90)
p-value	NA	0.1595	<0.0001	<0.0001
Change in ESS Score from Baseline to Week 12				
LS Mean (SE)	-1.6 (0.65)	-3.8 (0.67)	-5.4 (0.66)	-6.4 (0.68)
LS Mean Difference	NA	-2.2	-3.8	-4.7
95% CI	NA	(-4.0, -0.3)	(-5.6, -2.0)	(-6.6, -2.9)
p-value	NA	0.0211	<0.0001	< 0.0001
Key Secondary Endpoint				
PGIc: Subjects Reported Improved at Week 12				
Yes	23 (39.7)	40 (67.8)	43 (78.2)	50 (84.7)
No	35 (60.3)	19 (32.2)	12 (21.8)	9 (15.3)
Percentage Difference (Yes) from Placebo (95% CI)	NA	28.1 (10.80, 45.48)	38.5 (21.86, 55.19)	45.1 (29.51, 60.67)
p-value	NA	0.0023[a]	<0.0001	<0.0001

Source: Sponsor's Table 13 in Clinical Study Report 14-002.

Four sensitivity analyses of the co-primary endpoints of CFB in MWT at Week 12 and CFB in ESS scores at Week 12 were performed. Sensitivity analyses 1 and 2 utilized an ANCOVA model, with change from baseline as the response variable, and fixed-effect model terms of treatment, baseline, and randomization stratification factor (presence or absence of cataplexy). Missing data were imputed using an LOCF approach in sensitivity analysis 1 and the corresponding treatment group mean in sensitivity analysis 2. Sensitivity analyses 3 and 4 utilized an MMRM model, with change from baseline as the response variable and fixed-effect of treatment, visit, treatment by visit, randomization stratification factor (presence or absence of cataplexy), covariate of baseline, and unstructured variance-covariance structure. Missing data were imputed using multiple imputation method by MCMC for non-monotone missing (sensitivity analysis 3) and regression method for monotone missing data (sensitivity analysis 4) within each treatment group. A summary of sensitivity analyses of the co-primary is presented in Table 19. In all sensitivity analyses, JZP-110 doses of 150 and 300 mg showed statistically significant treatment effect in MWT and ESS compared with placebo. In addition, for some of the sensitivity analysis, JZP-110 75 mg dose group showed statistically significant treatment effect.

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Table 19: Summary of Sensitivity Analyses of Change in MWT and ESS from Baseline to Week 12 – 14-002

Analysis	Endpoint	P-value		
		75 mg JZP-110 N = 59	150 mg JZP-110 N = 55	300 mg JZP-110 N = 59
Sensitivity Analysis 1[a]	MWT Mean Sleep Latency	0.2014	< 0.0001	< 0.0001
	ESS Score	0.0261	<0.0001	< 0.0001
Sensitivity Analysis 2[b]	MWT Mean Sleep Latency	0.0413	< 0.0001	< 0.0001
	ESS Score	0.0197	< 0.0001	< 0.0001
Sensitivity Analysis 3[c]	MWT Mean Sleep Latency	0.1313	< 0.0001	< 0.0001
	ESS Score	0.0283	< 0.0001	< 0.0001
Sensitivity Analysis 4[d]	MWT Mean Sleep Latency			
	K=0%	0.1483	< 0.0001	< 0.0001
	K=10%	0.1514	< 0.0001	< 0.0001
	K=20%	0.1546	< 0.0001	< 0.0001
	K=30%	0.1581	< 0.0001	< 0.0001
	K=40%	0.1618	< 0.0001	< 0.0001
	K=50%	0.1657	< 0.0001	< 0.0001
	K=60%	0.1698	< 0.0001	< 0.0001
	K=70%	0.1742	< 0.0001	< 0.0001
	K=80%	0.1788	< 0.0001	< 0.0001
	K=90%	0.1836	< 0.0001	< 0.0001
	K=100%	0.1886	< 0.0001	< 0.0001
	ESS Score			
	K=0%	0.0190	<0.0001	<0.0001
	K=10%	0.0203	<0.0001	<0.0001
	K=20%	0.0217	<0.0001	<0.0001
	K=30%	0.0232	<0.0001	<0.0001
	K=40%	0.0249	<0.0001	<0.0001
	K=50%	0.0268	<0.0001	<0.0001
	K=60%	0.0289	<0.0001	<0.0001
	K=70%	0.0311	<0.0001	<0.0001
	K=80%	0.0355	<0.0001	<0.0001
	K=90%	0.0362	<0.0001	<0.0001
	K=100%	0.0391	0.0001	0.0001

Source:.Sponsor's Table 16 in Clinical Study Report 14-002.

Two sensitivity analyses performed on the key secondary endpoint, the percentage of subjects reporting improvement at Week 12 on the PGIc. In sensitivity analysis 1, missing

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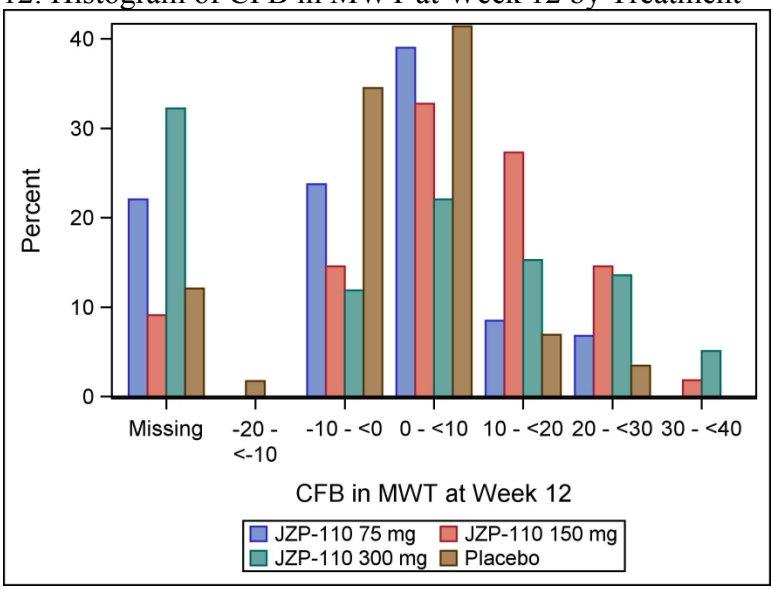
data at Week 12 were imputed by early termination reason (subjects discontinued due to LOE or AE were considered non-responders). In sensitivity analysis 2, missing data at Week 12 were imputed by worst case (subjects with missing data were considered non-responders). For both sensitivity analyses 1 and 2 of the key secondary endpoint, an increase in the percentage of subjects reporting improvement at Week 12 on the PGIc relative to placebo was observed for all 3 JZP-110 groups and supported the primary analysis of this key secondary endpoint. The increases in the percentage of subjects reporting improvement on the PGIc relative to placebo were 24.8% (p = 0.0074), 40.3% (p <0.0001), and 35.0% (p = 0.0001) for the 75, 150, and 300 mg JZP-110 groups, respectively for sensitivity analysis 1. The increases in the percentage of subjects reporting improvement on the PGIc relative to placebo were 21.5% (p = 0.0192), 41.8% (p <0.0001) and 30.0% (p = 0012) for the 75, 150, and 300 mg JZP-110 groups, respectively for sensitivity analysis 2.

Reviewer's Results and Conclusions:

Figure 12 to Figure 14 display the histograms of the co-primary endpoints and the key secondary endpoint by treatment, respectively.

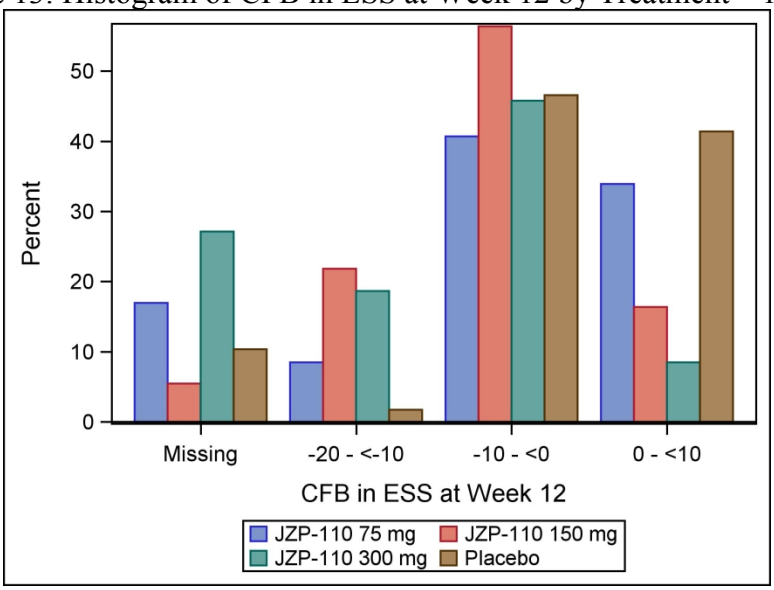
Figure 12: Histogram of CFB in MWT at Week 12 by Treatment – 14-002



Source: This reviewer.

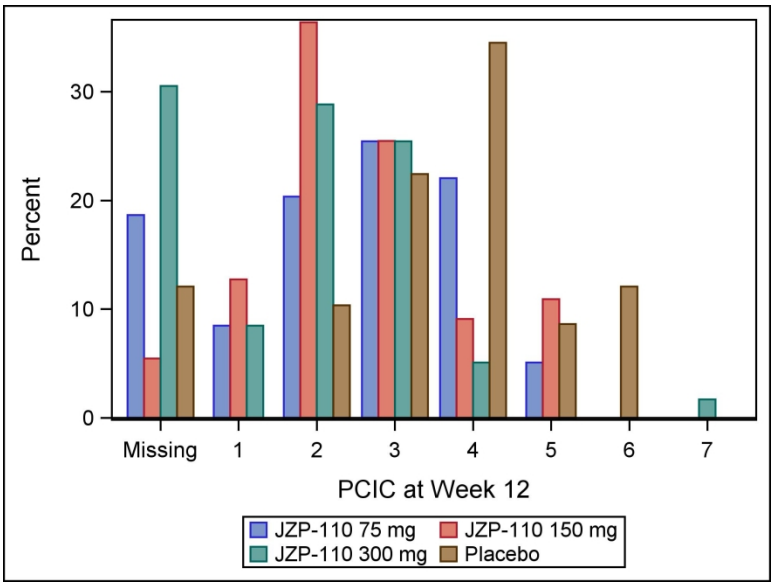
Reference ID: 4324053

Figure 13: Histogram of CFB in ESS at Week 12 by Treatment – 14-002



Source: this reviewer.

Figure 14: Histogram of PGIc at Week 12 by Treatment – 14-002



Source: this reviewer.

The Sponsor performed the pre-specified primary analyses on co-primary and key secondary endpoints. For the two co-primary endpoints, the Sponsor excluded few observations assessed at unscheduled time to enable the primary analysis programs to converge. For example, Week 4 is a scheduled visit, but Weeks 3 and 5 were not, so observations collected at Week 3 or 5 were excluded from the primary analysis by the Sponsor. This reviewer does not consider this practice informative enough because it does

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not utilize all available observations during the double-blind phase. Instead, this reviewer thinks it is more reasonable to have an assessment window (±1 week) for each scheduled visit; for example, count the data assessed at Weeks 3 and 5 as Week 4. Therefore, this reviewer re-coded the visits to the nearest visits within 1 week and performed the pre-specified analyses on co-primary endpoints. The reviewer repeated the pre-specified primary analysis of the key secondary endpoint. The reviewer's primary analysis results are summarized in Table 20. The reviewer reaches the same conclusion as the Sponsor that JZP-110 doses of 150 and 300 mg met co-primary and key secondary endpoints while JZP-110 dose of 75 mg failed on one of the co-primary endpoints.

Table 20: Reviewer's Primary Analysis Results on Co-Primary and Key Secondary Efficacy Endpoints – 14-002

Co-Primary and Key Secondary Endpoints	JZP-110 75 mg vs Placebo	JZP-110 150 mg vs Placebo	JZP-110 300 mg vs Placebo
MWT			
Diff (95% CI)	2.62 (-1.03, 6.27)	7.63 (3.99, 11.27)	10.04 (6.29, 13.78)
P-value	0.159	<0.0001	<0.0001
ESS			
Diff (95% CI)	-2.17 (-4.01, -0.33)	-3.77 (-5.6, -1.94)	-4.74 (-6.61, -2.88)
P-value	0.021	<0.0001	<0.0001
PGIc: Subjects reported improved at Week 12			
Percentage Difference (Yes) from Placebo (95% CI)	28.1 (10.8, 45.5)	38.5 (21.9, 55.2)	45.1 (29.5, 60.7)
P-value	0.0023	<0.0001	<0.0001

Source: this reviewer.

This reviewer also plotted the CDF of the co-primary endpoints and the key secondary endpoint with two imputation methods in Figure 15 to Figure 20.

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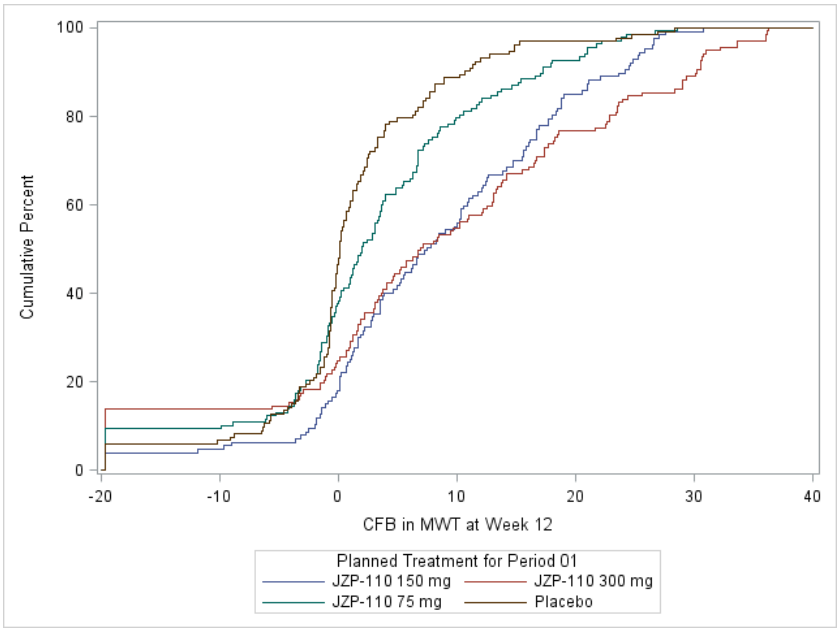
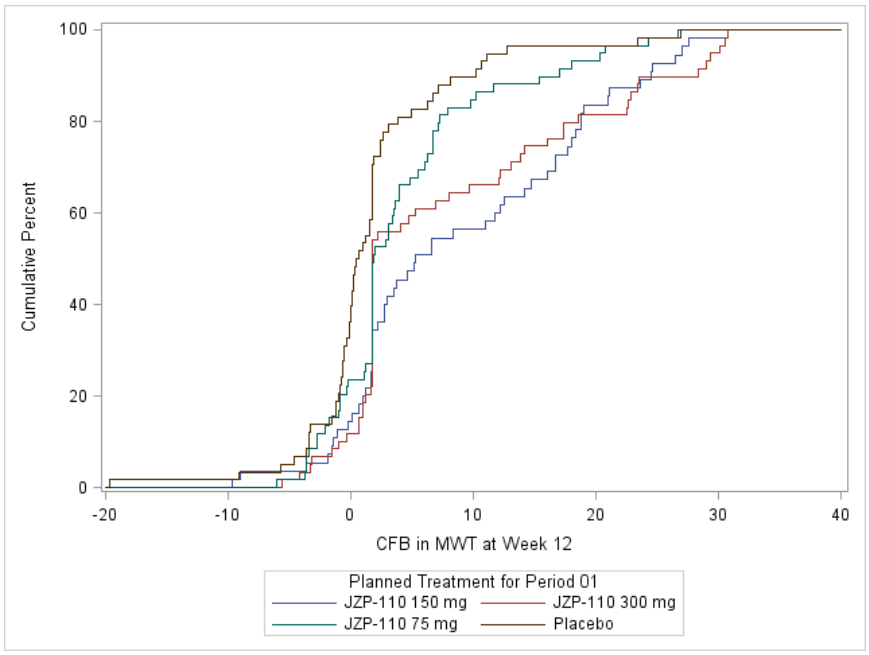
Figure 15: CDF of CFB in MWT at Week 12 by Treatment (Imputed by the Worst Score) – 14-002



Source: this reviewer.

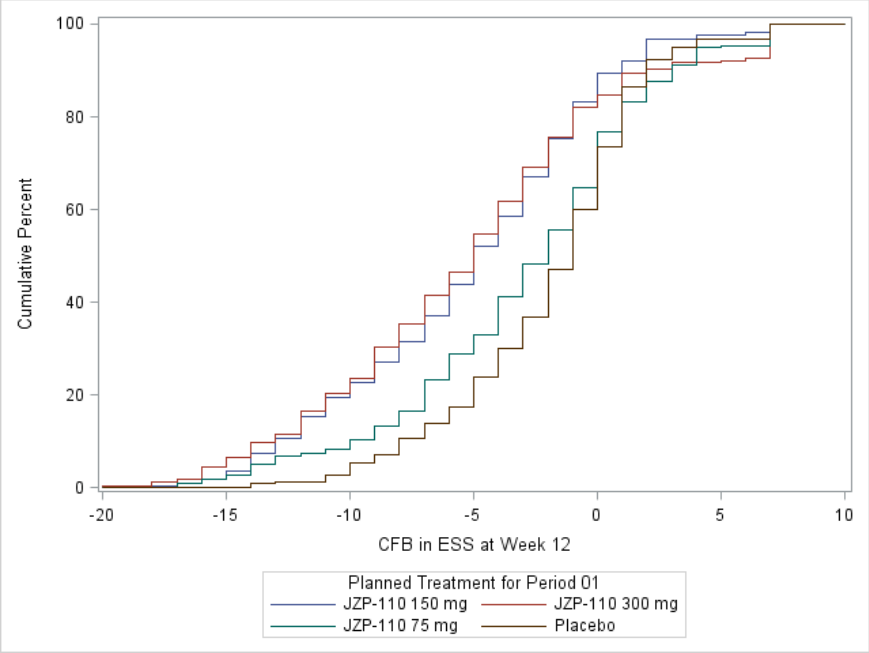
Figure 16: CDF of CFB in MWT at Week 12 by Treatment (Imputed by Placebo Mean) – 14-002



Source: this reviewer.

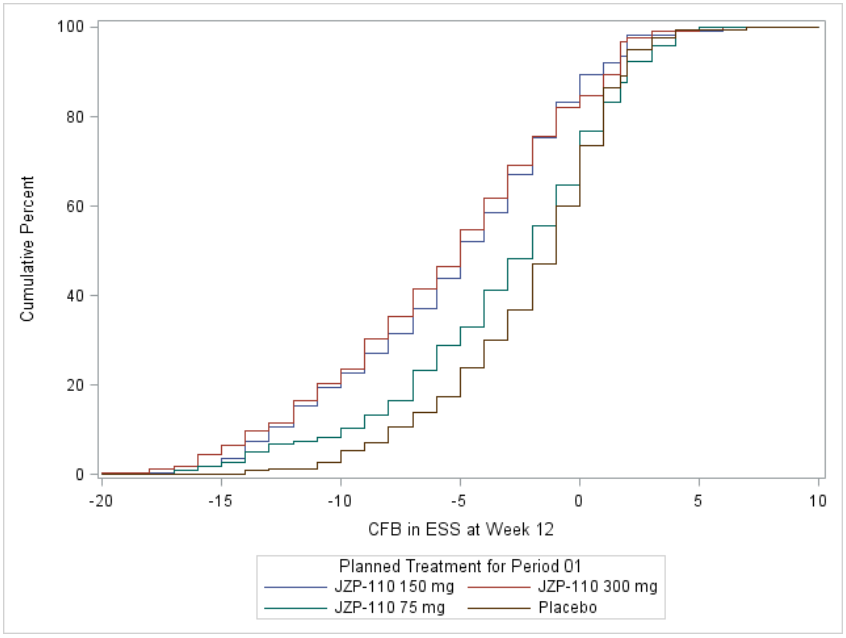
Reference ID: 4324053

Figure 17: CDF of CFB in ESS at Week 12 by Treatment (Imputed by the Worst Score) – 14-002



Source: this reviewer.

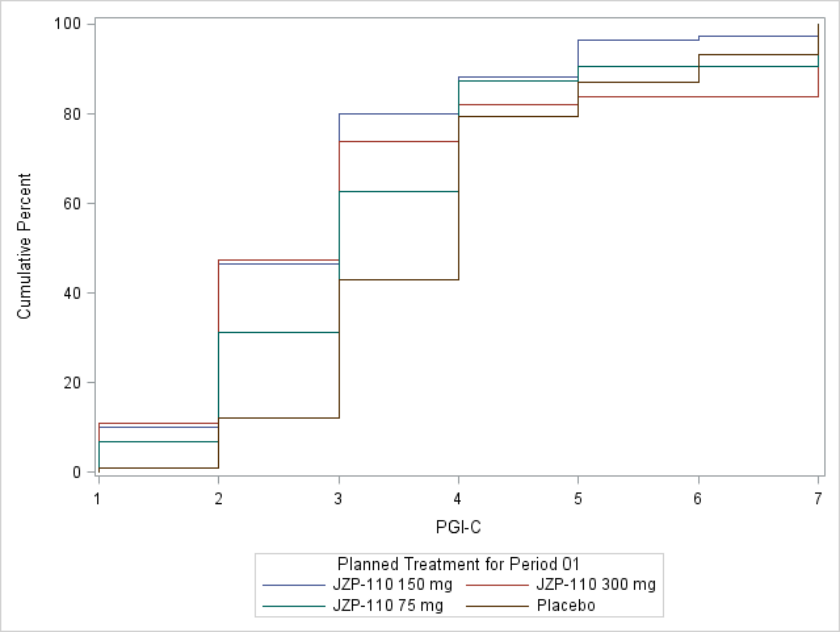
Figure 18: CDF of CFB in ESS at Week 12 by Treatment (Imputed by Placebo Mean) – 14-002



Source: This reviewer.

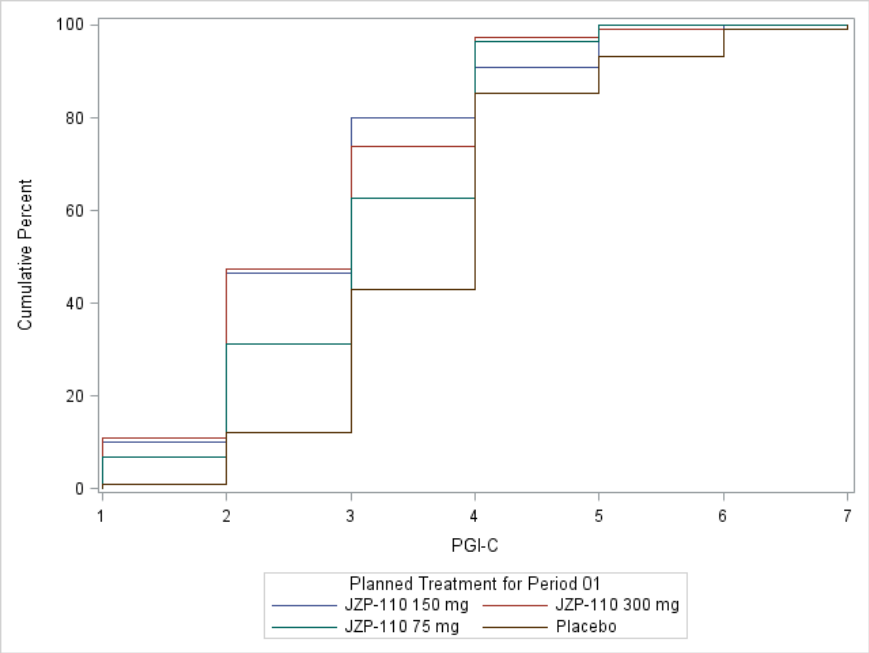
Reference ID: 4324053

Figure 19: CDF of PGIc at Week 12 by Treatment (Imputed by the Worst Score) – 14-002



Source: this reviewer.

Figure 20: CDF of PGIc at Week 12 by Treatment (Imputed by Placebo Median) – 14-002



Source: this reviewer.

3.2.4.3 14-003

Sponsor's Results and Conclusions:

The Sponsor performed the pre-specified primary analyses on co-primary and key secondary endpoints. However, the Sponsor excluded few data assessed at unscheduled visits to enable the program to converge. The pre-specified fixed hierarchical testing sequence was utilized. At all dose levels of JZP-110, improvement was statistically significant compared with placebo for the co-primary endpoints of change from Baseline to Week 12 in MWT mean sleep latency (in minutes) and for change from Baseline to Week 12 in ESS score at a statistical significance level of 0.05. For the key secondary endpoint of improvement at Week 12 on the PGIc, all doses of JZP-110, except 37.5 mg, showed improvement as compared with placebo at statistical significance level of 0.05.

Table 21: Primary Analysis Results on Co-Primary and Key Secondary Efficacy Endpoints – 14-003

Primary and Key Secondary Endpoints	**Placebo N = 114**	**37.5 mg JZP-110 N = 56**	**75 mg JZP-110 N = 58**	**150 mg JZP-110 N = 116**	**300 mg JZP-110 N = 115**
Co-Primary Endpoints					
Change in MWT from Baseline to Wk 12					
LS Mean (SE)	0.21 (0.997)	4.74 (1.418)	9.08 (1.358)	10.96 (0.973)	12.99 (1.038)
LS Mean Difference	NA	4.53	8.87	10.74	12.77
95% CI	NA	(1.16, 7.90)	(5.59, 12.14)	(8.05, 13.44)	(10.00, 15.55)
P-Value	NA	0.0086	< 0.0001	< 0.0001	< 0.0001
Change in ESS Score from Baseline to Wk 12					
LS Mean (SE)	-3.3 (0.45)	-5.1 (0.64)	-5.0 (0.62)	-7.7 (0.44)	-7.9 (0.46)
LS Mean Difference	NA	-1.9	-1.7	-4.5	-4.7
95% CI	NA	(-3.4, -0.3)	(-3.2, -0.2)	(-5.7, -3.2)	(-5.9, -3.4)
P-Value	NA	0.0161	0.0233	< 0.0001	< 0.0001
Key Secondary Endpoint					
PGIc: Subjects Reported Improved at Wk 12					
Subjects Improved (%)					
Yes	56 (49.1)	31 (55.4)	42 (72.4)	104 (89.7)	102 (88.7)
No	58 (50.9)	25 (44.6)	16 (27.6)	12 (10.3)	13 (11.3)
% Difference from Placebo (95% CI)	NA	6.2 (-9.69, 22.16)	23.3 (8.58, 38.01)	40.5 (29.81, 51.25)	39.6 (28.72, 50.42)
P-Value	NA	0.4447	0.0035	< 0.0001	< 0.0001

Source: Sponsor's Table 13 of Clinical Study Report of 14-003.

Four sensitivity analyses of the co-primary endpoints of change from baseline to Week 12 in MWT mean sleep latency and ESS scores were performed. Sensitivity analysis 1 and sensitivity analysis 2 utilized an ANCOVA model, with change from baseline as the response variable, and fixed-effect model terms of treatment, baseline, and randomization stratification factor (compliant or non-compliant use of a primary OSA therapy at

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Screening). Missing data were imputed using an LOCF approach in sensitivity analysis 1 and the corresponding treatment group mean in sensitivity analysis 2. Sensitivity analysis 3 and 4 utilized an MMRM model, with change from baseline as the response variable and fixed-effect of treatment, visit, treatment by visit, randomization stratification factor (compliant or non-compliant use of a primary OSA therapy at Screening), covariate of baseline, and unstructured variance-covariance structure. Missing data were imputed using multiple imputation method by MCMC for non-monotone missing (sensitivity analysis 3) and regression method for monotone missing data (sensitivity analysis 4) within each treatment group. Sensitivity analysis 4 applied progressively more stringent analysis criteria by subtracting an increasingly greater percentage of the treatment effect (K) which accounted for dropouts due to AEs or LOE. A summary of sensitivity analyses of the co-primary is presented in Table 22. The results of sensitivity analyses were consistent with those of the primary analyses, with increases observed from Baseline to Week 12 in MWT mean sleep latency (in minutes) and reductions in mean ESS Score for all JZP-110 dose groups compared with placebo.

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Table 22: Summary of Sensitivity Analyses of Change in MWT and ESS from Baseline to Week 12 – 14-003

Analysis	Test	37.5 mg JZP-110 N = 56	75 mg JZP-110 N = 58	150 mg JZP-110 N = 116	300 mg JZP-110 N = 115
Sensitivity Analysis 1[a]	MWT	0.0088	< 0.0001	< 0.0001	< 0.0001
	ESS	0.0293	0.0427	< 0.0001	< 0.0001
Sensitivity Analysis 2[b]	MWT	0.0041	< 0.0001	< 0.0001	< 0.0001
	ESS	0.0012	0.0059	< 0.0001	< 0.0001
Sensitivity Analysis 3[c]	MWT	0.0100	< 0.0001	< 0.0001	< 0.0001
	ESS	0.0162	0.0192	< 0.0001	< 0.0001
Sensitivity Analysis 4[d]	MWT				
	K = 0%	0.0100	< 0.0001	< 0.0001	< 0.0001
	K = 10%	0.0105	< 0.0001	< 0.0001	< 0.0001
	K = 20%	0.0110	< 0.0001	< 0.0001	< 0.0001
	K = 30%	0.0116	< 0.0001	< 0.0001	< 0.0001
	K = 40%	0.0122	< 0.0001	< 0.0001	< 0.0001
	K = 50%	0.0129	< 0.0001	< 0.0001	< 0.0001
	K = 60%	0.0137	< 0.0001	< 0.0001	< 0.0001
	K = 70%	0.0145	< 0.0001	< 0.0001	< 0.0001
	K = 80%	0.0154	< 0.0001	< 0.0001	< 0.0001
	K = 90%	0.0163	< 0.0001	< 0.0001	< 0.0001
	K = 100%	0.0174	< 0.0001	< 0.0001	< 0.0001
Sensitivity Analysis 4[d]	ESS				
	K = 0%	0.0148	0.0187	< 0.0001	< 0.0001
	K = 10%	0.0153	0.0187	< 0.0001	< 0.0001
	K = 20%	0.0160	0.0188	< 0.0001	< 0.0001
	K = 30%	0.0166	0.0189	< 0.0001	< 0.0001
	K = 40%	0.0174	0.0190	< 0.0001	< 0.0001
	K = 50%	0.0181	0.0192	< 0.0001	< 0.0001
	K = 60%	0.0190	0.0194	< 0.0001	< 0.0001
	K = 70%	0.0199	0.0197	< 0.0001	< 0.0001
	K = 80%	0.0210	0.0200	< 0.0001	< 0.0001
	K = 90%	0.0220	0.0204	< 0.0001	< 0.0001
	K = 100%	0.0232	0.0208	< 0.0001	< 0.0001

Source: Sponsor's Table 16 of Clinical Study Report 14-003.

Two sensitivity analyses were performed on the key secondary endpoint, the percentage of subjects reporting improvement at Week 12 on the PGIc. In sensitivity analysis 1, missing data at Week 12 were imputed by early termination reason (subjects discontinued due to

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LOE or AE were considered non-responders). In sensitivity analysis 2, missing data at Week 12 were imputed by worst case (subjects with missing data were considered non-responders).

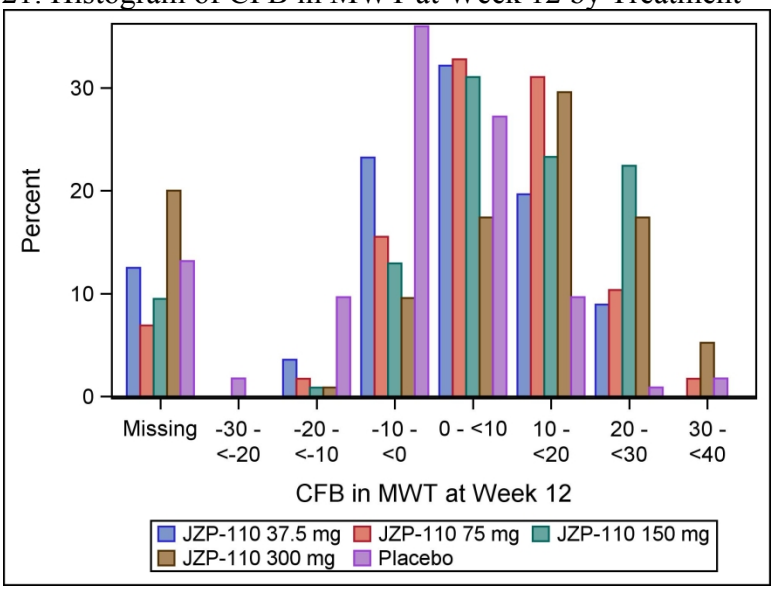
Using the first approach imputing by ET reason, percentage differences for subjects reported as improved relative to placebo were 4.4% (p=0.5881), 25.0% (p=0.0018), 38.8% (p<0.0001), and 31.8% (p<0.0001) for each of the 37.5, 75, 150, and 300 mg JZP-110 dose groups, respectively.

Using the second approach imputing by worst case, percentage differences for subjects reported as improved relative to placebo were 5.2% (p=0.5190), 26.0% (p=0.0013), 40.6% (p<0.0001), and 30.9% (p<0.0001) for each of the 37.5, 75, 150, and 300 mg JZP-110 dose groups, respectively.

Reviewer's Results and Conclusions:

Figure 21 to Figure 23 display the histograms of the co-primary endpoints and the key secondary endpoint by treatment, respectively.

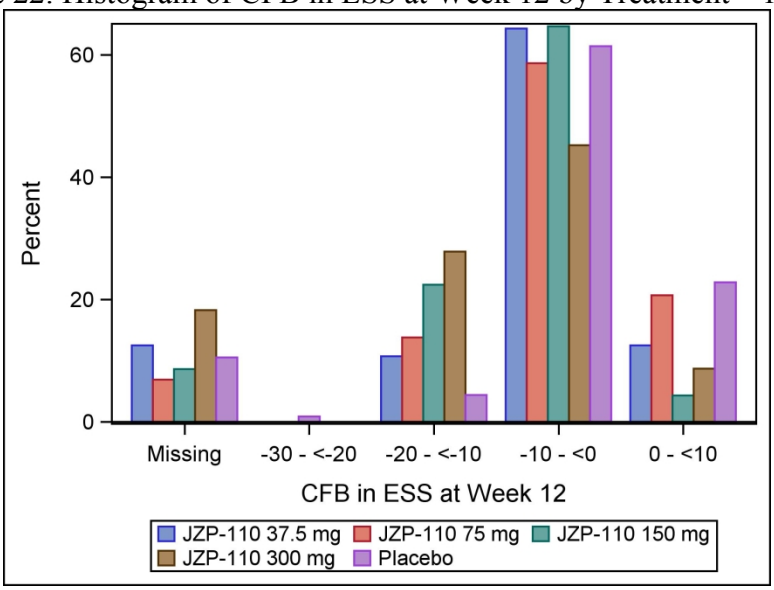
Figure 21: Histogram of CFB in MWT at Week 12 by Treatment – 14-003



Source: this reviewer.

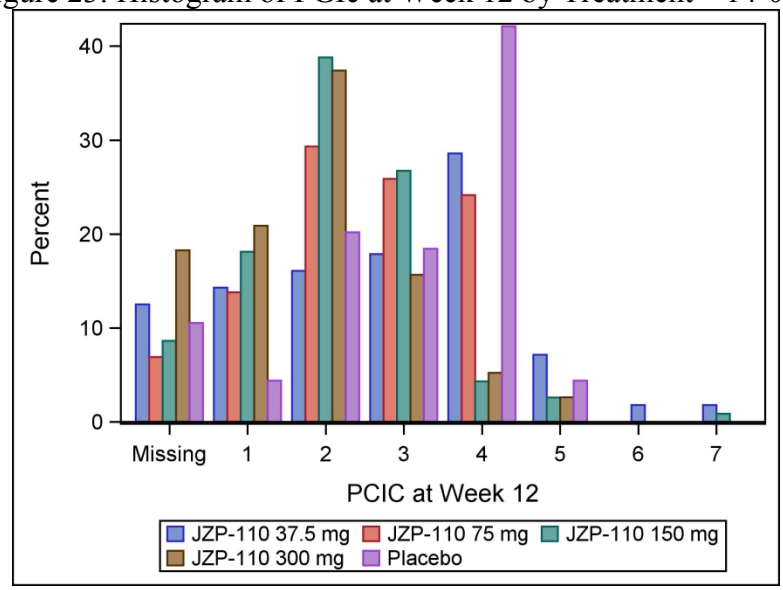
Reference ID: 4324053

Figure 22: Histogram of CFB in ESS at Week 12 by Treatment – 14-003



Source: this reviewer.

Figure 23: Histogram of PGIc at Week 12 by Treatment – 14-003



Source: this reviewer.

The Sponsor performed the pre-specified primary analyses on co-primary and key secondary endpoints. As what the Sponsor did in Trial 14-002, for the two primary endpoints, the Sponsor excluded few observations assessed at unscheduled visits to enable the primary analysis programs to converge. This reviewer re-coded the visits to the nearest visits within 1 week and performed the pre-specified analyses on co-primary endpoints. The reviewer repeated the pre-specified primary analysis of the key secondary endpoint. The reviewer's primary analysis results are summarized in Table 20. After applying the

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pre-specified multiplicity adjustment procedure, the reviewer reaches the same conclusion that all JZP-110 doses won on co-primary and key secondary endpoints except the JZP-110 37.5 mg dose for the key secondary endpoints.

Table 23: Reviewer's Primary Analysis Results on Co-Primary and Key Secondary Efficacy Endpoints – 14-003

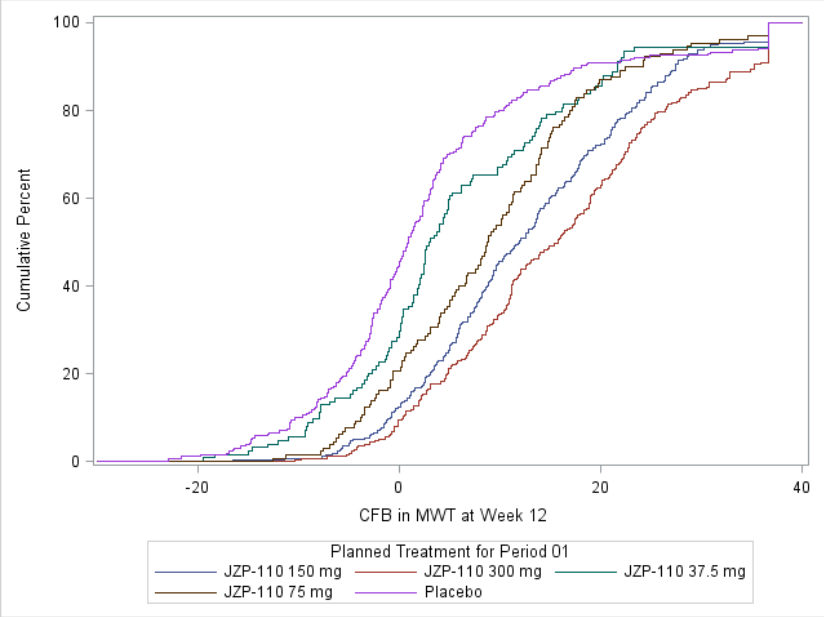
Co-Primary and Key Secondary Endpoints	JZP-110 37.5 mg vs Placebo	JZP-110 75 mg vs Placebo	JZP-110 150 mg vs Placebo	JZP-110 300 mg vs Placebo
MWT				
LS Mean Difference	4.53	8.87	10.74	12.77
95% CI	(1.16, 7.90)	(5.59, 12.14)	(8.05, 13.44)	(10.00, 15.55)
p-value	0.0086	<0.0001	<0.0001	<0.0001
ESS				
LS Mean Difference (p-value)	-1.89	-1.71	-4.42	-4.58
95% CI	(-3.42, -0.37)	(-3.20, -0.23)	(-5.63, -3.20)	(-5.81, -3.34)
P-value	0.0148	0.0236	<0.0001	<0.0001
PGIc: Subjects reported improved at Week 12				
Percentage Difference (Yes) from Placebo (95% CI)	6.2 (-9.7, 22.2)	23.3 (8.6, 38.0)	40.5 (29.8, 51.3)	40.0 (28.7, 50.4)
P-value	0.4447	0.0035	<0.0001	<0.0001

Source: this reviewer.

This reviewer plotted the CDF of the primary endpoint and key secondary endpoints with two imputation methods in Figure 24 to Figure 29.

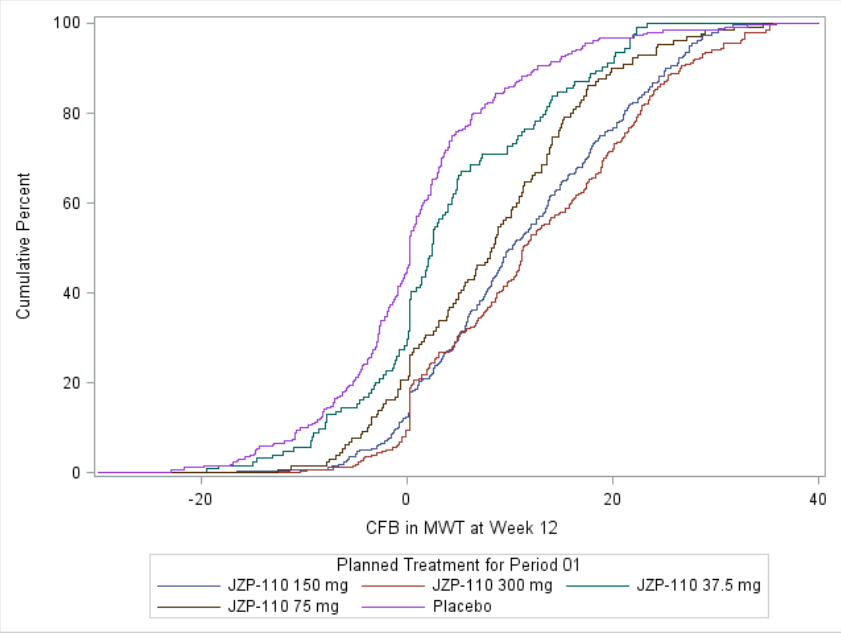
Reference ID: 4324053

Figure 24: CDF of CFB in MWT at Week 12 by Treatment (Imputed by the Worst Score) – 14-003



Source: this reviewer.

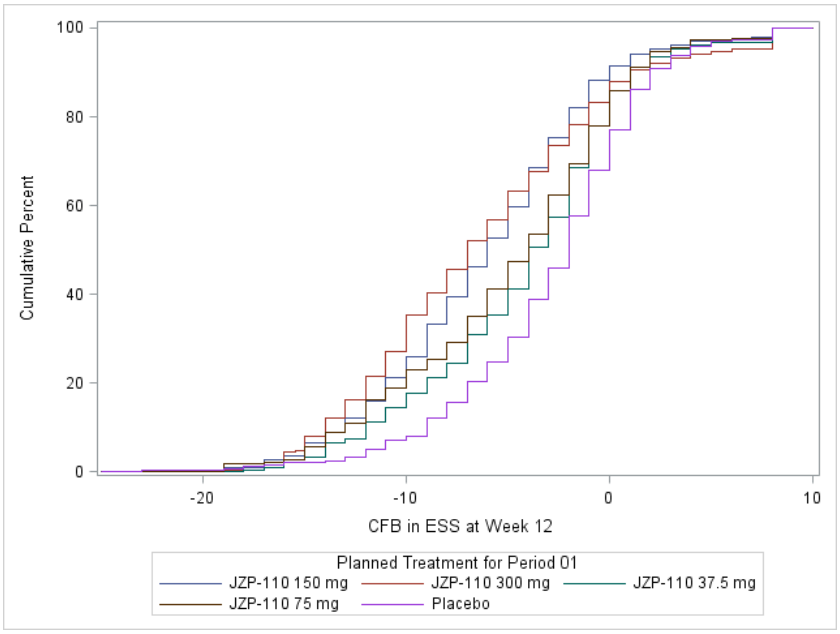
Figure 25: CDF of CFB in MWT at Week 12 by Treatment (Imputed by Placebo Mean) – 14-003



Source: this reviewer.

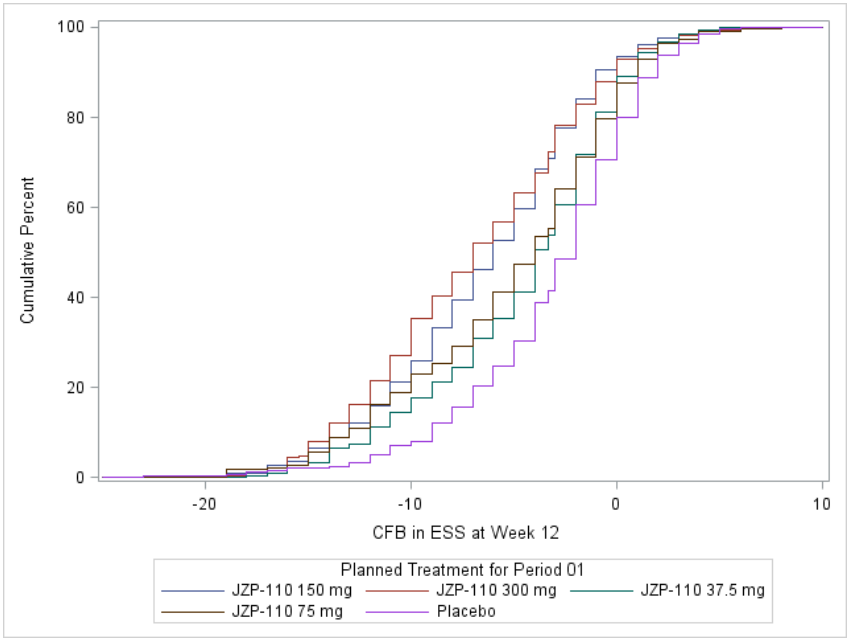
Reference ID: 4324053

Figure 26: CDF of CFB in ESS at Week 12 by Treatment (Imputed by the Worst Score) – 14-003



Source: this reviewer.

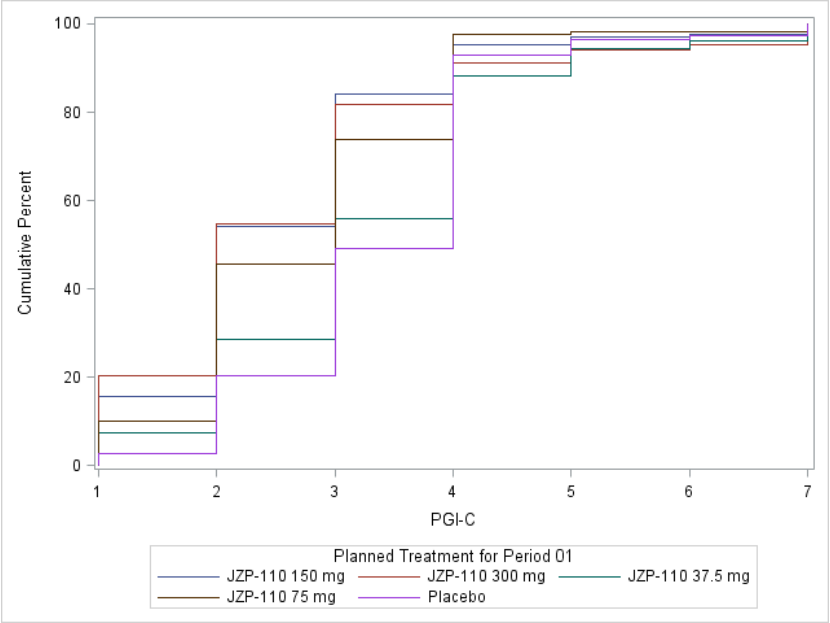
Figure 27: CDF of CFB in ESS at Week 12 by Treatment (Imputed by Placebo Mean) – 14-003



Source: this reviewer.

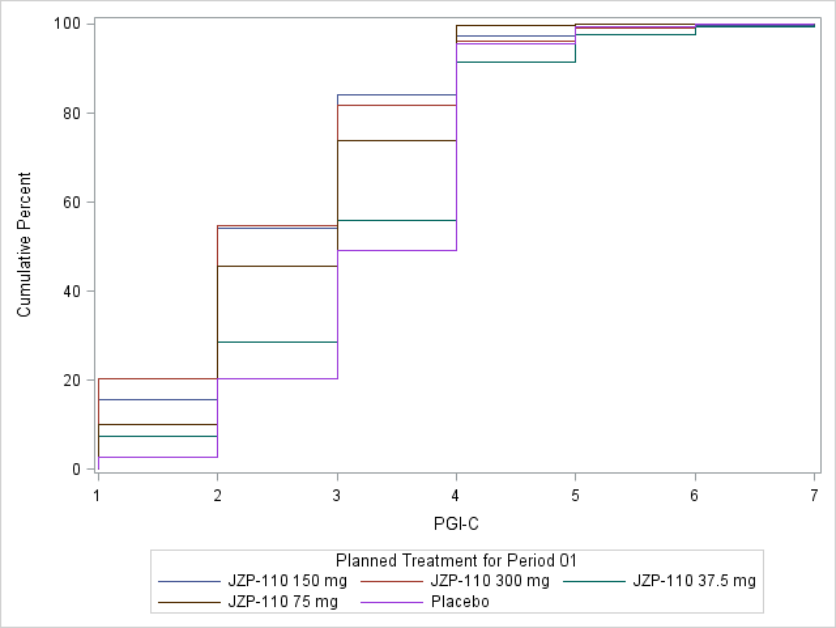
Reference ID: 4324053

Figure 28: CDF of PGIc at Week 12 by Treatment (Imputed by the Worst Score) – 14-003



Source: this reviewer.

Figure 29: CDF of PGIc at Week 12 by Treatment (Imputed by Placebo Median) – 14-003



Source: this reviewer.

3.2.4.3 14-004

The Sponsor performed the pre-specified primary analyses on co-primary and key secondary endpoints. The pre-specified fixed hierarchical testing sequence was utilized.

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Improvement was statistically significant compared with placebo for the co-primary endpoints (change from Week 4 to Week 6 in MWT and change from Week 4 to Week 6 in ESS score) and the key secondary endpoint of improvement at Week 6 on the PGIc at a statistical significance level of 0.05.

Table 24: Primary Analysis Results on Co-Primary and Key Secondary Efficacy Endpoints – 14-004

Endpoint	Placebo (N=62)	Combined JZP-110 (N=60)
Co-Primary Endpoints		
Change in MWT[a]		
LS mean (SE)	-12.11 (1.326)	-0.96 (1.350)
LS mean difference (95% CI)		11.16 (7.75, 14.57)
P-value		<0.0001
Change in ESS[a]		
LS mean (SE)	4.5 (0.71)	-0.1 (0.73)
LS mean difference		-4.6 (-6.4, -2.8)
P-value		<0.0001
Key Secondary Endpoint		
Subjects Reported as Worse on PGIc[b]		
Yes	31 (50.0)	12 (20.0)
% (difference (Yes) from placebo		-30.0 (-46.04, -13.96)
P-value		0.0005

[a] Change from efficacy baseline (Week 4) to Week 6.
[b] Minimally worse, much worse, or very much worse as measured from efficacy baseline to Week 6.

Source: The Sponsor's Table 14 in Clinical Study Report of 14-004.

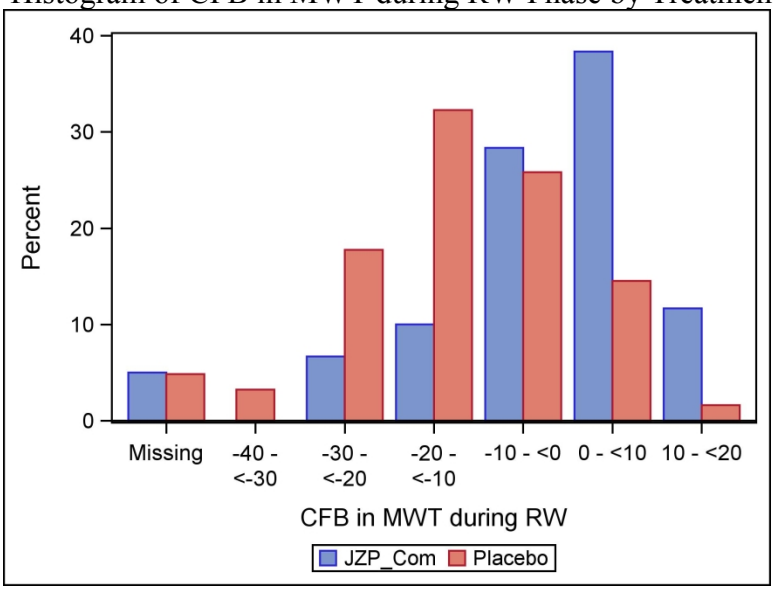
The Sponsor performed the pre-specified sensitivity analyses. All the results yield the same conclusion as the primary analyses. Because of the negligible number of subjects (6/122 for MWT, 0/122 for ESS, and 0/122 for PGIc) with missing values, the sensitivity analysis results are not shown in this review.

Reviewer's Results and Conclusions:

Figure 30 to Figure 32 display the histograms of the co-primary and the key secondary endpoints by treatment, respectively.

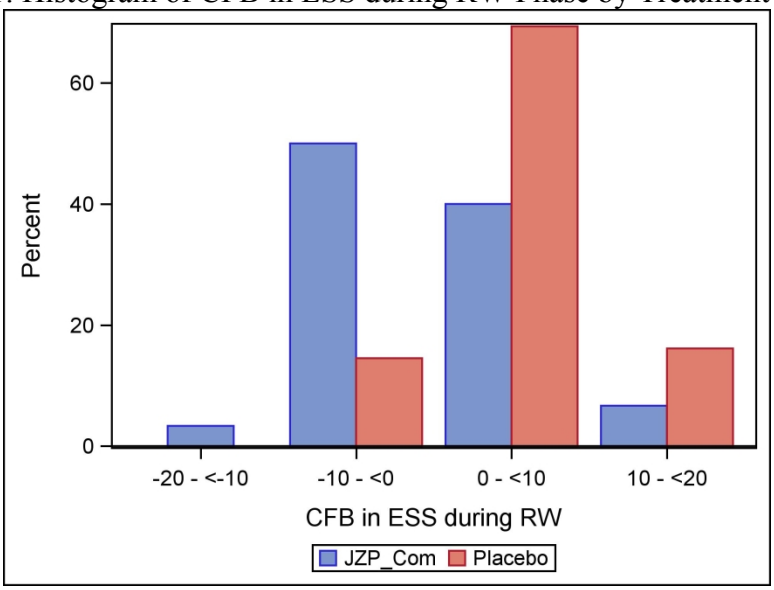
Reference ID: 4324053

Figure 30: Histogram of CFB in MWT during RW Phase by Treatment – 14-004



Source: this reviewer.

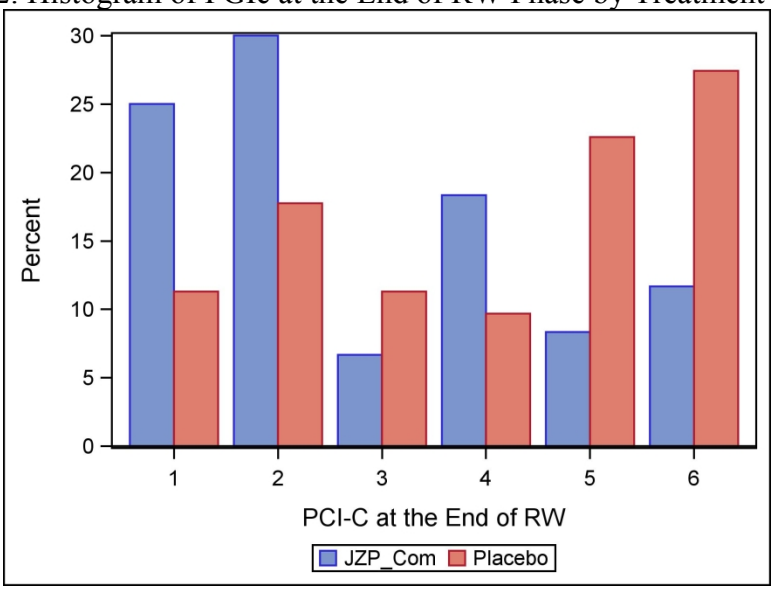
Figure 31: Histogram of CFB in ESS during RW Phase by Treatment – 14-004



Source: this reviewer.

Reference ID: 4324053

Figure 32: Histogram of PGIc at the End of RW Phase by Treatment – 14-004



Source: this reviewer.

This reviewer performed the pre-specified primary analyses on co-primary and key secondary endpoints and obtained the same results. Because of the negligible number of subjects (6/122 for MWT, 0/122 for ESS, and 0/122 for PGIc) with missing values, no sensitivity analyses were performed by the reviewer.

3.2.4.3 14-005

The Sponsor performed the pre-specified primary analyses on primary and key secondary endpoints. The pre-specified fixed hierarchical testing sequence was utilized. Improvement was statistically significant compared with placebo for the primary endpoints and the key secondary endpoints. Since there are no missing data in the primary endpoints and negligible missing data (11/280 for PGIc and 3/280 for CGIc) in the key secondary endpoints, sensitivity analysis results are almost identical to the primary analysis results.

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Table 25: Primary Analysis Results on Primary and Key Secondary Efficacy Endpoints – 14-005

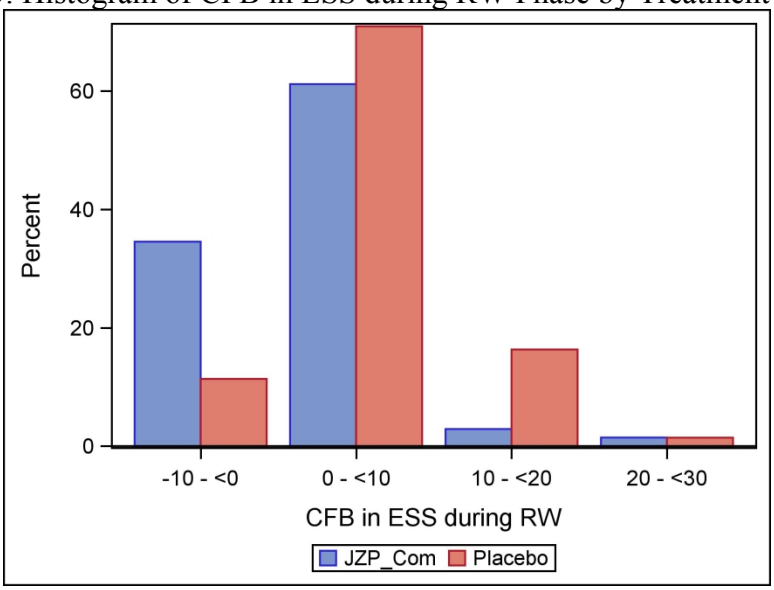
Endpoint	Overall		OSA		Narcolepsy	
	Placebo (N=141)	Combined JZP-110 (N=139)	Placebo (N=101)	Combined JZP-110 (N=101)	Placebo (N=40)	Combined JZP-110 (N=38)
Primary Endpoints						
Change in ESS[a]						
LS mean (SE)	5.3 (0.41)	1.6 (0.41)	4.9 (0.48)	1.1 (0.48)	4.9 (0.59)	1.1 (0.60)
LS mean difference	NA	-3.7 (-4.80, -2.65)	NA	-3.7 (-5.07, -2.38)	NA	-3.8 (-5.51, -2.15)
P-value	NA	<0.0001	NA	<0.0001	NA	<0.0001
Key Secondary Endpoints						
Subjects Reported as Worse on PGIc[b]						
Yes	89 (64.5)	37 (28.2)	59 (59.0)	26 (27.7)	30 (78.9)	11 (29.7)
% (difference (Yes) from placebo	NA	-36.2 [-47.35, -25.15]	NA	-31.3 [-44.56, -18.12]	NA	-49.2 [-68.84, -29.60]
P-value	NA	<0.0001	NA	<0.0001	NA	<0.0001
Subjects Reported as Worse on CGIc[b]						
Yes	90 (63.8)	39 (28.7)	63 (62.4)	27 (27.0)	27 (67.5)	12 (33.3)
% (difference (Yes) from placebo	NA	-35.2 [-46.14, -24.17]	NA	-35.4 [-48.22, -22.53]	NA	-34.2 [-55.33, -13.01]
P-value	NA	<0.0001	NA	<0.0001	NA	0.0029

Source: Sponsor's Table 19 in Clinical Study Report of 14-005.

Reviewer's Results and Conclusions:

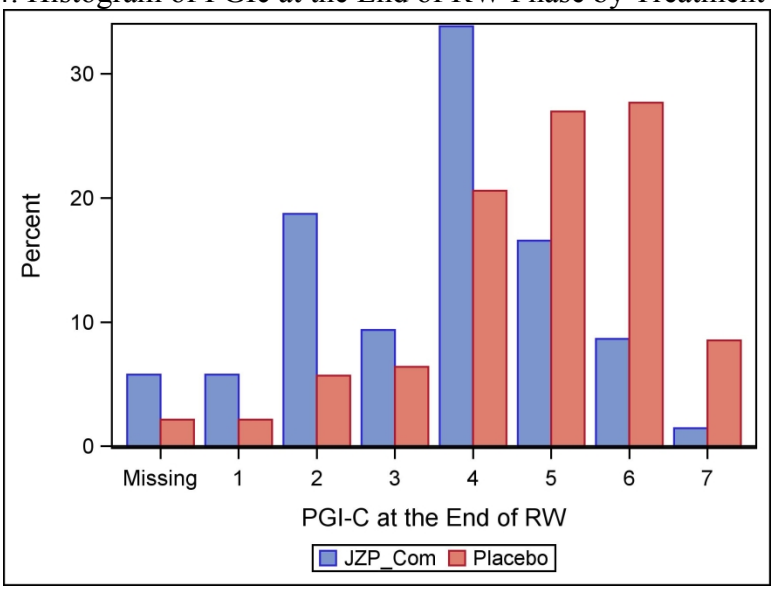
Figure 33 to Figure 35 display the histograms of the primary endpoint and the key secondary endpoints by treatment, respectively.

Figure 33: Histogram of CFB in ESS during RW Phase by Treatment – 14-005



Source: this reviewer.

Figure 34: Histogram of PGIc at the End of RW Phase by Treatment – 14-005



Source: this reviewer.

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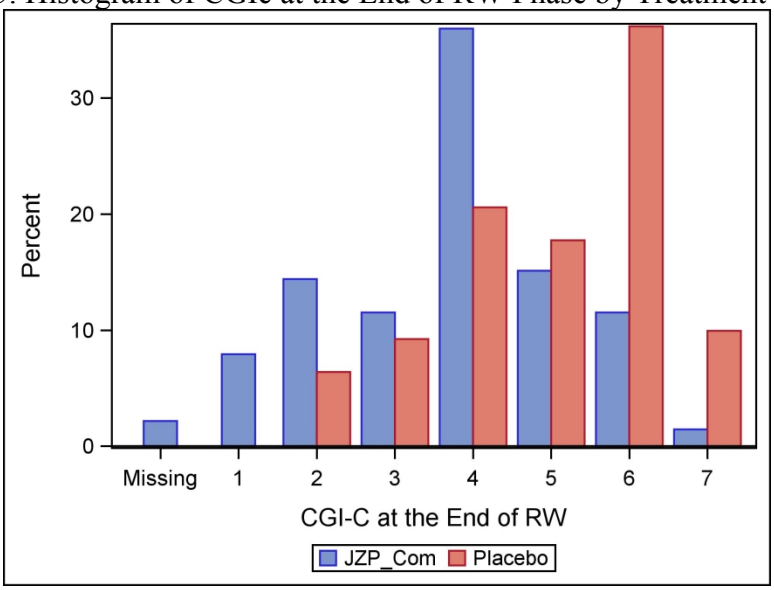
Figure 35: Histogram of CGIc at the End of RW Phase by Treatment – 14-005



Source: this reviewer.

This reviewer performed the pre-specified primary analyses on primary and key secondary endpoints and obtained the same results. Because of the negligible amount of missing data, no sensitivity analyses were performed by the reviewer.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS OF STUDY

The subgroup analyses presented in this section are all exploratory. The main objective of the exploratory subgroup analysis is to assess consistency across subgroups with respect to the primary analysis results. Because of the exploratory purpose of the subgroup analyses, those p-values are not presented here.

4.1 Gender, Race, Age Group and Region

For all the studies, the patients age 18 and above. Therefore, no subgroup analysis was performed on age group. Most of the patients are white. The other races were combined into one race "Non-White" for the subgroup analysis on race. The results are presented in Table 26 to Table 33. There are a few subgroups showing a different treatment direction on one or both co-primary endpoints from that of the overall population. These subgroup results are highlighted in red font in the summary tables below. Except one subgroup which is dosed with 150 mg JZP-110, the rest of the subgroups are dosed with the lower doses, 37.5 mg and 75 mg JZP-110. The lower dose treatment groups (37.5 mg and 75 mg) have smaller overall treatment effects compared to the other dose groups. Therefore, different treatment directions may be expected for some subgroups. Across the 5 trials and co-primary endpoints, the one inconsistent result of the male subgroup of 150 mg JZP-110 in Study 14-002 may be due to chance.

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Study ADX-N05-202

This study is conducted in the US. Therefore, no subgroup analysis is performed on region.

Table 26: Subgroup Analysis Results on MWT – Study ADX-N05-202

	Subgroup	JZP-100 LS Mean (SE) (n)	Placebo LS Mean (SE) (n)	LS Mean Diff (SE) JZP-100-Placebo)
Overall		13.2 (1.51) (43)	1.9 (1.42) (47)	11.4 (2.09)
Gender	Female	14.2 (1.76) (29)	2.5 (1.80) (28)	11.6 (2.53)
	Male	11.6 (2.86) (14)	1.1 (2.33) (19)	10.5 (3.73)
Race	White	13.1 (1.77) (29)	2.4 (1.45) (39)	10.6 (2.30)
	Non-White	13.0 (3.19) (14)	0.1 (4.94) (8)	12.9 (5.88)

Source: This reviewer.

Study 14-002

Table 27: Subgroup Analysis Results on MWT - 14-002

Dose (mg)		Subgroup	JZP-100 LS Mean (SE) (n)	Placebo LS Mean (SE) (n)	LS Mean Diff (SE) (HLD200-Placebo)
75	Overall		4.7 (1.33) (54)	2.1 (1.29) (56)	2.6 (1.85)
	Gender	F	5.2 (1.73) (34)	0.6 (1.69) (34)	4.6 (2.42)
		M	3.7 (2.12) (20)	4.3 (2.01) (22)	-0.6 (2.93)
	Race	NON-WHITE	4.3 (2.80) (12)	2.1 (2.80) (12)	2.2 (3.93)
		WHITE	4.9 (1.54) (42)	2.0 (1.47) (44)	2.9 (2.13)
	Region	Europe	2.7 (2.60) (14)	8.3 (4.09) (6)	-5.6 (4.60)
		North America	5.8 (1.56) (40)	1.4 (1.36) (50)	4.5 (2.07)
150	Overall		9.8 (1.32) (52)	2.1 (1.29) (56)	7.6 (1.85)
	Gender	F	11.0 (1.63) (37)	0.6 (1.69) (34)	10.3 (2.36)
		M	7.3 (2.33) (15)	4.3 (2.01) (22)	3.0 (3.08)
	Race	NON-WHITE	9.1 (2.85) (11)	2.1 (2.80) (12)	7.0 (3.94)
		WHITE	10.0 (1.52) (41)	2.0 (1.47) (44)	8.1 (2.13)
	Region	Europe	10.5 (3.45) (10)	8.3 (4.09) (6)	2.2 (4.95)
		North America	10.0 (1.46) (42)	1.4 (1.36) (50)	8.6 (1.99)
300	Overall		12.2 (1.39) (56)	2.1 (1.29) (56)	10.0 (1.90)
	Gender	F	13.7 (1.81) (37)	0.6 (1.69) (34)	13.1 (2.49)
		M	9.9 (2.16) (19)	4.3 (2.01) (22)	5.5 (2.96)
	Race	NON-WHITE	11.5 (3.26) (10)	2.1 (2.80) (12)	9.3 (4.25)
		WHITE	12.5 (1.56) (46)	2.0 (1.47) (44)	10.5 (2.16)
	Region	Europe	11.8 (3.25) (11)	8.3 (4.09) (6)	3.5 (4.77)
		NorthAmerica	12.5 (1.58) (45)	1.4 (1.36) (50)	11.2 (2.09)

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Source: This reviewer.

Table 28: Subgroup Analysis Results on ESS - 14-002

Dose (mg)		Subgroup	JZP-100 LS Mean (SE) (n)	Placebo LS Mean (SE) (n)	LS Mean Diff (SE) (HLD200-Placebo)
75	Overall		-3.8 (0.67) (59)	-1.6 (0.65) (58)	-2.2 (0.93)
	Gender	F	-4.2 (0.86) (37)	-0.7 (0.85) (34)	-3.6 (1.21)
		M	-3.1 (1.00) (22)	-3.2 (0.96) (24)	0.1 (1.39)
	Race	NON-WHITE	-5.1 (1.94) (13)	0.3 (2.03) (12)	-5.4 (2.80)
		WHITE	-3.5 (0.69) (46)	-2.1 (0.66) (46)	-1.4 (0.95)
	Region	Europe	-2.7 (1.36) (16)	-3.6 (2.20) (7)	0.9 (2.39)
		North America	-4.3 (0.79) (43)	-1.3 (0.70) (51)	-3.0 (1.05)
150	Overall		-5.4 (0.66) (55)	-1.6 (0.65) (58)	-3.8 (0.93)
	Gender	F	-6.5 (0.81) (39)	-0.7 (0.85) (34)	-5.8 (1.18)
		M	-2.9 (1.11) (16)	-3.2 (0.96) (24)	0.3 (1.48)
	Race	NON-WHITE	-4.9 (1.99) (11)	0.3 (2.03) (12)	-5.2 (2.82)
		WHITE	-5.6 (0.68) (44)	-2.1 (0.66) (46)	-3.5 (0.95)
	Region	Europe	-4.9 (1.76) (10)	-3.6 (2.20) (7)	-1.3 (2.48)
		North America	-5.5 (0.74) (45)	-1.3 (0.70) (51)	-4.2 (1.02)
300	Overall		-6.4 (0.68) (59)	-1.6 (0.65) (58)	-4.7 (0.95)
	Gender	F	-6.1 (0.88) (40)	-0.7 (0.85) (34)	-5.5 (1.22)
		M	-7.0 (1.04) (19)	-3.2 (0.96) (24)	-3.8 (1.42)
	Race	NON-WHITE	-6.7 (2.24) (11)	0.3 (2.03) (12)	-7.0 (3.01)
		WHITE	-6.4 (0.68) (48)	-2.1 (0.66) (46)	-4.3 (0.95)
	Region	Europe	-6.9 (1.70) (11)	-3.6 (2.20) (7)	-3.3 (2.44)
		North America	-6.3 (0.79) (48)	-1.3 (0.70) (51)	-4.9 (1.05)

Source: This reviewer.

Study 14-003

Table 29: Subgroup Analysis Results on MWT - 14-003

Dose (mg)		Subgroup	JZP-100 LS Mean (SE) (n)	Placebo LS Mean (SE) (n)	LS Mean Diff (SE) (HLD200-Placebo)
37.5	Overall		4.7 (1.42) (52)	0.2 (1.00) (109)	4.5 (1.71)
	Gender	F	6.3 (2.35) (19)	-0.3 (1.61) (39)	6.5 (2.83)
		M	3.9 (1.78) (33)	0.5 (1.28) (70)	3.4 (2.16)
	Race	NON-WHITE	10.1 (3.22) (11)	1.0 (1.96) (30)	9.1 (3.75)
		WHITE	3.1 (1.57) (41)	-0.2 (1.16) (79)	3.3 (1.93)
	Region	Europe	4.0 (5.51) (2)	0.8 (4.65) (4)	3.2 (6.39)
		North America	5.1 (1.45) (50)	0.3 (1.01) (105)	4.8 (1.75)
75	Overall		9.1 (1.36) (55)	0.2 (1.00) (109)	8.9 (1.67)

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	Gender	F	11.5 (2.00) (25)	-0.3 (1.61) (39)	11.8 (2.55)
		M	7.1 (1.84) (30)	0.5 (1.28) (70)	6.6 (2.21)
	Race	NON-WHITE	10.2 (2.77) (15)	1.0 (1.96) (30)	9.1 (3.37)
		WHITE	8.5 (1.57) (40)	-0.2 (1.16) (79)	8.7 (1.92)
	Region	North America	9.0 (1.36) (55)	0.3 (1.01) (105)	8.7 (1.68)
150	Overall		11.0 (0.97) (111)	0.2 (1.00) (109)	10.7 (1.37)
	Gender	F	13.0 (1.58) (42)	-0.3 (1.61) (39)	13.3 (2.24)
		M	9.8 (1.23) (69)	0.5 (1.28) (70)	9.3 (1.74)
	Race	NON-WHITE	10.2 (2.40) (22)	1.0 (1.96) (30)	9.2 (3.11)
		WHITE	11.0 (1.07) (89)	-0.2 (1.16) (79)	11.2 (1.54)
	Region	Europe	3.7 (6.38) (2)	0.8 (4.65) (4)	2.9 (6.31)
		North America	11.0 (0.98) (109)	0.3 (1.01) (105)	10.8 (1.39)
300	Overall		13.0 (1.04) (104)	0.2 (1.00) (109)	12.8 (1.41)
	Gender	F	14.7 (1.68) (40)	-0.3 (1.61) (39)	15.0 (2.32)
		M	12.0 (1.33) (64)	0.5 (1.28) (70)	11.5 (1.80)
	Race	NON-WHITE	17.1 (2.20) (27)	1.0 (1.96) (30)	16.0 (2.93)
		WHITE	11.5 (1.18) (77)	-0.2 (1.16) (79)	11.7 (1.61)
	Region	Europe	17.1 (3.56) (6)	0.8 (4.65) (4)	16.3 (5.59)
		North America	13.2 (1.07) (98)	0.3 (1.01) (105)	12.9 (1.45)

Source: This reviewer.

Table 30: Subgroup Analysis Results on ESS - 14-003

Dose (mg)		Subgroup	JZP-100 LS Mean (SE) (n)	Placebo LS Mean (SE) (n)	LS Mean Diff (SE) (HLD200-Placebo)
37.5	Overall		-5.2 (0.64) (56)	-3.3 (0.45) (114)	-1.9 (0.77)
	Gender	F	-6.5 (1.07) (19)	-2.6 (0.72) (41)	-3.9 (1.28)
		M	-4.5 (0.80) (37)	-3.6 (0.58) (73)	-0.9 (0.97)
	Race	NON-WHITE	-5.8 (1.33) (13)	-3.3 (0.82) (32)	-2.4 (1.56)
		WHITE	-4.9 (0.72) (43)	-3.1 (0.53) (82)	-1.7 (0.88)
	Region	Europe	0.9 (3.15) (2)	-1.3 (2.42) (4)	2.2 (3.57)
		North America	-5.4 (0.65) (54)	-3.3 (0.46) (110)	-2.0 (0.79)
75	Overall		-5.0 (0.62) (58)	-3.3 (0.45) (114)	-1.7 (0.75)
	Gender	F	-5.7 (0.91) (25)	-2.6 (0.72) (41)	-3.1 (1.15)
		M	-4.5 (0.84) (33)	-3.6 (0.58) (73)	-0.8 (1.00)
	Race	NON-WHITE	-3.8 (1.16) (15)	-3.3 (0.82) (32)	-0.5 (1.42)
		WHITE	-5.3 (0.72) (43)	-3.1 (0.53) (82)	-2.2 (0.88)
	Region	North America	-5.0 (0.62) (58)	-3.3 (0.46) (110)	-1.6 (0.76)
150	Overall		-7.7 (0.44) (116)	-3.3 (0.45) (114)	-4.4 (0.62)
	Gender	F	-7.7 (0.70) (44)	-2.6 (0.72) (41)	-5.1 (1.00)
		M	-7.8 (0.56) (72)	-3.6 (0.58) (73)	-4.1 (0.79)
	Race	NON-WHITE	-8.1 (0.98) (23)	-3.3 (0.82) (32)	-4.8 (1.28)

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		WHITE	-7.4 (0.49) (93)	-3.1 (0.53) (82)	-4.2 (0.70)
	Region	Europe	-8.2 (3.19) (2)	-1.3 (2.42) (4)	-6.9 (3.54)
		North America	-7.7 (0.44) (114)	-3.3 (0.46) (110)	-4.3 (0.63)
300	Overall		-7.8 (0.46) (115)	-3.3 (0.45) (114)	-4.6 (0.63)
	Gender	F	-9.0 (0.72) (43)	-2.6 (0.72) (41)	-6.4 (1.01)
		M	-7.1 (0.60) (72)	-3.6 (0.58) (73)	-3.5 (0.81)
	Race	NON-WHITE	-9.0 (0.90) (28)	-3.3 (0.82) (32)	-5.7 (1.20)
		WHITE	-7.4 (0.53) (87)	-3.1 (0.53) (82)	-4.2 (0.73)
	Region	Europe	-8.5 (1.80) (7)	-1.3 (2.42) (4)	-7.2 (2.59)
		North America	-7.8 (0.48) (108)	-3.3 (0.46) (110)	-4.5 (0.65)

Source: This reviewer.

Study 14-004

Table 31: Subgroup Analysis Results on MWT -Study 14-004

	Subgroup	JZP-100 LS Mean (SE) (n)	Placebo LS Mean (SE) (n)	LS Mean Diff (SE) JZP-100-Placebo)
Overall		-1.0 (1.35) (57)	-12.1 (1.33) (59)	11.2 (1.72)
Gender	Female	0.1 (1.96) (24)	-11.8 (2.15) (21)	11.9 (2.82)
	Male	-1.7 (2.03) (33)	-12.2 (1.82) (38)	10.4 (2.26)
Race	White	-1.5 (1.55) (45)	-11.6 (1.59) (42)	10.1 (2.00)
	Non-White	1.1 (2.88) (12)	-13.4 (2.50) (17)	14.5 (3.53)
Region	Europe	0.4 (2.55) (12)	-6.9 (2.71) (11)	7.2 (3.60)
	North America	-1.8 (1.57) (45)	-13.5 (1.52) (48)	11.7 (1.97)

Source: This reviewer.

Table 32: Subgroup Analysis Results on ESS - Study 14-004

	Subgroup	JZP-100 LS Mean (SE) (n)	Placebo LS Mean (SE) (n)	LS Mean Diff (SE) JZP-100-Placebo)
Overall		-0.1 (0.73) (60)	4.5 (0.71) (62)	-4.6 (0.91)
Gender	Female	-1.3 (1.06) (26)	5.9 (1.20) (21)	-7.2 (1.54)
	Male	0.9 (1.04) (34)	3.9 (0.88) (41)	-3.0 (1.11)
Race	White	0.6 (0.76) (48)	4.8 (0.77) (45)	-4.1 (0.97)
	Non-White	-3.3 (1.69) (12)	4.2 (1.46) (17)	-7.5 (2.06)
Region	Europe	0.8 (1.35) (12)	2.6 (1.47) (11)	-1.8 (1.92)
	North America	-0.1 (0.84) (48)	5.1 (0.79) (51)	-5.2 (1.01)

Source: This reviewer.

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Study 14-005

Table 33: Subgroup Analysis Results on ESS -Study 14-005

		Subgroup	JZP-100 LS Mean (SE) (n)	Placebo LS Mean (SE) (n)	LS Mean Diff (SE) JZP-100-Placebo
OSA + Narcolepsy	Overall		1.6 (0.41) (139)	5.3 (0.41) (141)	-3.7 (0.55)
	Gender	Female	1.2 (0.48) (64)	5.0 (0.51) (56)	-3.8 (0.70)
		Male	1.6 (0.69) (75)	5.0 (0.69) (85)	-3.5 (0.80)
	Race	White	1.5 (0.47) (111)	5.2 (0.46) (110)	-3.7 (0.61)
		Non-White	1.7 (0.93) (28)	5.6 (0.93) (31)	-3.9 (1.27)
	Region	Europe	-0.16 (1.09) (15)	3.7 (1.22) (12)	-3.9 (1.67)
		North America	1.8 (0.45) (124)	5.5 (0.45) (129)	-3.7 (0.58)
OSA	Overall		1.1 (0.48) (101)	4.9 (0.48) (101)	-3.7 (0.68)
	Gender	Female	0.6 (0.62) (39)	4.5 (0.73) (28)	-3.8 (0.96)
		Male	1.5 (0.66) (62)	5.0 (0.61) (73)	-3.4 (0.90)
	Race	White	1.2 (0.52) (84)	4.8 (0.54) (78)	-3.6 (0.76)
		Non-White	0.7 (1.27) (17)	5.2 (1.09) (23)	-4.5 (1.67)
	Region	Europe	-0.6 (1.78) (8)	6.0 (2.26) (5)	-6.6 (2.92)
		North America	1.3 (0.50) (93)	4.8 (0.50) (96)	-3.5 (0.71)
Narcolepsy	Overall		1.1 (0.60) (38)	4.9 (0.59) (40)	-3.8 (0.84)
	Gender	Female	1.6 (0.76) (25)	5.4 (0.72) (28)	-3.8 (1.05)
		Male	0.2 (0.95) (13)	3.9 (0.98) (12)	-3.7 (1.37)
	Race	White	0.6 (0.70) (27)	5.0 (0.64) (32)	-4.3 (0.95)
		Non-White	2.2 (1.24) (11)	4.9 (1.46) (8)	-2.7 (1.92)
	Region	Europe	0.4 (1.07) (7)	2.2 (1.07) (7)	-1.7 (1.54)
		North America	1.3 (0.70) (31)	5.5 (0.68) (33)	-4.2 (0.98)

Source: This reviewer.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Before DPP took over the review of applications for this class of indications, the submitted protocol and the SAP of ADX-N05 202 were not reviewed by the statistical team then. The design of the study is appropriate for the objectives of the study. However, the choices of

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primary endpoints are not appropriate because we would not accept CGI-C as a primary endpoint, and additionally the duration for measuring improvement should have been a fixed duration instead of varying durations depending on the time when subject dropped out. For the other Phase 3 trials with similar designs included in the NDA, the co-primary endpoints FDA agreed upon are the CFB in MWT at Week 12 and CFB in ESS at Week 12. The Sponsor did not pre-specify the multiplicity adjustment for the primary endpoints and secondary endpoints in the protocol and SAP. CFB in ESS and PGIc are considered as exploratory endpoints in this study.

JZP-110 37.5 mg dose group failed to show a statistically significant improvement in terms of percentage of subjects reported improved at Week 12 by PGIc in Study 14-003. JZP-110 75 mg dose group failed in Study 14-002.

5.2 Collective Evidence

5.2.1 Short-term Efficacy in Narcolepsy and OSA

The acute efficacy of JZP-100 to improve wakefulness and reduce excessive sleepiness has been evaluated in 3 short-term placebo-controlled studies (2 in adult with narcolepsy and 1 in adult with OSA). There are two co-primary endpoints in each study. There is no key secondary endpoint in one study and one key secondary endpoint in the other two studies. The Sponsor and the FDA agreed upon the choice of the co-primary endpoints (CFB in MWT at Week 12 and CFB in ESS at Week 12) and the key secondary endpoint (percentage subjects reported improved by PGIc) for two of the studies. The primary efficacy results and key secondary efficacy results of three positive short-term studies are summarized in Table 34 and Table 35.

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Table 34: Primary Efficacy Results for Short-term Efficacy Studies

Population	Study Number	Region/ Conduct Date	Co-Primary Endpoint	Dose (mg)	Treatment Difference (95%CI)	Unadjusted p-value (adjusted significance)
Narcolepsy	ADX-N05_202	US only/ (9/17-2012 - 9/5/2013)	CFB in MWT at the last postbaseline assessment (Not agreed)	300	10.7 (7.9, 10.7)	<0.0001 (Yes)
			Percentage of improved subjects by CGI-C at the last postbaseline assessment (Not agreed)	300	47.8% (30.4%, 65.1%)	<0.0001 (Yes)
Narcolepsy	14-002	US and Europe/ (5/19/2015 – 2/14/2017)	CFB in MWT at Week 12	75	2.6 (-1.0, 6.3)	0.1595 (No)
				150	7.7 (4.0, 11.3)	<0.0001 (Yes)
				300	10.1 (6.4, 13.9)	<0.0001 (Yes)
			CFB in ESS at Week 12	75	-2.2 (-4.0, -0.3)	0.0211 (Yes)
				150	-3.8 (-5.6, -2.0)	<0.0001 (Yes)
				300	-4.7 (-6.6, -2.9)	<0.0001 (Yes)
OSA	14-003	US and Europe/ (5/19/2015 – 12/23/2016)	CFB in MWT at Week 12	37.5	4.5 (1.2, 7.9)	0.0086 (Yes)
				75	8.9 (5.6, 12.1)	<0.0001 (Yes)
				150	10.7 (8.1, 13.4)	<0.0001 (Yes)
				300	12.8 (10.0, 15.6)	<0.0001 (Yes)
			CFB in ESS at Week 12	37.5	-1.9 (-3.4, -0.3)	0.0161 (Yes)
				75	-1.7 (-3.2, -0.2)	0.0233 (Yes)
				150	-4.5 (-5.7, -3.2)	<0.0001 (Yes)
				300	-4.7 (-5.9, -3.4)	<0.0001 (Yes)

Source: reviewer's summary based on sponsor's clinical study reports.

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Table 35: Key Secondary Efficacy Results for Short-term Efficacy Studies

Population	Study Number	Region/ Conduct Date	Key Secondary Endpoint	Dose (mg)	Treatment Difference (95%CI)	Unadjusted p-value (adjusted significance)
Narcolepsy	14-002	US and Europe/ (5/19/2015 – 2/14/2017)	Percentage of Subjects Reported Improved by PGIc at Week 12	75	28.1% (10.8%, 45.5%)	0.0023 (No)
				150	38.5% (21.9%, 55.2%)	<0.0001 (Yes)
				300	45.1% (29.5%, 60.7%)	<0.0001 (Yes)
OSA	14-003	US and Europe/ (5/19/2015 – 12/23/2016)	Percentage of Subjects Reported Improved by PGIc at Week 12	37.5	6.2% (-9.7%, 22.2%)	0.4447 (No)
				75	23.3% (8.6%, 38.0%)	0.0035 (Yes)
				150	40.5% (29.8%, 51.3%)	<0.0001 (Yes)
				300	39.6% (28.7%, 50.4%)	<0.0001 (Yes)

Source: reviewer's summary based on sponsor's clinical study reports.

5.2.2 Maintenance Effect in Narcolepsy and OSA

The maintenance effect of JZP-100 in patients with narcolepsy and OSA was established in two randomized withdrawal, placebo controlled studies (14-004 and 14-005). The primary efficacy results and key secondary efficacy results of two positive randomized withdrawal studies are summarized in Table 36.

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Table 36: Efficacy Results for Random Withdrawal Studies

Population	Study Number	Region/ Conduct Date	Primary Endpoint	Overall/ Subgroup	Treatment Difference (95%CI)	Unadjusted p-value (adjusted significance)
OSA	14-004	US and Europe / 5/19/2015 – 11/11/2016	Co-Primary Endpoints			
			CFB in MWT during RW	Overall	11.2 (7.8, 14.6)	<0.0001 (Yes)
			CFB in ESS during RW	Overall		
			Key Secondary Endpoint			
			Percentage Subjects Reported as Worse on PGIc during RW	Overall	-30.0% (-46.0%, -14.0%)	0.0005 (Yes)
OSA and Narcolepsy	14-005	North America and Europe / 5/26/2015-4/21/2017 (Interim cut-off)	Primary Endpoint			
			CFB in ESS during RW	Overall	-3.7 (-4.8, 2.7)	<0.0001 (Yes)
				OSA	-3.7 (-5.1, 2.4)	<0.0001
				Narcolepsy	-3.8 (-5.5, 2.2)	<0.0001
			Key Secondary Endpoint			
			Percentage Subjects Reported as Worse on PGIc during RW	Overall	-36.2% (-47.4%, -25.2%)	<0.0001 (Yes)
				OSA	-31.3% (-44.6%, -18.1%)	<0.0001
				Narcolepsy	-49.2% (-68.8%, -29.6%)	<0.0001
			Percentage Subjects Reported as Worse on CGIc during RW	Overall	-35.2% (-46.1%, -24.2%)	<0.0001 (Yes)
				OSA	-35.4% (-48.2%, -22.5%)	<0.0001
				Narcolepsy	-34.2% (-55.3%5, -13.0%)	0.0029

Source: reviewer's summary based on sponsor's clinical study reports.

5.3 Conclusions and Recommendations

This reviewer concludes, based on statistical evidence found in the efficacy data of studies ADX-N05 202 (doses titration from 150 mg during the first 4 weeks to 300 mg during the last 8 weeks), 14-002 (fixed doses at 75 mg, 150 mg, and 300 mg), and 14-005 (flexible

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doses at 75 mg, 150 mg, and 300 mg) that JZP-110 doses of 150 mg and 300 mg showed statistically significant treatment effect compared to placebo in subjects with narcolepsy.

Based on statistical evidence found in the efficacy data of studies 14-003 (fixed doses at 37.5 mg, 75 mg, 150 mg, and 300 mg), 14-004 (flexible doses at 75 mg, 150 mg, and 300 mg), and 14-005 (flexible doses at 75 mg, 150 mg, and 300 mg) that JZP-110 doses of 37.5 mg, 75 mg, 150 mg, and 300 mg showed statistically significant treatment effect compared to placebo in subjects with OSA.

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

/s/

JINGLIN ZHONG
09/20/2018

PEILING YANG
09/21/2018

HSIEN MING J HUNG
09/21/2018

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA 211230/0001
Supplement Number:	NA
Drug Name:	Solriamfetol (JZP-110)
Indication(s):	Treatment of excessive sleepiness in adult patients with narcolepsy or obstructive sleep apnea; (b) (4)
Applicant:	Jazz Pharmaceuticals
Date(s):	Date of Document: 12/20/2017 Consult received date: 2/2/2018 Completion date: 7/20/2018
Review Priority:	P (45 days)
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Wei Liu, Ph.D., Mathematical Statistician, QT-CSS/DBVI/OB/OTS
Concurring Reviewers:	Qianyu Dang, Ph.D., Team Leader, DBVI/OB/OTS Yi Tsong, Ph.D., Division Director, DBVI/OB/OTS
Medical Division:	Controlled Substance Staff
The CSS Team:	Shalini Bansil, MD., OD/CSS Martin Rusinowitz, MD., OD/CSS
Project Manager:	Sandra Saltz, OD/CSS
Keywords: NDA review, clinical studies, Crossover design; Clinical abuse potential study; Self-reported endpoint; Multiple endpoints, stimulant	

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EXECUTIVE SUMMARY

Data of NDA 211230 were submitted by Jazz Pharmaceuticals Ireland Limited (the sponsor) for requesting FDA approval of solriamfetol (JZP-110) (referencing IND 107203 -for narcolepsy, and IND 122590 -for OSA) for improve wakefulness and reduce excessive sleepiness in adult patients with narcolepsy and improve wakefulness and reduce excessive sleepiness in adult patients with obstructive sleep apnea.

This was a single-center, randomized, double-blind, placebo-controlled crossover study comparing the abuse potential of JZP-110 to placebo and phentermine (a C-IV stimulant positive control) in healthy, recreational polydrug abusers with recent histories of stimulant use.

Confirmation of abuse-potential:

There was a total of 43 subjects randomized to the Treatment phase after a Qualification phase. The numbers of completers who completed all treatment sessions and had no major protocol deviations were 37 (86%). This analysis results by this reviewer are summarized in Table I, supporting the sponsor's conclusion that JZP-110 has abuse potential that is like or lower than the C-IV stimulant phentermine.

Table I. Summary of the Analysis of Primary Endpoint on Completers population (N=37)

		difference (90% CI)								
		Mixed-effects[2], mean			Paired t-test, mean			Sign test, median		
param	Label[1]	diff	LB	UB	diff	LB	UB	diff	LB	UB
Drug liking	C vs P	20.7	16.3	25.2	22.2	17.6	26.7	23	18	27
	Ch vs P	31.7	27.2	36.2	33.6	30.1	37.1	35	30	39
	C vs T	8.5	4.1	13.0	9.6	4.0	15.2	4	1	11
	C vs Tm	4.2	-0.2	8.7	3.9	-0.3	8.2	0	-3	6
	C vs Th	-4.2	-8.7	0.2	-4.7	-9.9	0.5	-5	-11	0
	Ch vs T	19.5	15.0	23.9	21.1	16.0	26.1	18	11	27
	Ch vs Tm	15.2	10.8	19.6	15.4	11.5	19.3	13	10	18
	Ch vs Th	6.8	2.3	11.2	6.8	2.4	11.1	0	0	7
	T vs P	12.2	7.8	16.6	12.6	7.7	17.4	4	0	15
	Tm vs P	16.5	12.1	20.9	18.2	14.3	22.1	16	10	21
	Th vs P	25.0	20.5	29.4	26.9	22.1	31.7	28	23	34

[1] C: PTN 45 mg; Ch: PTN 90 mg; P: placebo; T: JZP-110 300 mg; Tm: JZP-110 600 mg ;Th: JZP-110 1200 mg

[2] The mixed-effects model included treatment, sequence, period, and first-order carryover effect as fixed effects, and subject nested within treatment sequence as a random effect. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. LB and UB are the lower and upper limits of the 90% confidence interval, respectively.

Statistical considerations that may limit the effect:

- The sponsor did not follow the recommendations in the FDA 2017 guidance of HAP studies for carrying out hypothesis tests that the margins of hypothesis tests should be pre-defined.

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- Six of the 43 subjects (14.0%) discontinued the study: 4 (9.3%) withdrew due to personal reasons and 2 (4.7%) discontinued due to adverse events.

Recommendations:

Recommendations for the proposed label are included in the subsection 2.2.3.2.3.

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INTRODUCTION

1.1 Overview

1.1.1 Background Information

On 2/2/2018 CSS sent a consults review request for statistical review for the resubmitted data of NDA 211230 for solriamfetol (JZP-110) (referenced IND 122590) by Jazz Pharmaceuticals Ireland Limited for improve wakefulness and reduce excessive sleepiness in adult patients with narcolepsy (Original 1) and improve wakefulness and reduce excessive sleepiness in adult patients with obstructive sleep apnea (OSA) (Original 2). Solriamfetol was developed under IND 107203 (for narcolepsy) and IND 122590 (for OSA). The test drug solriamfetol studied in the NDA submission is considered NME.

There are two human abuse potential (HAP) studies were conducted with JZP-110 as summarized in Table 1.

Table 2.1: Summary of Trials for Statistical Review

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
(b) (4) SAB-101	SC, R, DB, CO, AC, PC trial (2 weeks)	Test Drug/ 18 Active contol/ Placebo/ 18	**Primary**: DRQS Liking and ARCI MBG scale score **Key Secondary**: AUC_{0-6h}	Study validation failed
14-001	SC, R, DB, CO, AC, PC trial (3 weeks)	Drug A/ 43 Active contol/43 Control/ 43	**Primary**: drug liking **Key Secondary**: overall drug liking, take drug again	JZP-110 has abuse potential that is similar to the positive control

* SC: single-center, R: randomized, DB: double-blind, CO: crossover design, PC: placebo controlled, AC: active controlled

The Study (b) (4) SAB-101 was entitled "A 2-Week, Double-Blind, Randomized, Placebo-Controlled, Crossover Study of Single Doses of (b) (4) and Methylphenidate in Adults With Polysubstance Abuse". The sponsor concluded that (\\Cdsesub1\evsprod\NDA211230\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\major-depr\5351-stud-rep-contr\sab-101)

> "No statistically significant separation of the active control, MPH, from placebo was seen in the primary variables of this study. Therefore, since assay sensitivity for the study cohort was not demonstrated, the study is invalid."

After discussion with the CSS medical reviewer, it is decided that this reviewer will not review this study.

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The Study 14-001 was entitled "A Randomized Double-Blind, Placebo-Controlled, Crossover, Human Abuse Liability Study of JZP-110 in Recreational Polydrug Users with Recent Histories of Stimulant Use" (\\Cdsesub1\evsprod\NDA211230\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\narcolepsy\5351-stud-rep-contr\14-001) and is reviewed statistically by this reviewer.

1.2 Data Sources

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

Application:	NDA 211-230
Company	Jazz Pharmaceuticals
Drug	Solriamfetol (JZP-110)
CDER EDR link	\\Cdsesub1\evsprod\NDA211230\0001\m5\datasets\14-001\analysis\adam\datasets \\Cdsesub1\evsprod\NDA211230\0001\m5\datasets\sab-101\analysis\adam\datasets
Letter date	December 20, 2017

2 STATISTICAL EVALUATION of Study 14-001

2.1 Data and Analysis Quality

In general, the data in its current format and analysis quality are acceptable.

2.2 Human Abuse Potential Study

2.2.1 Overview

2.2.1.1 Objectives of the Study

Primary Objective

To evaluate the abuse potential of JZP-110 compared to phentermine and placebo in 30 recreational polydrug users with recent histories of stimulant use.

Secondary Objective

- To evaluate the safety and subjective effect profile of JZP-110 compared to phentermine and placebo in 30 recreational polydrug users with recent histories of stimulant use.

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2.2.1.2 Study Design

This was a single-center, randomized, double-blind, placebo-controlled crossover study comparing the abuse potential of JZP-110 to placebo and phentermine (a C-IV stimulant positive control) in healthy, recreational polydrug abusers with recent histories of stimulant use. This study involved three phases: a Screening Phase, a Qualification Phase, and a Test Phase.

Qualification Phase

Subjects who met screening criteria and were admitted to the Qualification Phase were randomized in a 1:1 ratio to receive a sequence of placebo on Day 1 and 60 mg phentermine on Day 4 or a sequence of 60 mg phentermine on Day 1 and placebo on Day 4 under double-blind conditions.

Only subjects who tolerated phentermine and who reported greater liking for phentermine versus placebo (peak liking at least 15 points higher on a bipolar liking-disliking visual analog scale [VAS]), time-dependent effects, and neutral liking for placebo (within 40 to 60 points on a bipolar liking-disliking VAS) were eligible for the Test Phase of the study.

Treatment Phase

Subjects who met eligibility criteria at the end of the Qualification Phase were randomized to one of six treatment sequences in the Test Phase that included the following (provided as identical-looking capsules):

- JZP-110 at 300, 600, and 1200 mg
- Phentermine 45 and 90 mg
- Placebo

The doses of 300, 600, and 1200 mg of JZP-110 were selected for the abuse liability study where the maximum planned therapeutic dose of this drug is 300 mg. The 1200 mg dose is the highest dose of JZP-100 that has been studied in humans in previous single studies.

JZP-110 produces stimulant-like therapeutic effects and adverse events. Thus, phentermine is used as the positive control because it is a stimulant that is in C-IV of the Controlled Substances Act. The doses of 45 and 90 mg are typically used in HAP studies.

The washout period between different phases of the Test and Qualification Phases is about 72 hours. This washout period represents 3-4 times the half-life of phentermine (20 hours) and 9 times the half-life of JZP-110 (5-8 hours).

Subjects received the study drugs following a fasting period of at least 8 hours. Subjects were fasted for at least 2 hours post-dose.

Subjects returned for an end-of-study safety Follow-up visit 5 to 10 days following the last drug administration in the Treatment phase.

The sponsor's design diagram is shown in Figure 2.1.

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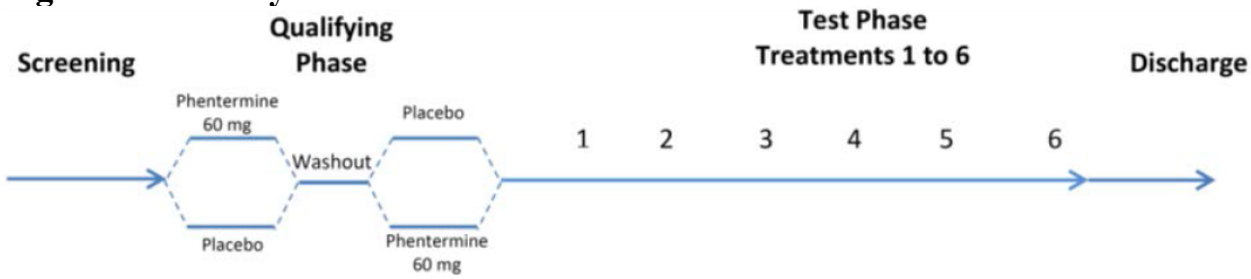
Figure 2.1 Study Schematic



2.2.1.3 Abuse Potential Measures

Primary PD endpoint:

Peak (Emax) ratings of Liking at the Moment across the first 12 hours of the drug effect on a bipolar VAS

Key secondary PD endpoints:

- Overall Drug Liking VAS (at 24 hours)
- Take Drug Again VAS (at 24 hours)

Other secondary endpoints:

- Peak (Emax) ratings across the first 12 hours of the drug effect for Bad Effects, Strength of drug effect, High, and Good Effects (rated on VAS)
- Peak (Emax) ratings across the first 12 hours of the drug effect for subjective effects (as rated on VAS: Anxiety, Agitation/Relaxation, Detached, Alertness/Drowsiness, Colors Brighter, Sounds Louder)
- Five scale scores (Amphetamine [A], Morphine-Benzedrine Group [MBG], Lysergic Acid Diethylamide [LSD], Benzedrine group [BG], and Pentobarbital Chlorpromazine Alcohol Group [PCAG]) of the 49-item Addiction Research Center Inventory at 2 and 6 hours
- Drug identification using drug-similarity VASs at 2 hours (momentary rating) and 24 hours (retrospective rating)
- Amount of money that subjects would pay to receive the drug again assessed the next day at 24 hours

2.2.1.4 Analysis Populations defined by the sponsor

- The intent-to-treat (ITT) population comprised all randomized subjects who received any amount of study drug.
- The Per Protocol (PP) population was a subset of subjects from the ITT population who completed all six treatments in the Test Phase and had no major protocol deviations that might impact the PD evaluations. This population was used for all pharmacodynamics analyses, which were based on the actual treatment received.

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Sample size estimate:

A power analysis based on the differences observed between placebo and 45 or 90 mg of phentermine on the primary endpoint of Liking at the moment (LS means [SD] of 19 [25.8] and 28 [22.58] for 45 and 90 mg, respectively) from a previous study (Schoedel et al. 2012) indicated that a sample size of 30 subjects would have >95% power to detect significant differences at the (two-tailed) 5% level. It was planned to enroll a minimum of 36 subjects in the Test Phase and to continue until at least 30 evaluable subjects, including approximately 20% female subjects, completed the study (all six treatments of the Test Phase).

2.2.1.5 Statistical Methodologies used in the Sponsor's Analyses

Hypothesis testing:

For each of the main effects, the null hypothesis was that there is no main effect, and the alternative hypothesis was that there is a main effect.

For each of the contrasts the null hypothesis was that there is no effect difference between the tested pair, and the alternative hypothesis was that there is an effect difference between the tested pair.

Statistical methodologies

Analysis of pharmacodynamic measures was performed using the PP population.

Analysis of primary and secondary endpoints (Emax, Emin, 2 hours, 6 hours, and 24 hours, as applicable) for all pharmacodynamics measures other than the Drug Similarity measure were done using a mixed effect Analysis of Covariance (ANCOVA) model when assumptions of normal distribution and/or homogeneity of the variance were met. The model included treatment, period and treatment sequence as fixed effects, and baseline (pre-dose) measurement as a covariate where applicable, and subject nested within sequence as a random effect. A first-order direct carryover effect from the treatment of previous period was included in the model if it was found significant at the 25% level; for the first treatment period, treatment 'F' (placebo) was used for all subjects and all pharmacodynamics endpoints.

For all endpoints, the assumption of normal distribution of the data required for the ANCOVA model was examined using the Shapiro-Wilk Normality test on the residuals from the mixed-effect model. Also, the homogeneity of variance between treatments was evaluated using the Levene test. If the normality assumption and/or the homogeneity assumption were not satisfied at a significance level of 0.05, a non-parametric method was used. In those cases, Friedman's method was used to test the overall treatment effect, and the Wilcoxon Signed Rank test was used to compare the pairwise treatment differences.

The assay sensitivity hypothesis was conducted by comparing the positive control phentermine (45 mg and 90 mg) with placebo for each pharmacodynamic endpoint.

For all primary and secondary endpoints, hypotheses related to the relative abuse potential of JZP-110 were tested by conducting three planned comparisons between JZP-110 doses (300 mg, 600 mg, 1200 mg) and phentermine 90 mg. Hypotheses related to the absolute abuse potential of JZP-110 were tested by conducting three contrasts between JZP-110 doses (300 mg, 600 mg, and 1200 mg) and placebo.

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For each pharmacodynamic endpoint, planned comparisons were conducted and multiplicity adjustments were not used. All comparisons were two tailed at the 5% level of significance.

Handling of Dropouts or Missing Data

Imputation was not performed for missing data.

Multiple Comparisons/Multiplicity

No Type I error adjustment due to multiple comparisons was performed.

2.2.1.6 Changes in the Conduct of the Study

The protocol, dated July 9, 2014, was amended 3 times.

Changes in the Planned Analyses

For analysis of the primary endpoint, the protocol specified that peak (Emax) ratings of Liking at the Moment across 12 hours change from baseline would be analyzed using a linear mixed-effects model including treatment, treatment sequence, and treatment period as fixed effects, with subject-within- sequence as a random effect.

2.2.2 Sponsor's Summary and Conclusions

Forty-three subjects were randomized into the test phase and all received study drug in that phase. Thirty-seven of the 43 subjects (86.0%) completed the study. Six of the 43 subjects (14.0%) discontinued the study: 4 (9.3%) withdrew due to personal reasons and 2 (4.7%) discontinued due to adverse events. Disposition is shown in Figure 2.

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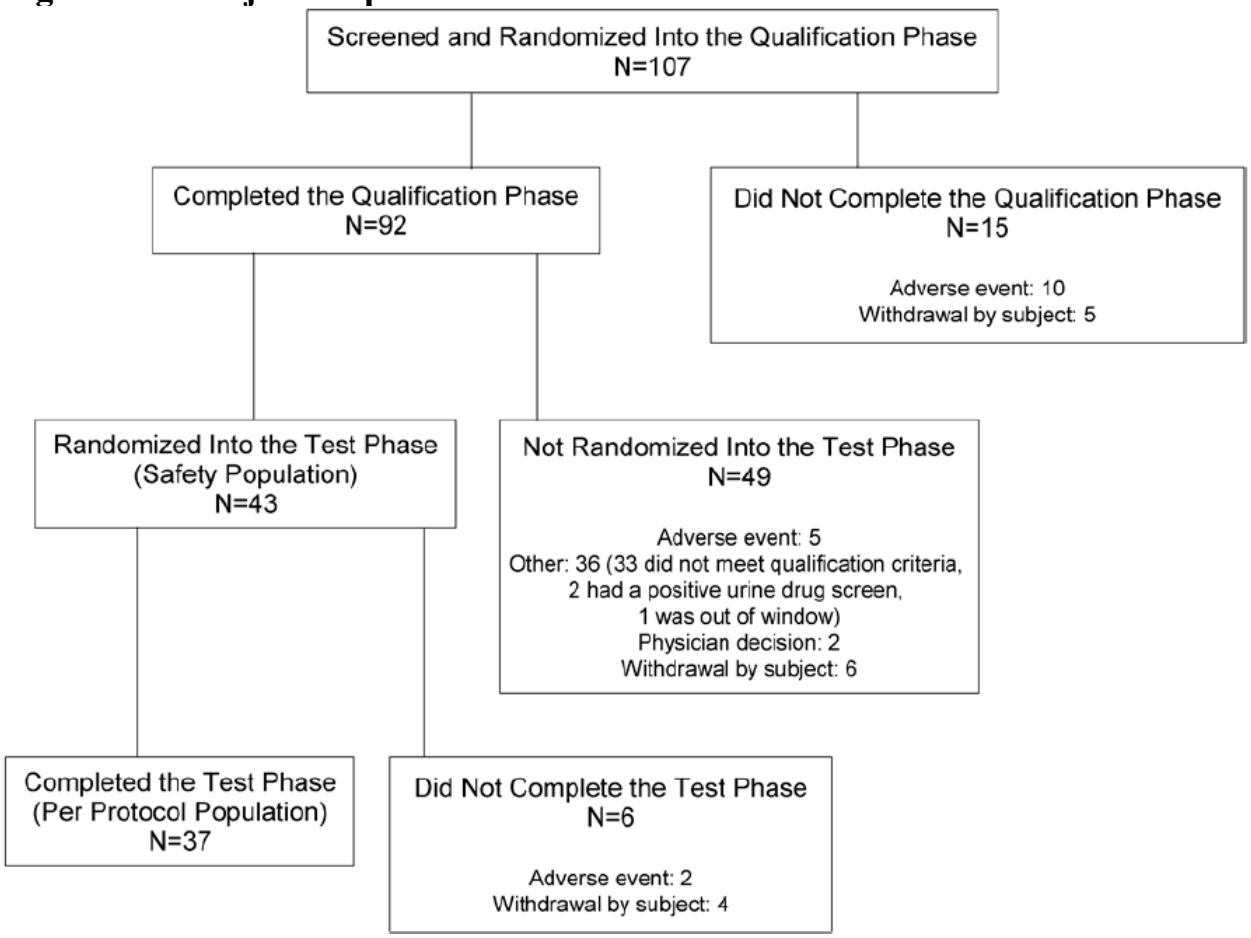
Figure 2.2 Subject Disposition



Sponsor's main results are summarized in Table 2.1. Others are attached in Appendix 1.

This was a valid abuse liability study: both doses of phentermine produced statistically higher ratings than placebo on the primary endpoint, peak (Emax) Liking at the Moment.

Primary analysis

During the qualification phase, in the PP population (N=37) the mean Emax on the Liking at the Moment VAS was 85.6 (SD=10.79) for phentermine 60 mg and 50.2 (SD=1.01) for placebo.

JZP-110 had statistically significantly higher ratings of peak Drug Liking at the Moment than placebo, indicating that JZP-110 might have potential for abuse; however, peak Liking at the Moment for all doses of JZP-110 was statistically lower than peak Liking at the Moment for the high dose of phentermine, suggesting that JZP-110 has lower abuse potential than phentermine. In addition, the time to peak Liking at the Moment (TEmax) was approximately 20 minutes later for JZP-110 1200 mg than for phentermine 90 mg, which is also suggestive of lower abuse potential of JZP-110 relative to phentermine.

Table 2.2: Drug Liking at the Moment VAS Emax Across 12 Hours: Pairwise Comparisons, PP Population (N=37)

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Pairwise Comparison	Median of Intra-Subject Difference	Inter-Quartile Range for Difference	P-value[a]
Overall Treatment Effect	NA	NA	<0.001
PTN 45 mg - Placebo	23.0	7.0, 34.0	<0.001
PTN 90 mg - Placebo	35.0	25.0, 48.0	<0.001
JZP-110 300 mg - PTN 45 mg	-4.0	-24.0, 1.0	0.005
JZP-110 600 mg - PTN 45 mg	0.0	-16.0, 4.0	0.276
JZP-110 1200 mg - PTN 45 mg	5.0	0.0, 12.0	0.067
JZP-110 300 mg - PTN 90 mg	-18.0	-33.0, -7.0	<0.001
JZP-110 600 mg - PTN 90 mg	-13.0	-23.0, -7.0	<0.001
JZP-110 1200 mg - PTN 90 mg	0.0	-14.0, 3.0	0.031
JZP-110 300 mg - Placebo	4.0	0.0, 28.0	<0.001
JZP-110 600 mg - Placebo	16.0	7.0, 28.0	<0.001
JZP-110 1200 mg - Placebo	28.0	17.0, 40.0	<0.001

VAS allowed ratings from 0 (strong disliking) to 100 (strong liking).

[a] Overall treatment effect was assessed using the Friedman test. Pairwise treatment comparisons were assessed using the Wilcoxon Sign-Rank test on the within-subject differences.

E_{max}=maximum effect score; NA=not applicable; PP=per protocol; PTN = phentermine; VAS=visual analog scale

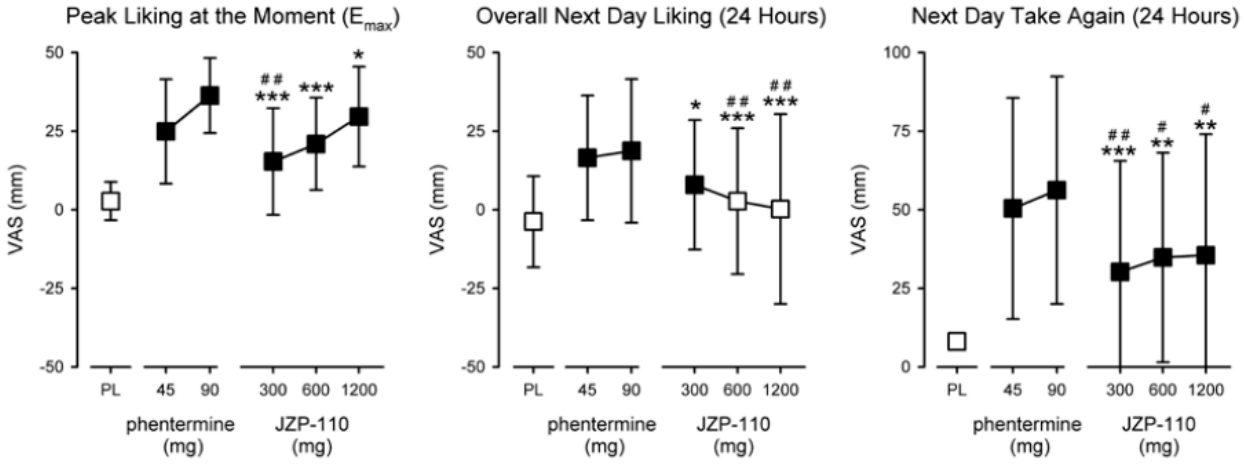
Source: sponsor's report study-14-001.pdf Tables 9

Key secondary endpoints (based on next day ratings)

- The 300 mg dose of JZP-110 was the only dose of JZP-110 that was rated as being liked more than placebo on the day after dosing. Next day Overall Drug Liking was not statistically different for the two highest doses of JZP-110 and placebo, suggesting that in contrast to Liking at the Moment, the overall drug liking for supratherapeutic doses of JZP-110 is no greater than placebo. Post hoc analyses showed that more than half of the subjects did not express any liking for JZP-110 1200 mg at 24 hours. In addition, next day Overall Drug Liking for the two highest doses of JZP-110 was significantly less than that for both doses of phentermine and all doses of JZP-110 had significantly lower next day Overall Drug Liking compared to the high dose of phentermine, suggesting that the abuse potential of JZP-110 is less than that of phentermine.

- All doses of JZP-110 had higher next day ratings of Take Drug Again relative to placebo; however, all doses of JZP-110 had significantly lower ratings of Take Drug Again at 24 hours after dosing compared to both doses of phentermine, suggesting that the abuse potential of JZP-110 is less than that of phentermine.

Figure 2.3. Primary and Key Secondary Pharmacodynamics Endpoints: Difference From Placebo of JZP-110 and Phentermine VAS Ratings, PP Population (N=37)

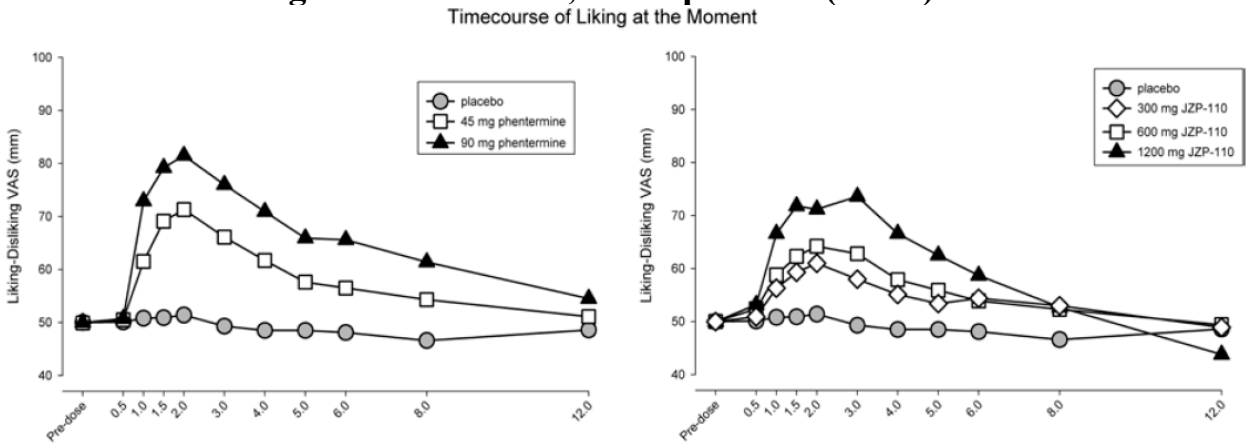


Source: sponsor's study-14-001.pdf Figure 4.

Filled squares indicate a statistically significant difference between the active condition (JZP-110 or phentermine) and placebo. Open squares indicate that the difference from placebo was not statistically significant. The asterisks (*) indicate a statistically significant difference from phentermine 90 mg and the pound signs (#) indicate a statically significant difference from phentermine 45 mg. The number of symbols corresponds to significance levels of $p<0.05$, $p<0.01$, and $p<0.001$, for one, two, and three symbols, respectively. For all measures, means ±1 SD are plotted. For Peak Liking at the Moment and next day Overall Drug Liking, the statistical significance of the pairwise comparisons was determined by the Wilcoxon Sign- Rank test. For next day Take Drug Again, the statistical significance of pairwise comparisons was tested in a mixed model ANCOVA. Note that Liking at the Moment and Overall Next Day Liking were rated on a bipolar VAS of 0-100, with neutral=50 and ratings below 50 indicating disliking. For this figure, that neutral point is shown as 0 for ease of comparison with Next Day Take Again, for which a 0 on the unipolar VAS indicated that the subject would not take the drug again.

Reference ID: 4294512

Figure 2.4. Time Course of Liking at the Moment and Strength of Drug Effect VAS: Mean Ratings Over 12 Hours, PP Population (N=37)



Source: sponsor's study-14-001.pdf Figure 5.

Sponsor's conclusion:

> This human abuse liability study conducted in recreational polydrug users with a recent history of stimulant use is a valid study in which both doses of the positive control phentermine separated from placebo on the primary endpoint of Drug Liking at the Moment. Ratings on all primary (Drug Liking at the Moment) and key secondary endpoints (Take drug Again at 24 Hours and Overall Drug Liking at 24 Hours) for the high dose of JZP-110 (1200 mg) were statistically lower than those for the high dose of phentermine (90 mg). The results from these primary and key secondary endpoints, as well as the consistency of those results with the other secondary measures of abuse liability, support the conclusion that JZP-110 has abuse potential that is similar to or lower than the C-IV stimulant phentermine.

2.2.3 Reviewer's Assessment

2.2.3.1 Descriptive Analysis

This reviewer checked the mean changes over time for drug liking VAS and high VAS as seen in Figure 2.5 and Figure 2.6, respectively.

Reference ID: 4294512

Figure 2.5 Time Course of Mean Drug Liking VAS Scores Over Post-dosing Hour (Completers, N = 37)

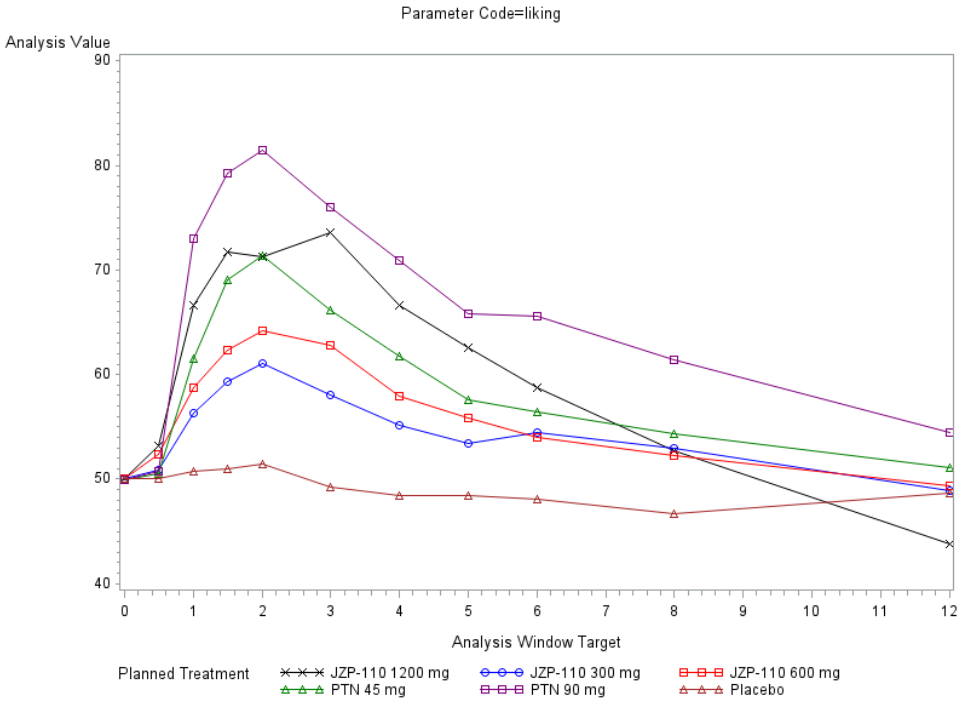
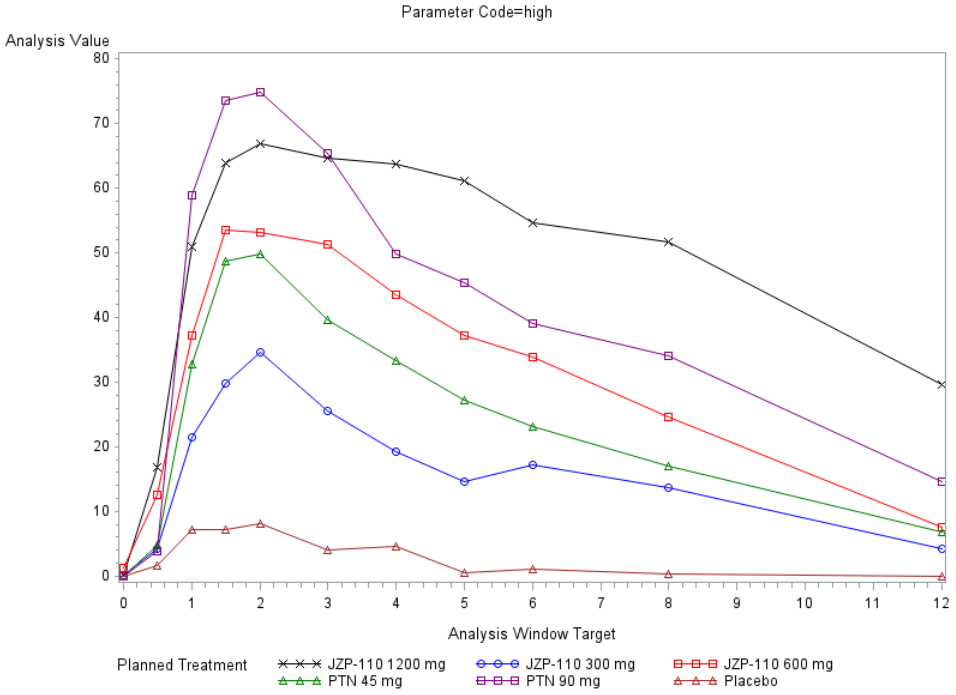


Figure 2.6 Time Course of Mean High VAS Scores Over Post-dosing Hour (Completers, N =37)



Reference ID: 4294512

Both plots showed that the Emax of JZP-110 1200 mg was located between the response curves of the two active controls (45 mg and 90 mg) and the response to JZP-110 300 mg was lower than the active control at both doses. Also, there appears no obvious difference in the TEmax between JZP-110 and PTN in those doses.

This reviewer verified the sponsor's statistical tests on the primary and key secondary endpoints as shown in Table 2.3.

The results of hypothesis tests at level of alpha=0.05 (one-side) show that

1. Validation test: The differences between the positive control at either dose (45 mg and 90 mg) and placebo are statistically significant in the primary and key secondary PD endpoints. For the primary outcome of drug liking Emax, the confidence interval lower bounds of the mean difference between the positive control PNT at either dose and placebo were greater than 15. Thus it validates the sensitivity and integrity of the study.
2. For all primary and key secondary PD endpoints, the mean difference between the positive control PTN and JZP-110 at any testing dose pair is either equal to or greater than 0, suggesting JZP-110 has similar or lower abuse potential comparing to the active control drug PNT.
3. For the primary outcome of drug liking Emax, the mean differences between JZP-110 and placebo are statistically significantly greater than 7, suggesting JZP-110 has abuse potential higher than placebo.

Reference ID: 4294512

Table 2.3: Summary of Analysis Results on the Primary and Key Secondary Endpoints (Completers populations, n=37)

		difference (90% CI)								
		Mixed-effects[2], mean			Paired t-test, mean			Sign test, median		
param	Label[1]	diff	LB	UB	diff	LB	UB	diff	LB	UB
Drug liking	C vs P	20.7	16.3	25.2	22.2	17.6	26.7	23	18	27
	Ch vs P	31.7	27.2	36.2	33.6	30.1	37.1	35	30	39
	C vs T	8.5	4.1	13.0	9.6	4.0	15.2	4	1	11
	C vs Tm	4.2	-0.2	8.7	3.9	-0.3	8.2	0	-3	6
	C vs Th	-4.2	-8.7	0.2	-4.7	-9.9	0.5	-5	-11	0
	Ch vs T	19.5	15.0	23.9	21.1	16.0	26.1	18	11	27
	Ch vs Tm	15.2	10.8	19.6	15.4	11.5	19.3	13	10	18
	Ch vs Th	6.8	2.3	11.2	6.8	2.4	11.1	0	0	7
	T vs P	12.2	7.8	16.6	12.6	7.7	17.4	4	0	15
	Tm vs P	16.5	12.1	20.9	18.2	14.3	22.1	16	10	21
	Th vs P	25.0	20.5	29.4	26.9	22.1	31.7	28	23	34
High	C vs P	41.7	32.0	51.4	45.2	34.4	55.9	49	31	63
	Ch vs P	66.2	56.4	75.9	70.1	62.5	77.6	77	69	85
	C vs T	14.4	4.7	24.2	16.4	3.6	29.3	12	1	23
	C vs Tm	-6.2	-15.9	3.5	-5.8	-14.4	2.8	-3	-6	2
	C vs Th	-18.1	-27.8	-8.3	-17.0	-27.5	-6.4	-11	-16	-3
	Ch vs T	38.9	29.2	48.6	41.3	30.9	51.8	33	22	47
	Ch vs Tm	18.3	8.6	28.0	19.1	12.3	25.9	15	5	23
	Ch vs Th	6.4	-3.2	16.1	7.9	-1.2	17.0	0	-5	0
	T vs P	27.3	17.6	36.9	28.8	18.1	39.4	21	2	47
	Tm vs P	47.9	38.2	57.6	51.0	42.1	59.9	58	41	69
	Th vs P	59.8	50.0	69.5	62.2	50.6	73.7	75	63	89
Overall drug liking	C vs P	19.0	10.8	27.1	20.2	12.1	28.4	12	4	20
	Ch vs P	20.9	12.7	29.1	22.5	13.6	31.4	20	12	28
	C vs T	8.6	0.4	16.7	8.6	2.3	14.9	1	0	8
	C vs Tm	14.8	6.7	23.0	13.8	5.9	21.8	5	0	18
	C vs Th	15.9	7.7	24.0	16.3	8.0	24.6	11	0	27
	Ch vs T	10.5	2.3	18.6	10.9	3.5	18.2	9	0	18
	Ch vs Tm	16.7	8.6	24.9	16.1	8.0	24.1	12	4	19
	Ch vs Th	17.8	9.7	25.9	18.5	10.8	26.2	18	13	23
	T vs P	10.4	2.4	18.5	11.6	3.4	19.8	0	0	6
	Tm vs P	4.2	-4.0	12.3	6.4	-1.6	14.5	5	0	9
	Th vs P	3.1	-5.0	11.3	3.9	-6.2	14.1	0	-2	19

Reference ID: 4294512

Table 2.3: Summary of Analysis Results on the Primary and Key Secondary Endpoints (Completers populations, n=37) -continued

		difference (90% CI)								
		Mixed-effects[2], mean			Paired t-test, mean			Sign test, median		
param	Label[1]	diff	LB	UB	diff	LB	UB	diff	LB	UB
Take drug again	C vs P	40.0	28.6	51.3	42.3	30.7	53.9	45	17	67
	Ch vs P	44.2	32.9	55.6	48.1	36.5	59.7	41	30	82
	C vs T	20.3	8.9	31.6	20.2	8.6	31.7	7	1	29
	C vs Tm	16.5	5.1	27.8	15.5	4.4	26.7	8	0	26
	C vs Th	15.0	3.6	26.3	14.9	2.2	27.6	3	0	35
	Ch vs T	24.5	13.2	35.8	26.0	14.7	37.3	17	9	32
	Ch vs Tm	20.7	9.4	32.0	21.3	10.1	32.5	9	0	24
	Ch vs Th	19.2	7.9	30.5	20.7	9.0	32.4	12	0	26
	T vs P	19.7	8.5	31.0	22.1	12.0	32.3	0	0	7
	Tm vs P	23.5	12.2	34.8	26.8	16.5	37.0	17	6	36
	Th vs P	25.0	13.7	36.4	27.4	15.9	38.9	15	2	48

[1] C: PTN 45 mg; Ch: PTN 90 mg; P: placebo; T: JZP-110 300 mg; Tm: JZP-110 600 mg ; Th: JZP-110 1200 mg

[2] The mixed-effects model included treatment, sequence, period, and first-order carryover effect as fixed effects, and subject nested within treatment sequence as a random effect. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. LB and UB are the lower and upper limits of the 90% confidence interval, respectively.

2.2.3.2 Conclusion

2.2.3.2.1 Statistical Issues

- The sponsor did not follow the recommendations in the FDA 2017 guidance of HAP studies for carrying out hypothesis tests that the margins of hypothesis test should be pre-defined.
- Six of the 43 subjects (14.0%) discontinued the study: 4 (9.3%) withdrew due to personal reasons and 2 (4.7%) discontinued due to adverse events.

2.2.3.2.2 Conclusions and Recommendations

The numbers of completers were 37 (86%) with a total of 43 subjects randomized to the treatment phase.

This analysis results by this reviewer support the sponsor's conclusion that JZP-110 has abuse potential that is similar to or lower than the C-IV stimulant phentermine.

2.2.3.2.3 Labeling Recommendations

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

NA.

Reference ID: 4294512

3 APPENDIX

3.1 Appendix 1

Appendix 1 Table 1

Table 5. Schedule of Events by Hour on Dosing Days

	Days Q1 and Q4 of the Qualification Phase and Dosing Days T2, T5, T8, T11, T14, and T17 of the Test Phase													
Time (hours post dose)	**-1**	**-0.5**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**24**
Vital signs		X		X	X	X	X	X	X	X	X	X	X	X
VASs[a]		X		X	X	X	X	X	X	X	X	X	X	X
ARCI							X				X			
Drug Similarity VASs							X							X
Subjective Drug Value														X
Dosing			X											
Light breakfast							X							
Lunch									X					
Allowed to smoke	X[b]										X	X	X	X[b]
Concomitant medications		→	→	→	→	→	→	→	→	→	→	→	→	→
Adverse events		→	→	→	→	→	→	→	→	→	→	→	→	→

[a] "At the moment" VAS ratings of drug effects included Drug Liking, Strength of Drug Effect, Good Effects, Bad Effects, High, Anxiety, Detached, Alertness/Drowsiness, Agitation/Relaxation, Colors Brighter, and Sounds Louder and will be completed at -0.5 through the 12-hour time point. VASs for rating Overall Drug Liking and Take Drug Again were only presented at the 24-hour (next day) time point.

[b] On dosing days, cigarette smokers were allowed to smoke 1 cigarette upon rising and then had to remain abstinent until the assessments scheduled for the 6-hour time point were completed. After completion of the 6-hour assessments, cigarette smokers were allowed to smoke ad libitum for the remainder of the day, but were not allowed to smoke within 30 minutes prior to the assessments scheduled for 8 and 12 hours after dosing.

Drug liking, mixed-this reviewer

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
trt	5	170	32.77	<.0001
sequence	5	31.6	1.60	0.1891
period	4	170	0.90	0.4643
CARRY	5	170	2.77	0.0198

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Reference ID: 4294512

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

/s/

WEI LIU
07/20/2018

QIANYU DANG
07/20/2018

YI TSONG
07/26/2018

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

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number:	NDA 211230
Drug Name:	Solriamfetol (JZP-110)
Indication(s):	To improve wakefulness and reduce excessive sleepiness in adult patients with narcolepsy or obstructive sleep apnea (OSA).
Studies	Two Year Oral Gavage Carcinogenicity Study in Rats and Mice.
Applicant:	Sponsor: Jazz Pharmaceuticals, Inc. 3180 Porter Drive, Palo Alto, California 94304 Test facility: (b) (4)
Documents Reviewed:	Electronic submission, dated: December 20, 2017 via SDN1 Electronic data submitted on February 1st, 2018 via SN0004.
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -VI
Statistical Reviewer:	Malick Mbodj, Ph.D.
Secondary Reviewer:	Hepei Chen
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Psychiatry Products (DPP)
Reviewing Pharmacologist:	Jia Yao, PhD
Project Manager:	Sarah H Seung, PharmD
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in regular mice. These studies were intended to assess the carcinogenic potential of Solriamfetol (JZP-110) in rats and mice when administered orally by gavage at appropriate drug levels for about 104 weeks in rats and in mice. Results of this review have been discussed with the reviewing pharmacologist Dr. Yao.

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

2. Rat Study

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups and one vehicle control group. Two hundred and eighty-six Sprague-Dawley rats of each sex were assigned to three treated groups and one vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 70 animals in the treated groups, and 76 animals in the vehicle control group, as indicated in Table 1. The dose levels for treated groups were 35, 80, and 200 mg/kg/day for both male and female rats. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The vehicle control group received the vehicle (deionized water), administered orally by gavage for about 104 weeks in the same manner as the treated groups. Due to early termination threshold of 20 survivor rats in the male and female vehicle control groups, early final scheduled necropsies were conducted (based on FDA recommendations) on Day 683 (Week 98) and on Day 706 (Week 101) for all surviving male and female rats, respectively.

Table 1: Experimental Design in Rat Study

Group Name	Group N0.	Dose Level (mg/kg/day)		Number of Animal	
		Male	Female	Males	Females
Vehicle Control	1	0	0	76	76
Low	2	35	35	70	70
Medium	3	80	80	70	70
High	4	200	200	70	70

Females in Group 2 were terminated On Day 687 (Week 99), beginning on Day 706 (Week 101), all remaining females (Groups 1, 3, and 4) were terminated

Dosing was terminated for all males in Group 4 on Day 681 (Week 98), all remaining male survivors within Groups (1, 2, 3, and 4) were terminated on Day 683 (Week 98)

During the administration period, all animals were checked for morbidity, mortality, injury, twice daily (a.m. and p.m.). The animals were removed from the cage, and detailed observations were conducted for each animal, prior to randomization, and weekly throughout the dosing phase. Detailed examinations for palpable masses were done weekly, the time of onset, location, size, appearance, and progression of each grossly visible or palpable mass, observed in carcinogenicity rats, was recorded weekly, particular attention being paid to the animals during and for the four hours after dosing. Any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively will be euthanized. Observations included, but were not limited to, evaluation of the skin, fur, eyes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs and feet, respiratory and circulatory effects, autonomic effects such as salivation, and nervous system effects including tremors, convulsions, reactivity to handling, and unusual behavior, and the palpation of masses. Histopathological examinations were performed on all animals found dead or killed moribund or sacrificed at the end of the

experiment. Body weights for all animals were measured and recorded at receipt, prior to randomization and once daily for the first 49 days (7 Weeks), weekly through Week 14, every two weeks until Week 28, and every four weeks thereafter.

2.1. Sponsor's analyses

2.1.1. Survival analysis

The Kaplan-Meier's curves were presented graphically for male and female rats separately. An overall test for survival was used to compare the homogeneity of survival rates across the groups using a log-rank test at the 0.05 significance level. If the survival rates were significantly different ($p < 0.05$), then a follow up analysis was done where each treatment group was compared to the vehicle control group using a log-rank test.

Any animal with accidental injury that causes its death or its unscheduled sacrifice was censored in the estimation. In addition, all animals still alive at the end of the experimental period were censored at the following day. Results of all pair-wise comparisons are reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests.

Sponsor's findings:

Sponsor's analysis showed the numbers of rats surviving to their terminal necropsy were 20, 26, 20, and 19 in the vehicle control group, low, medium, and high dose groups, in male rats, respectively, and 20, 15, 17, and 26, in female rats, respectively. The sponsor's report concluded that, there was no statistically significant increase in mortality across the vehicle control group and the three treated groups in either sex of rats. The pairwise comparisons showed no statistically significant increase or decrease in mortality between each of the treated groups, and the vehicle control group in either sex of rats.

2.1.2. Tumor data analysis

Tumor incidence data were analyzed within each sex, using both survival adjusted and unadjusted tests. The unadjusted tests will be based on the incidence and number of sites examined for each tumor type. The Cochran-Armitage trend test will be calculated and Fisher's exact test will be used to compare each treatment group with the vehicle control group. The survival adjusted test will be conducted according to the prevalence/mortality methods described by Peto et al. The incidence of each tumor type was analyzed with a one-sided trend test using the positive dose response relationship in tumor occurrence across vehicle control and treated groups. In addition, one-sided pairwise comparisons of vehicle control and treated groups were conducted. The analysis of tumors was based on the following fixed time intervals: Weeks 1-13, 14-26, 27-39, 40-52, 53-65, 66-78, 79-91, 92-98, and terminal sacrifice for male rats and Weeks 1-13, 14-26, 27-39, 40-52, 53-65, 66-78, 79-91,92-101, and terminal sacrifice for female rats. The actual dose levels were used as the scores. All animals that died or were sacrificed after the first animal of that sex was terminally sacrificed were included in the scheduled terminal sacrifice interval for the incidental finding analyses. All tumors in the scheduled terminal sacrifice interval were considered incidental for statistical analysis.

Adjustment for the multiplicity:

For multiplicity adjustment, the sponsor used significance levels of 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05

for common and rare tumors, respectively in pairwise comparisons. Site-specific background historical control database was used to determine whether the tumors should be designated as rare or common.

Sponsor's findings:

Following the multiple testing adjustment method described above, the sponsor's analysis showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased Solriamfetol dose. The pairwise comparisons also showed no tumor types with a statistically significant increase in tumor incidences in Solriamfetol treated groups, when compared to the vehicle control group in either male or female rats.

2.2 Reviewer's analyses

To verify sponsor's analysis and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed the survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically on January 30, 2017 via SN0004.

2.2.1 Survival analysis

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

Reviewer's findings:

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 20, 26, 20, and 19 in the vehicle control group, low, medium, and high dose groups, in male rats, respectively, and 20, 15, 17, and 26, in female rats, respectively. This reviewer's analysis showed no statistically significant increase in mortality across the vehicle control group and the three treated groups in either sex of rats. The pairwise comparisons showed no statistically significant increase or decrease in mortality between each of the treated groups and the vehicle control group in either sex of rats.

2.2.2. Tumor data analysis

In the reviewer's analysis, the tumor data were analyzed for dose response relationship across vehicle control group and the treated groups, as well as the pairwise comparisons of vehicle control group with each of the treated groups using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method, an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice with development of the tumor type being tested gets a score of s_h =1. An animal that dies at Week w_h without development of the given tumor type before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}} \right)^k$ <1. The adjusted group size is defined as Σs_h . As an interpretation, an animal with

score s_h =1 can be considered as a whole animal, while an animal with score s_h <1 can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal develops the given tumor being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise comparison) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104-week standard rat and mouse studies, a value of k=3 is suggested in the literature [Gebregziabher and Hoel (2009), Moon et al. (2003), Portier, et al. (1986)]. Hence, this reviewer used k=3 for the analysis of the data. Based on the intent to treat (ITT) principle Wmax was considered as 105 for both male and female rats.

For the calculation of p-values, if there were less than 10 tumor bearing animals across all treatment groups for a given tumor type, the exact tests based on the discrete permutation distribution were used, with dose levels (0, 35, 80, and 200 for both male and female rats) as scores, and asymptotic tests were used for tumor types with higher incidences. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male rats and female rats, respectively.

Multiple testing adjustments:

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

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

Reviewer's findings:

Table 2: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons

Treated Groups and Vehicle Control Group in Rats

Sex	Organ Name	Tumor Name	0 mg/Kg Veh. Cont. (N=76) P - Trend	35 mg/kg Low (N=70) P - VC vs. L	80 mg/kg Med (N=70) P - VC vs. M	200 mg/kg High (N=70) P - VC vs. H
Male	Pancreas	Carcinoma, Islet Cell	0/76 (37) 0.6801	5/70 (40) 0.0333*	1/70 (38) 0.5067	1/70 (38) 0.5067
	Thyroid Gland	Adenoma, C-Cell	2/76 (38) 0.0395@	2/70 (39) 0.7023	2/70 (39) 0.7023	6/70 (40) 0.1486
Female	Mammary Gland	Fibroadenoma	27/76 (55) 0.9318	38/70 (52) 0.0093*	31/70 (50) 0.1287	21/70 (48) 0.7702
	Thyroid Gland	Adenoma/Carcinoma C-Cell	4/76 (45) 0.0499@	2/70 (38) 0.8554	7/70 (41) 0.2087	8/70 (44) 0.1655

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

NC = Not calculable

*: Statistically significant at 0 01 and 0 05 for common and rare tumors, respectively in pairwise comparisons

@: not statistically significant at 0 025 and 0 005 level in rare and common tumor, respectively, for tests of dose response relationship.

Following the multiple testing adjustment method described above, this reviewer's analyses showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased Solriamfetol dose in either sex of rats. The pairwise comparisons showed statistically significant increases in the low dose groups for the incidences of carcinoma, islet cell in the pancreas when compared to the vehicle control group in male rats (p-values =0.0333) since this tumor type was considered as rare tumors. Also, the pairwise comparisons showed statistically significant increases in the low dose groups for the incidences of fibroadenoma in the mammary gland when compared to the vehicle control group in female rats (p-values =0.0093) whether this tumor type was considered as common or rare tumor.

3. Mouse Study

Two separate experiments were conducted, one in male mice and one in female mice. Two hundred fifty-six CD-1 mice of each sex were assigned randomly to one of the four groups which included three treated groups and one vehicle control group in equal size of 60 animals in the treated groups, and 76 animals in the vehicle control group, as indicated in Table 3. The dose levels for treated groups were 20, 65, and 200 mg/kg/day for both male and female mice. In this review, these dose groups would be referred to as the low, medium, and high dose group, respectively. The vehicle control group received the vehicle (deionized water), administered orally by gavage for up to 105 weeks (731 days) in the same manner as the treated groups.

Table 3: Experimental Design in Mouse Study

Group Name	Group N0.	Dose Level (mg/kg/day)		Number of Animal	
		Male	Female	Males	Females
Vehicle Control	1	0	0	76	76
Low	2	20	20	60	60
Medium	3	65	65	60	60
High	4	200	200	60	60

During the administration period, all animals were checked for morbidity, mortality, injury, twice daily (a.m. and p.m.), Beginning on Week 53, a third mortality check in the evening was conducted. The animals were removed from the cage, and detailed observations were conducted for each animal prior to randomization, and weekly throughout the dosing phase. Detailed examinations for palpable masses were done weekly, the time of onset, location, size, appearance, and progression of each grossly visible or palpable mass, observed in carcinogenicity mice, was recorded weekly, particular attention being paid to the animals during and for the four hours after dosing. The observations included, but were not limited to, evaluation of the skin, fur, eyes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs and feet, respiratory and circulatory effects, autonomic effects such as salivation, and nervous system effects including tremors, convulsions, reactivity to handling, and unusual behavior, and the palpation of masses. Any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively will be euthanized. Histopathological examinations were performed on all animals found dead, killed moribund, or sacrificed at the end of the experiment. Body weights for all animals were measured and recorded within three days of receipt, prior to randomization, Day -1, once daily for the first 56 days (8 Weeks), weekly through Week 14, every two weeks until Week 28, and every four weeks thereafter.

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:

Sponsor's analysis showed the numbers of mice surviving to their terminal necropsy were 41, 22, 20, and 24, in vehicle control, low, medium, and high dose groups in male mice, respectively, and 27, 25, 16, and 20, in female mice, respectively. The sponsor's report concluded that there were no statistically significant findings in survival rate in either sex of mice.

3.1.2 Tumor data analysis

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

The analysis of tumors was based on the following fixed time intervals: Weeks 1-13, 14-26, 27-39, 40-52, 53-65, 66-78, 79-91, 92-104, and terminal sacrifice for both male and female mice. The actual dose levels were used as the scores.

Multiple testing adjustment:

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

Sponsor's findings:

Sponsor's analyses showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased Solriamfetol dose. The pairwise comparisons also showed no tumor types with a statistically significant increase in tumor incidences in Solriamfetol treated groups, when compared to the vehicle control in either male or female mice.

3.2 Reviewer's analyses

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

3.2.1 Survival analysis

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

Reviewer's findings:

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy were 41, 22, 20, and 24, in vehicle control, low, medium, and high dose groups in male mice, respectively, and 27, 25, 16, and 20, in female mice, respectively. This reviewer's analysis showed no statistically significant increase in mortality across the vehicle control group and the three treated groups in either sex of mice. The pairwise comparisons in male mice showed a statistically significant increased mortality in medium dose group when compared to the vehicle control group with p-value = 0.0087. The pairwise comparisons in female mice showed no statistically significant increase or decrease in mortality between each of the treated groups and the vehicle control group.

3.2.2 Tumor data analysis

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

Multiple testing adjustment:

For mouse study, this reviewer used similar test levels of significance as those used for rat study to adjust for multiple testing. This reviewer used the number of animals bearing tumors in the vehicle control group to determine the common or rare tumor status.

Reviewer's findings:

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

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

(lymphoma, leukemia on a per organ basis excluded)

Sex	Organ Name	Tumor Name	0 mg/Kg Veh. Cont. (N=76) P - Trend	20 mg/kg Low (N=60) P - VC vs. L	65 mg/kg Med (N=60) P - VC vs. M	200 mg/kg High (N=60) P - VC vs. H
Male	Kidneys	Adenoma, Tubular Cell	0/76 (58) 0.0461@	0/60 (42) NC	1/60 (37) 0.3895	2/60 (42) 0.1739
	Stomach, Glandular	Adenoma	0/76 (58) 0.0461@	0/60 (42) NC	1/60 (37) 0.3895	2/60 (42) 0.1739

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

NC = Not calculable

@: not statistically significant at 0 025 and 0 05 level in rare tumor, respectively for tests of dose response relationship

Following the multiple testing adjustment method described above, this reviewer's analyses showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased Solriamfetol dose in either sex of mice. The pairwise comparisons also showed no tumor types with a statistically significant increase in tumor incidences in Solriamfetol treated groups, when compared to the vehicle control in either male or female mice.

4. Summary

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in regular mice. These studies were intended to assess the carcinogenic potential of Solriamfetol (JZP-110) in rats and mice when administered orally by gavage at appropriate drug levels for about 104 weeks.

Rat Study:

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups and one vehicle control group. Two hundred and eighty-six Sprague-Dawley rats of each sex were assigned to three treated groups and one vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 70 animals in the treated groups, and 76 animals in the vehicle control group, as indicated in Table 1. The dose levels for treated groups were 35, 80, and 200 mg/kg/day for both male and female rats. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The vehicle control group received the vehicle (deionized water), administered orally by gavage for about 104 weeks in the same manner as the treated groups. Due to early termination threshold of 20 survivor rats in the male and female vehicle control groups, early final scheduled necropsies were conducted (based on FDA recommendations) on Day 683 (Week 98) and on Day 706 (Week 101) for all surviving male and female rats, respectively.

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 20, 26, 20, and 19 in the vehicle control group, low, medium, and high dose groups, in male rats, respectively, and 20, 15, 17, and 26, in female rats, respectively. This reviewer's analysis showed no statistically significant increase in mortality across the vehicle control group and the three treated groups in either sex of rats. The pairwise comparisons showed no statistically significant increase or decrease in mortality between each of the treated groups and the vehicle control group in either sex of rats.

For tumor data, following the multiple testing adjustment method described above, this reviewer's analyses showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased Solriamfetol dose in either sex of rats. The pairwise comparisons showed statistically significant increases in the low dose groups for the incidences of carcinoma, islet cell in the pancreas when compared to the vehicle control group in male rats (p-values =0.0333) since this tumor type was considered as rare tumors. Also, the pairwise comparisons showed statistically significant increases in the low dose groups for the incidences of fibroadenoma in the mammary gland when compared to the vehicle control group in female rats (p-values =0.0093) whether this tumor type was considered as common or rare tumor.

No other significant dose response relationship or pairwise comparisons were noted in either sex.

Mouse Study:

Two separate experiments were conducted, one in male mice and one in female mice. Two hundred fifty-six CD-1 mice of each sex were assigned randomly to one of the four groups which included three treated groups and one vehicle control group in equal size of 60 animals in the treated groups, and 76 animals in the vehicle control group, as indicated in Table 3. The dose levels for treated groups were 20, 65, and 200 mg/kg/day for both male and female mice. In this review, these dose groups would be referred to as the low, medium, and high dose group, respectively. The vehicle control group received the vehicle (deionized water), administered orally by gavage for up to 105 weeks (731 days) in the same manner as the treated groups.

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy were 41, 22, 20, and 24, in vehicle control, low, medium, and high dose groups in male mice, respectively, and 27, 25, 16, and 20, in female mice, respectively. This reviewer's analysis showed no statistically significant increase in mortality across the vehicle control group and the three treated groups in either sex of mice. The pairwise comparisons in male mice showed a statistically significant increased mortality in medium dose groups when compared to the vehicle control group with p-value = 0.0087. The pairwise comparisons in female mice showed no statistically significant increase or decrease in mortality between each of the treated groups and the vehicle control group.

For tumor data, following the multiple testing adjustment method described above, this reviewer's analyses showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased Solriamfetol dose in either sex of mice. The pairwise comparisons also showed no tumor types with a statistically significant increase in tumor incidences in Solriamfetol treated groups, when compared to the vehicle control in either male or female mice.

Malick Mbodj, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D. Team Leader, DBVI
Hepei Chen, secondary reviewer

cc:
Archival NDA 211230- Solriamfetol (JZP-110)
Dr. Tsong Ms. Patrician
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5. Appendix

Table1A: Intercurrent Mortality Rate
Male Rats

	0 mg|kg|day		35 mg|kg|day		80 mg|kg|day		200 mg|kg|day	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
1 - 13	1	1.32	.	.	.	.	.	.
14 - 26	1	2.63	.	.	.	.	.	.
27 - 39	1	3.95	1	1.43	1	1.43	2	2.86
40 - 52	6	11.84	4	7.14	4	7.14	3	7.14
53 - 65	12	27.63	11	22.86	9	20.00	5	14.29
66 - 78	14	46.05	6	31.43	6	28.57	13	32.86
79 - 91	11	60.53	15	52.86	18	54.29	14	52.86
91 - 98	10	73.68	7	62.86	12	71.43	14	72.86
Ter. Sac.	20	26.32	26	37.14	20	28.57	19	27.14
Total	76	100.00	70	100.00	70	100.00	70	100.00

Earlier terminal necropsies, Ter. Sac. = Week 98

Table1B: Intercurrent Mortality Rate
Female Rats

	0 mg|kg|day		35 mg|kg|day		80 mg|kg|day		200 mg|kg|day	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
1 - 13	.	.	.	.	1	1.43	.	.
14 - 26	1	1.32	.	.	.	.	1	1.43
27 - 39	.	.	.	.	.	.	2	4.29
40 - 52	2	3.95	4	5.71	2	4.29	3	8.57
53 - 65	8	14.47	9	18.57	4	10.00	6	17.14
66 - 78	13	31.58	10	32.86	17	34.29	7	27.14
79 - 91	18	55.26	25	68.57	19	61.43	18	52.86
92 - 101	14	73.68	7	78.57	10	75.71	7	62.86
Ter. Sac.	20	26.32	15	21.43	17	24.29	26	37.14
Total	76	100.00	70	100.00	70	100.00	70	100.00

Earlier terminal necropsies, Ter. Sac. = Week 101

Table 2A: Intercurrent Mortality Comparison for
Male Rats

Test Statistics	P-value for Vehicle Cont. Low, Med, high	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs High
Dose-Response (Likelihood Ratio)	0.9217	0.1729	0.4859	0.5409
Homogeneity (Log-Rank)	0.5457	0.1688	0.4813	0.5354

Table 2B: Intercurrent Mortality Comparison for
Female Rats

Test Statistics	P-value for Vehicle Cont. Low, Med, high	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs High
Dose-Response (Likelihood Ratio)	0.1268	0.1998	0.6318	0.2884
Homogeneity (Log-Rank)	0.2025	0.1913	0.6264	0.2834

Table3A: Tumor Rates and P-Values for Dose Response Relationship and the Pairwise Comparisons

Male Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	35 mg Low (N=70) P - C vs. L	80 mg Med (N=70) P - C vs. M	200 mg High (N=70) P - C vs. H
Adrenal Glands	Adenoma, Cortical	2/76 (38) 0.3110	0/70 (38) 1.0000	1/70 (39) 0.8847	2/70 (39) 0.7023
	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Pheochromocytoma	10/76 (40) 0.6664	6/70 (41) 0.9272	13/70 (42) 0.3623	7/70 (40) 0.8629
	Sarcoma, Histiocytic	0/76 (37) 0.5033	0/70 (38) NC	2/70 (39) 0.2600	0/70 (38) NC
Bone Marrow, Femur	Fibrosarcoma, Pleomorphic	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Leukemia, Granulocytic	0/76 (37) 0.2517	0/70 (38) NC	0/70 (38) NC	1/70 (38) 0.5067
	Lymphoma	0/76 (37) 0.5033	0/70 (38) NC	1/70 (38) 0.5067	0/70 (38) NC
	Sarcoma, Histiocytic	1/76 (38) 0.1752	0/70 (38) 1.0000	2/70 (39) 0.5099	2/70 (39) 0.5099
Bone Marrow, Sternum	Fibrosarcoma, Pleomorphic	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Leukemia, Granulocytic	0/76 (37) 0.2517	0/70 (38) NC	0/70 (38) NC	1/70 (38) 0.5067
	Lymphoma	1/76 (38) 0.7517	0/70 (38) 1.0000	1/70 (38) 0.7533	0/70 (38) 1.0000
	Sarcoma, Histiocytic	1/76 (38) 0.1752	0/70 (38) 1.0000	2/70 (39) 0.5099	2/70 (39) 0.5099
Bone Marrow, Tibia	Fibrosarcoma, Pleomorphic	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
Bone, Femur	Leukemia, Granulocytic	0/76 (37) 0.2517	0/70 (38) NC	0/70 (38) NC	1/70 (38) 0.5067
	Sarcoma, Histiocytic	0/76 (37) 0.2034	0/70 (38) NC	2/70 (39) 0.2600	1/70 (38) 0.5067
Bone, Mandible	Odontoma	0/76 (37) 0.5066	0/70 (38) NC	1/70 (39) 0.5132	0/70 (38) NC
Bone, Sternum	Leukemia, Granulocytic	0/76 (37) 0.2517	0/70 (38) NC	0/70 (38) NC	1/70 (38) 0.5067
	Sarcoma, Histiocytic	0/76 (37) 0.2034	0/70 (38) NC	2/70 (39) 0.2600	1/70 (38) 0.5067

Male Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	35 mg Low (N=70) P - C vs. L	80 mg Med (N=70) P - C vs. M	200 mg High (N=70) P - C vs. H
Brain	Astrocytoma	2/76 (39) 0.5456	0/70 (38) 1.0000	2/70 (39) 0.6925	1/70 (38) 0.8751
	Ependymoma	0/76 (37) 0.2566	0/70 (38) NC	0/70 (38) NC	1/70 (39) 0.5132
	Fibrosarcoma, Pleomorphic	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Granular Cell Tumor	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Mixed Glioma	1/76 (38) 0.7517	0/70 (38) 1.0000	1/70 (38) 0.7533	0/70 (38) 1.0000
	Papilloma, Choroid Plexus	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
	Sarcoma, Histiocytic	0/76 (37) 0.1945	0/70 (38) NC	1/70 (39) 0.5132	1/70 (39) 0.5132
	Schwannoma	2/76 (39) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
Cavity, Thoracic	Lymphoma	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
Coagulating Glands	Sarcoma, Histiocytic	0/76 (37) 0.2566	0/70 (38) NC	0/70 (38) NC	1/70 (39) 0.5132
Diaphragm	Leiomyosarcoma	0/76 (37) 0.2517	0/70 (38) NC	0/70 (38) NC	1/70 (38) 0.5067
Ears	Schwannoma	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
Epididymides	Carcinoma, Tubular Cell	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Sarcoma, Histiocytic	0/76 (37) 0.2566	0/70 (38) NC	0/70 (38) NC	1/70 (39) 0.5132
Eyes	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Lymphoma	0/76 (37) 0.5033	0/70 (38) NC	1/70 (38) 0.5067	0/70 (38) NC
	Sarcoma, Histiocytic	1/76 (38) 0.1752	0/70 (38) 1.0000	2/70 (39) 0.5099	2/70 (39) 0.5099
Eyes, Optic Nerves	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Schwannoma	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000

Male Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	35 mg Low (N=70) P - C vs. L	80 mg Med (N=70) P - C vs. M	200 mg High (N=70) P - C vs. H
Galt	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Sarcoma, Histiocytic	0/76 (37) 0.2093	0/70 (38) NC	2/70 (39) 0.2600	1/70 (39) 0.5132
Harderian Glands	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Sarcoma, Histiocytic	0/76 (37) 0.0762	0/70 (38) NC	2/70 (39) 0.2600	2/70 (39) 0.2600
	Schwannoma	2/76 (39) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
Heart	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Lymphoma	0/76 (37) 0.5033	0/70 (38) NC	1/70 (38) 0.5067	0/70 (38) NC
	Neuroendocrine Tumor	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
	Sarcoma, Histiocytic	1/76 (38) 0.3791	0/70 (38) 1.0000	2/70 (39) 0.5099	1/70 (39) 0.7597
Joint, Tibiofemoral	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Leukemia, Granulocytic	0/76 (37) 0.2517	0/70 (38) NC	0/70 (38) NC	1/70 (38) 0.5067
	Sarcoma, Histiocytic	0/76 (37) 0.0762	0/70 (38) NC	2/70 (39) 0.2600	2/70 (39) 0.2600
Kidneys	Adenoma, Renal Tubule	0/76 (37) 0.2566	0/70 (38) NC	0/70 (38) NC	1/70 (39) 0.5132
	Adenoma, Renal Tubule, (Av) Type	0/76 (37) 0.5303	3/70 (41) 0.1401	2/70 (39) 0.2600	1/70 (39) 0.5132
	Carcinoma, Tubular Cell	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
	Adenoma/Carcinoma Tubular Cell	1/76 (38) 0.4461	0/70 (38) 1.0000	0/70 (38) 1.0000	1/70 (39) 0.7597
	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Lymphoma	0/76 (37) 0.5033	0/70 (38) NC	1/70 (38) 0.5067	0/70 (38) NC
	Sarcoma, Histiocytic	1/76 (38) 0.1752	0/70 (38) 1.0000	2/70 (39) 0.5099	2/70 (39) 0.5099
Lacrimal Glands, Exorbital	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Sarcoma, Histiocytic	1/76 (38) 0.1752	0/70 (38) 1.0000	2/70 (39) 0.5099	2/70 (39) 0.5099

Male Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	35 mg Low (N=70) P - C vs. L	80 mg Med (N=70) P - C vs. M	200 mg High (N=70) P - C vs. H
Large Intestine, Cecum	Sarcoma, Histiocytic	0/76 (37) 0.1945	0/70 (38) NC	1/70 (39) 0.5132	1/70 (39) 0.5132
Large Intestine, Colon	Sarcoma, Histiocytic	0/76 (37) 0.5066	0/70 (38) NC	1/70 (39) 0.5132	0/70 (38) NC
Larynx	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Sarcoma, Histiocytic	0/76 (37) 0.0650	0/70 (38) NC	1/70 (39) 0.5132	2/70 (39) 0.2600
Lip	Papilloma, Squamous Cell	0/76 (37) 0.5066	0/70 (38) NC	1/70 (39) 0.5132	0/70 (38) NC
Liver	Adenoma, Hepatocellular	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
	Carcinoma, Hepatocellular	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Adenoma/Carcinoma Hepatocellular	1/76 (38) 0.9395	1/70 (39) 0.7597	0/70 (38) 1.0000	0/70 (38) 1.0000
	Fibrosarcoma, Pleomorphic	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Lymphoma	1/76 (38) 0.7517	0/70 (38) 1.0000	1/70 (38) 0.7533	0/70 (38) 1.0000
	Pheochromocytoma	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Sarcoma, Histiocytic	2/76 (39) 0.3127	0/70 (38) 1.0000	3/70 (40) 0.5122	2/70 (39) 0.6925
Lung	Fibrosarcoma, Pleomorphic	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Lymphoma	1/76 (38) 0.7517	0/70 (38) 1.0000	1/70 (38) 0.7533	0/70 (38) 1.0000
	Sarcoma, Histiocytic	1/76 (38) 0.1944	0/70 (38) 1.0000	4/70 (40) 0.1957	2/70 (39) 0.5099
Lymph Node, Axillary	Sarcoma, Histiocytic	0/76 (37) 0.5033	0/70 (38) NC	1/70 (38) 0.5067	0/70 (38) NC
Lymph Node, Hepatic	Fibrosarcoma, Pleomorphic	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
Lymph Node, Inguinal	Lymphoma	0/76 (37) 0.5033	0/70 (38) NC	1/70 (38) 0.5067	0/70 (38) NC
Lymph Node, Mandibular	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC

Male Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	35 mg Low (N=70) P - C vs. L	80 mg Med (N=70) P - C vs. M	200 mg High (N=70) P - C vs. H
	Lymphoma	0/76 (37) 0.5033	0/70 (38) NC	1/70 (38) 0.5067	0/70 (38) NC
	Sarcoma, Histiocytic	1/76 (38) 0.1752	0/70 (38) 1.0000	2/70 (39) 0.5099	2/70 (39) 0.5099
Lymph Node, Mediastinal	Sarcoma, Histiocytic	0/76 (37) 0.5033	0/70 (38) NC	1/70 (38) 0.5067	0/70 (38) NC
Lymph Node, Mesenteric	Hemangiosarcoma	1/76 (38) 0.4387	0/70 (38) 1.0000	0/70 (38) 1.0000	1/70 (38) 0.7533
	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Lymphoma	0/76 (37) 0.5033	0/70 (38) NC	1/70 (38) 0.5067	0/70 (38) NC
	Sarcoma, Histiocytic	1/76 (38) 0.1752	0/70 (38) 1.0000	2/70 (39) 0.5099	2/70 (39) 0.5099
Mammary Gland	Fibroadenoma	0/76 (37) 0.3234	1/70 (39) 0.5132	2/70 (39) 0.2600	1/70 (38) 0.5067
	Sarcoma, Histiocytic	0/76 (37) 0.0650	0/70 (38) NC	1/70 (39) 0.5132	2/70 (39) 0.2600
Mediastinum	Sarcoma, Histiocytic	0/76 (37) 0.5033	0/70 (38) NC	1/70 (38) 0.5067	0/70 (38) NC
	Schwannoma	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
Mesentery/Peritoneum	Adenocarcinoma	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
	Adenocarcinoma, Ductal Cell	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Carcinoma, Tubular Cell	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
	Fibroma	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
	Fibrosarcoma, Pleomorphic	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Liposarcoma	0/76 (37) 0.5033	0/70 (38) NC	1/70 (38) 0.5067	0/70 (38) NC
	Lymphoma	0/76 (37) 0.5033	0/70 (38) NC	1/70 (38) 0.5067	0/70 (38) NC
Multicentric Neoplasm	Hemangiosarcoma	1/76 (38) 0.4387	0/70 (38) 1.0000	0/70 (38) 1.0000	1/70 (38) 0.7533
	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Leukemia, Granulocytic	0/76 (37) 0.2517	0/70 (38) NC	0/70 (38) NC	1/70 (38) 0.5067

Male Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	35 mg Low (N=70) P - C vs. L	80 mg Med (N=70) P - C vs. M	200 mg High (N=70) P - C vs. H
	Lymphoma	2/76 (39) 0.8894	0/70 (38) 1.0000	1/70 (38) 0.8751	0/70 (38) 1.0000
	Sarcoma, Histiocytic	2/76 (39) 0.4020	1/70 (39) 0.8799	4/70 (40) 0.3498	2/70 (39) 0.6925
Nerve, Sciatic	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Sarcoma, Histiocytic	1/76 (38) 0.6900	0/70 (38) 1.0000	2/70 (39) 0.5099	0/70 (38) 1.0000
Nerve, Trigeminal	Schwannoma	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
Nose, Level A	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Sarcoma, Histiocytic	1/76 (38) 0.1752	0/70 (38) 1.0000	2/70 (39) 0.5099	2/70 (39) 0.5099
Nose, Level B	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Sarcoma, Histiocytic	1/76 (38) 0.1752	0/70 (38) 1.0000	2/70 (39) 0.5099	2/70 (39) 0.5099
Nose, Level C	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Lymphoma	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
	Sarcoma, Histiocytic	1/76 (38) 0.1752	0/70 (38) 1.0000	2/70 (39) 0.5099	2/70 (39) 0.5099
Nose, Level D	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Leukemia, Granulocytic	0/76 (37) 0.2517	0/70 (38) NC	0/70 (38) NC	1/70 (38) 0.5067
	Sarcoma, Histiocytic	1/76 (38) 0.1752	0/70 (38) 1.0000	2/70 (39) 0.5099	2/70 (39) 0.5099
	Schwannoma	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
Pancreas	Adenocarcinoma, Ductal Cell	0/76 (37) 0.8162	2/70 (39) 0.2600	0/70 (38) NC	0/70 (38) NC
	Adenoma, Acinar Cell	0/76 (37) 0.4461	2/70 (40) 0.2666	0/70 (38) NC	1/70 (39) 0.5132
	Adenoma, Islet Cell	4/76 (39) 0.5441	2/70 (39) 0.8999	3/70 (39) 0.7845	3/70 (39) 0.7845
	Carcinoma, Acinar Cell	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Carcinoma, Islet Cell	0/76 (37) 0.6801	5/70 (40) 0.0333*	1/70 (38) 0.5067	1/70 (38) 0.5067

Male Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	35 mg Low (N=70) P - C vs. L	80 mg Med (N=70) P - C vs. M	200 mg High (N=70) P - C vs. H
	Adenoma/Carcinoma Acinar Cell	0/76 (37) 0.5432	3/70 (40) 0.1351	0/70 (38) NC	1/70 (39) 0.5132
	Adenoma/ Carcinoma Islet Cell	4/76 (39) 0.6532	7/70 (41) 0.2891	4/70 (39) 0.6443	4/70 (39) 0.6443
	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Lymphoma	0/76 (37) 0.5033	0/70 (38) NC	1/70 (38) 0.5067	0/70 (38) NC
	Sarcoma, Histiocytic	0/76 (37) 0.0650	0/70 (38) NC	1/70 (39) 0.5132	2/70 (39) 0.2600
Parathyroid Glands	Adenoma	2/76 (38) 0.8022	0/70 (38) 1.0000	3/70 (39) 0.5125	0/70 (38) 1.0000
	Sarcoma, Histiocytic	0/76 (37) 0.2566	0/70 (38) NC	0/70 (38) NC	1/70 (39) 0.5132
Pharynx	Sarcoma, Histiocytic	0/76 (37) 0.5066	0/70 (38) NC	1/70 (39) 0.5132	0/70 (38) NC
	Schwannoma	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
Pituitary Gland	Adenoma, Pars Distalis	42/76 (56) 0.3736	43/70 (58) 0.6254	37/70 (54) 0.8333	44/70 (57) 0.4789
	Adenoma, Pars Intermedia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Adenoma Pars Distalis/Intermedia	42/76 (56) 0.3823	44/70 (59) 0.6048	37/70 (54) 0.8333	44/70 (57) 0.4789
	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Sarcoma, Histiocytic	0/76 (37) 0.2034	0/70 (38) NC	2/70 (39) 0.2600	1/70 (38) 0.5067
	Schwannoma	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
Preputial Glands	Adenocarcinoma	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Sarcoma, Histiocytic	1/76 (38) 0.1721	0/70 (38) 1.0000	1/70 (39) 0.7597	2/70 (39) 0.5099
Prostate Gland	Adenocarcinoma	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
	Adenoma	0/76 (37) 0.2517	0/70 (38) NC	0/70 (38) NC	1/70 (38) 0.5067
	Carcinoma, Tubular Cell	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000

Male Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	35 mg Low (N=70) P - C vs. L	80 mg Med (N=70) P - C vs. M	200 mg High (N=70) P - C vs. H
	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Sarcoma, Histiocytic	1/76 (38) 0.1752	0/70 (38) 1.0000	2/70 (39) 0.5099	2/70 (39) 0.5099
Salivary Gland, Mandibular	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Lymphoma	0/76 (37) 0.5033	0/70 (38) NC	1/70 (38) 0.5067	0/70 (38) NC
	Sarcoma, Histiocytic	0/76 (37) 0.1945	0/70 (38) NC	1/70 (39) 0.5132	1/70 (39) 0.5132
Salivary Gland, Parotid	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Sarcoma, Histiocytic	0/76 (37) 0.2093	0/70 (38) NC	2/70 (39) 0.2600	1/70 (39) 0.5132
Salivary Gland, Sublingual	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Sarcoma, Histiocytic	0/76 (37) 0.1945	0/70 (38) NC	1/70 (39) 0.5132	1/70 (39) 0.5132
Seminal Vesicles	Sarcoma, Histiocytic	0/76 (37) 0.2566	0/70 (38) NC	0/70 (38) NC	1/70 (39) 0.5132
Skeletal Muscle, Biceps Femoris	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Sarcoma, Histiocytic	0/76 (37) 0.5066	0/70 (38) NC	1/70 (39) 0.5132	0/70 (38) NC
Skeletal Muscle, Quadriceps	Rhabdomyosarcoma	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
Skin	Adenoma, Sebaceous Cell	0/76 (37) 0.6291	1/70 (39) 0.5132	1/70 (38) 0.5067	0/70 (38) NC
	Carcinoma, Basosquamous Cell	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
	Fibroma	1/76 (38) 0.9395	1/70 (39) 0.7597	0/70 (38) 1.0000	0/70 (38) 1.0000
	Hemangioma	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
	Keratoacanthoma	2/76 (38) 0.8922	0/70 (38) 1.0000	1/70 (38) 0.8800	0/70 (38) 1.0000
	Papilloma, Fibrous	1/76 (38) 0.7549	0/70 (38) 1.0000	1/70 (39) 0.7597	0/70 (38) 1.0000
	Sarcoma, Histiocytic	1/76 (38) 0.7549	0/70 (38) 1.0000	1/70 (39) 0.7597	0/70 (38) 1.0000
	Schwannoma	0/76 (37) 0.2517	0/70 (38) NC	0/70 (38) NC	1/70 (38) 0.5067

Male Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	35 mg Low (N=70) P - C vs. L	80 mg Med (N=70) P - C vs. M	200 mg High (N=70) P - C vs. H
Skin, Subcutis	Adenoma, Sebaceous Cell	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
	Carcinoma, Squamous Cell	0/76 (37) 0.2566	0/70 (38) NC	0/70 (38) NC	1/70 (39) 0.5132
	Fibroma	1/76 (38) 0.5117	4/70 (40) 0.1957	5/70 (39) 0.1060	2/70 (39) 0.5099
	Fibrosarcoma	0/76 (37) 0.5033	0/70 (38) NC	2/70 (39) 0.2600	0/70 (38) NC
	Fibrosarcoma, Pleomorphic	0/76 (37) 0.2517	0/70 (38) NC	0/70 (38) NC	1/70 (38) 0.5067
	Histiocytoma	0/76 (37) 0.5066	0/70 (38) NC	1/70 (39) 0.5132	0/70 (38) NC
	Lipoma	1/76 (38) 0.9387	2/70 (39) 0.5099	0/70 (38) 1.0000	0/70 (38) 1.0000
	Liposarcoma	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Myxoma	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Osteosarcoma	0/76 (37) 0.2517	0/70 (38) NC	0/70 (38) NC	1/70 (38) 0.5067
	Sarcoma, Histiocytic	0/76 (37) 0.6431	1/70 (39) 0.5132	2/70 (39) 0.2600	0/70 (38) NC
	Sarcoma, Undifferentiated	0/76 (37) 0.2566	0/70 (38) NC	0/70 (38) NC	1/70 (39) 0.5132
	Schwannoma	3/76 (39) 0.9600	2/70 (40) 0.8285	2/70 (39) 0.8208	0/70 (38) 1.0000
Small Intestine, Duodenum	Sarcoma, Histiocytic	0/76 (37) 0.5033	0/70 (38) NC	2/70 (39) 0.2600	0/70 (38) NC
Small Intestine, Ileum	Sarcoma, Histiocytic	0/76 (37) 0.5033	0/70 (38) NC	2/70 (39) 0.2600	0/70 (38) NC
Small Intestine, Jejunum	Adenoma	0/76 (37) 0.5033	0/70 (38) NC	1/70 (38) 0.5067	0/70 (38) NC
	Sarcoma, Histiocytic	0/76 (37) 0.5066	0/70 (38) NC	1/70 (39) 0.5132	0/70 (38) NC
Spinal Cord, Cervical	Granular Cell Tumor	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
Spinal Cord, Thoracic	Granular Cell Tumor	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
Spleen	Fibrosarcoma, Pleomorphic	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC

Male Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	35 mg Low (N=70) P - C vs. L	80 mg Med (N=70) P - C vs. M	200 mg High (N=70) P - C vs. H
	Lymphoma	1/76 (38) 0.7517	0/70 (38) 1.0000	1/70 (38) 0.7533	0/70 (38) 1.0000
	Osteosarcoma	0/76 (37) 0.2517	0/70 (38) NC	0/70 (38) NC	1/70 (38) 0.5067
	Sarcoma, Histiocytic	2/76 (39) 0.3087	0/70 (38) 1.0000	2/70 (39) 0.6925	2/70 (39) 0.6925
Stomach, Glandular	Adenocarcinoma	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Sarcoma, Histiocytic	0/76 (37) 0.5066	0/70 (38) NC	1/70 (39) 0.5132	0/70 (38) NC
Testes	Adenoma, Interstitial Cell	0/76 (37) 0.3234	1/70 (39) 0.5132	3/70 (39) 0.1300	1/70 (38) 0.5067
	Lymphoma	0/76 (37) 0.5033	0/70 (38) NC	1/70 (38) 0.5067	0/70 (38) NC
	Sarcoma, Histiocytic	0/76 (37) 0.1945	0/70 (38) NC	1/70 (39) 0.5132	1/70 (39) 0.5132
Thymus	Leukemia	0/76 (37) 0.7566	1/70 (39) 0.5132	0/70 (38) NC	0/70 (38) NC
	Lymphoma	0/76 (37) 0.5033	0/70 (38) NC	1/70 (38) 0.5067	0/70 (38) NC
	Sarcoma, Histiocytic	0/76 (37) 0.2032	0/70 (38) NC	2/70 (40) 0.2666	1/70 (38) 0.5067
	Schwannoma	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000
	Thymoma	0/76 (37) 0.5033	0/70 (38) NC	1/70 (38) 0.5067	0/70 (38) NC
Thyroid Gland	Adenoma, C-Cell	2/76 (38) 0.0395	2/70 (39) 0.7023	2/70 (39) 0.7023	6/70 (40) 0.1486
	Adenoma, Follicular Cell	1/76 (38) 0.3786	0/70 (38) 1.0000	2/70 (38) 0.5000	1/70 (39) 0.7597
	Carcinoma, C-Cell	0/76 (37) 0.8104	3/70 (39) 0.1300	1/70 (39) 0.5132	0/70 (38) NC
	Adenoma/Carcinoma C-Cell	2/76 (38) 0.1294	5/70 (40) 0.2374	3/70 (39) 0.5125	6/70 (40) 0.1486
	Sarcoma, Histiocytic	0/76 (37) 0.1945	0/70 (38) NC	1/70 (39) 0.5132	1/70 (39) 0.5132
Tongue	Carcinoma, Squamous Cell	0/76 (37) 0.2517	0/70 (38) NC	0/70 (38) NC	1/70 (38) 0.5067
Trachea	Sarcoma, Histiocytic	0/76 (37) 0.5066	0/70 (38) NC	1/70 (39) 0.5132	0/70 (38) NC

Male Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	35 mg Low (N=70) P - C vs. L	80 mg Med (N=70) P - C vs. M	200 mg High (N=70) P - C vs. H
Ureters	Lymphoma	0/76 (37) 0.5033	0/70 (38) NC	1/70 (38) 0.5067	0/70 (38) NC
	Sarcoma, Histiocytic	0/76 (37) 0.1945	0/70 (38) NC	1/70 (39) 0.5132	1/70 (39) 0.5132
Urinary Bladder	Sarcoma, Histiocytic	0/76 (37) 0.0646	0/70 (38) NC	0/70 (38) NC	2/70 (39) 0.2600
Zymbal`S Gland	Carcinoma, Zymbals Gland	1/76 (38) 0.3931	0/70 (38) 1.0000	1/70 (39) 0.7597	1/70 (38) 0.7533
	Sarcoma, Histiocytic	0/76 (37) 0.1945	0/70 (38) NC	1/70 (39) 0.5132	1/70 (39) 0.5132
	Schwannoma	1/76 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000	0/70 (38) 1.0000

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

NC = Not calculable

*: Statistically significant at 0 005 and 0 025 for common and rare tumors, respectively in dose response relationship or 0 01 and 0 05 for common and rare tumors, respectively in pairwise comparisons

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Female Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	35 mg Low (N=70) P - C vs. L	80 mg Med (N=70) P - C vs. M	200 mg High (N=70) P - C vs. H
Adrenal Glands	Adenoma, Cortical	2/76 (46) 0.1226	1/70 (37) 0.8348	3/70 (40) 0.4332	4/70 (43) 0.3065
	Carcinoma, Cortical	0/76 (45) 0.6154	1/70 (38) 0.4578	1/70 (40) 0.4706	0/70 (42) NC
	Adenoma/Carcinoma Cortical	2/76 (46) 0.1767	2/70 (38) 0.6165	4/70 (40) 0.2737	4/70 (43) 0.3065
	Lymphoma	1/76 (45) 1.0000	0/70 (37) 1.0000	0/70 (40) 1.0000	0/70 (42) 1.0000
	Pheochromocytoma	7/76 (47) 0.8846	4/70 (39) 0.8323	2/70 (41) 0.9750	3/70 (43) 0.9392
	Sarcoma, Histiocytic	0/76 (45) 0.5000	0/70 (37) NC	1/70 (40) 0.4706	0/70 (42) NC
Bone Marrow, Femur	Lymphoma	1/76 (45) 1.0000	0/70 (37) 1.0000	0/70 (40) 1.0000	0/70 (42) 1.0000
Bone Marrow, Sternum	Lymphoma	1/76 (45) 1.0000	0/70 (37) 1.0000	0/70 (40) 1.0000	0/70 (42) 1.0000
Brain	Astrocytoma	1/76 (45) 0.5125	1/70 (37) 0.7019	2/70 (40) 0.4554	1/70 (43) 0.7414
	Carcinoma, Pars Distalis	3/76 (46) 0.9665	1/70 (37) 0.9112	1/70 (40) 0.9232	0/70 (42) 1.0000
	Granular Cell Tumor	1/76 (45) 0.4041	0/70 (37) 1.0000	1/70 (40) 0.7227	1/70 (43) 0.7414
	Mixed Glioma	0/76 (45) 0.3108	1/70 (38) 0.4578	0/70 (40) NC	1/70 (43) 0.4886
Cavity, Abdominal	Sex-Cord/Stromal Tumor	1/76 (46) 1.0000	0/70 (37) 1.0000	0/70 (40) 1.0000	0/70 (42) 1.0000
Harderian Glands	Adenoma	0/76 (45) 0.2606	0/70 (37) NC	0/70 (40) NC	1/70 (43) 0.4886
	Schwannoma	0/76 (45) 0.2606	0/70 (37) NC	0/70 (40) NC	1/70 (43) 0.4886
Heart	Carcinosarcoma	0/76 (45) 0.7273	1/70 (38) 0.4578	0/70 (40) NC	0/70 (42) NC
	Sarcoma, Histiocytic	0/76 (45) 0.5000	0/70 (37) NC	1/70 (40) 0.4706	0/70 (42) NC
	Schwannoma, Endocardial	0/76 (45) 0.0667	0/70 (37) NC	0/70 (40) NC	2/70 (43) 0.2359
Kidneys	Liposarcoma	2/76 (45) 1.0000	0/70 (37) 1.0000	0/70 (40) 1.0000	0/70 (42) 1.0000
	Lymphoma	1/76 (45) 1.0000	0/70 (37) 1.0000	0/70 (40) 1.0000	0/70 (42) 1.0000
	Sarcoma, Histiocytic	0/76 (45) 0.5061	0/70 (37) NC	2/70 (40) 0.2185	0/70 (42) NC

Female Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	35 mg Low (N=70) P - C vs. L	80 mg Med (N=70) P - C vs. M	200 mg High (N=70) P - C vs. H
Large Intestine, Colon	Adenocarcinoma	0/76 (45) 0.5000	0/70 (37) NC	1/70 (40) 0.4706	0/70 (42) NC
Liver	Adenoma, Hepatocellular	0/76 (45) 0.6169	1/70 (37) 0.4512	1/70 (40) 0.4706	0/70 (42) NC
	Lymphoma	1/76 (45) 1.0000	0/70 (37) 1.0000	0/70 (40) 1.0000	0/70 (42) 1.0000
	Sarcoma, Histiocytic	0/76 (45) 0.5000	0/70 (37) NC	1/70 (40) 0.4706	0/70 (42) NC
Lung	Adenocarcinoma	1/76 (46) 0.9272	2/70 (38) 0.4279	0/70 (40) 1.0000	0/70 (42) 1.0000
	Adenoma, Bronchiolar Alveolar	0/76 (45) 0.6168	1/70 (38) 0.4578	1/70 (41) 0.4767	0/70 (42) NC
	Carcinoma, Bronchiolar Alveol	1/76 (45) 1.0000	0/70 (37) 1.0000	0/70 (40) 1.0000	0/70 (42) 1.0000
	Carcinoma, Cortical	0/76 (45) 0.7273	1/70 (38) 0.4578	0/70 (40) NC	0/70 (42) NC
	Pheochromocytoma	1/76 (45) 1.0000	0/70 (37) 1.0000	0/70 (40) 1.0000	0/70 (42) 1.0000
	Sarcoma, Histiocytic	0/76 (45) 0.5000	0/70 (37) NC	1/70 (40) 0.4706	0/70 (42) NC
	Schwannoma	0/76 (45) 0.2606	0/70 (37) NC	0/70 (40) NC	1/70 (43) 0.4886
Lymph Node, Axillary	Carcinosarcoma	0/76 (45) 0.7273	1/70 (38) 0.4578	0/70 (40) NC	0/70 (42) NC
Lymph Node, Iliac	Sarcoma, Histiocytic	0/76 (45) 0.5000	0/70 (37) NC	1/70 (40) 0.4706	0/70 (42) NC
Lymph Node, Inguinal	Adenocarcinoma	0/76 (45) 0.5000	0/70 (37) NC	1/70 (40) 0.4706	0/70 (42) NC
Mammary Gland	Adenocarcinoma	27/76 (56) 0.9676	22/70 (47) 0.6330	19/70 (48) 0.8603	16/70 (50) 0.9714
	Adenoma	7/76 (48) 0.6941	9/70 (41) 0.2654	4/70 (41) 0.8442	6/70 (44) 0.6647
	Adeno/Adenocarcinoma	31/76 (58) 0.9512	29/70 (49) 0.3449	21/70 (49) 0.9009	21/70 (51) 0.9297
	Carcinosarcoma	0/76 (45) 0.7273	1/70 (38) 0.4578	0/70 (40) NC	0/70 (42) NC
	Fibroadenoma	27/76 (55) 0.9318	38/70 (52) 0.0093*	31/70 (50) 0.1287	21/70 (48) 0.7702
	Sarcoma, Histiocytic	0/76 (45) 0.4512	0/70 (37) NC	3/70 (41) 0.1042	0/70 (42) NC
Mediastinum	Sarcoma, Histiocytic	0/76 (45) 0.5000	0/70 (37) NC	1/70 (40) 0.4706	0/70 (42) NC
Mesentery/Peritoneum	Carcinosarcoma	0/76 (45) 0.7273	1/70 (38) 0.4578	0/70 (40) NC	0/70 (42) NC

Female Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	35 mg Low (N=70) P - C vs. L	80 mg Med (N=70) P - C vs. M	200 mg High (N=70) P - C vs. H
	Sarcoma, Histiocytic	0/76 (45) 0.5000	0/70 (37) NC	1/70 (40) 0.4706	0/70 (42) NC
Multicentric Neoplasm	Hemangiosarcoma	0/76 (45) 0.3108	1/70 (38) 0.4578	0/70 (40) NC	1/70 (43) 0.4886
	Lymphoma	1/76 (45) 1.0000	0/70 (37) 1.0000	0/70 (40) 1.0000	0/70 (42) 1.0000
	Sarcoma, Histiocytic	0/76 (45) 0.4512	0/70 (37) NC	3/70 (41) 0.1042	0/70 (42) NC
Nerve, Sciatic	Sarcoma, Histiocytic	0/76 (45) 0.5000	0/70 (37) NC	1/70 (40) 0.4706	0/70 (42) NC
Nose, Level A	Schwannoma	0/76 (45) 0.2606	0/70 (37) NC	0/70 (40) NC	1/70 (43) 0.4886
Nose, Level B	Schwannoma	0/76 (45) 0.2606	0/70 (37) NC	0/70 (40) NC	1/70 (43) 0.4886
Nose, Level C	Schwannoma	0/76 (45) 0.2606	0/70 (37) NC	0/70 (40) NC	1/70 (43) 0.4886
Nose, Level D	Schwannoma	0/76 (45) 0.2606	0/70 (37) NC	0/70 (40) NC	1/70 (43) 0.4886
Ovaries	Leiomyosarcoma	0/76 (45) 0.2606	0/70 (37) NC	0/70 (40) NC	1/70 (43) 0.4886
	Lymphoma	1/76 (45) 1.0000	0/70 (37) 1.0000	0/70 (40) 1.0000	0/70 (42) 1.0000
	Sarcoma, Histiocytic	0/76 (45) 0.5000	0/70 (37) NC	1/70 (40) 0.4706	0/70 (42) NC
	Sex-Cord/Stromal Tumor	2/76 (46) 0.6090	0/70 (37) 1.0000	0/70 (40) 1.0000	1/70 (43) 0.8663
Oviducts	Lymphoma	1/76 (45) 1.0000	0/70 (37) 1.0000	0/70 (40) 1.0000	0/70 (42) 1.0000
Pancreas	Adenoma, Islet Cell	0/76 (45) 0.3035	3/70 (38) 0.0918	2/70 (40) 0.2185	2/70 (43) 0.2359
	Carcinoma, Islet Cell	0/76 (45) 0.5000	0/70 (37) NC	1/70 (40) 0.4706	0/70 (42) NC
	Lymphoma	1/76 (45) 1.0000	0/70 (37) 1.0000	0/70 (40) 1.0000	0/70 (42) 1.0000
	Sarcoma, Histiocytic	0/76 (45) 0.5000	0/70 (37) NC	1/70 (40) 0.4706	0/70 (42) NC
Parathyroid Glands	Adenoma	1/76 (45) 0.5539	1/70 (37) 0.7019	0/70 (40) 1.0000	1/70 (43) 0.7414
Pituitary Gland	Adenoma, Pars Distalis	50/76 (64) 0.3829	53/70 (61) 0.1467	51/70 (62) 0.3606	49/70 (59) 0.3233
	Adenoma, Pars Intermedia	1/76 (45) 1.0000	0/70 (37) 1.0000	0/70 (40) 1.0000	0/70 (42) 1.0000
	Carcinoma, Pars Distalis	4/76 (46) 0.8842	1/70 (37) 0.9528	1/70 (40) 0.9606	1/70 (43) 0.9670

Female Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	35 mg Low (N=70) P - C vs. L	80 mg Med (N=70) P - C vs. M	200 mg High (N=70) P - C vs. H
	Adenoma/Carcinoma Pars Distalis/Intermediate	54/76 (65) 0.5267	54/70 (61) 0.2690	52/70 (63) 0.6235	50/70 (59) 0.4980
Skeletal Muscle	Carcinoma, Squamous Cell	0/76 (45) 0.2606	0/70 (37) NC	0/70 (40) NC	1/70 (43) 0.4886
Skeletal Muscle, Biceps Femoris	Sarcoma, Histiocytic	0/76 (45) 0.5061	0/70 (37) NC	2/70 (40) 0.2185	0/70 (42) NC
Skin	Papilloma, Squamous Cell	1/76 (45) 0.7515	0/70 (37) 1.0000	1/70 (40) 0.7227	0/70 (42) 1.0000
	Sarcoma, Histiocytic	0/76 (45) 0.5000	0/70 (37) NC	1/70 (40) 0.4706	0/70 (42) NC
Skin, Subcutis	Fibroma	1/76 (46) 0.9235	1/70 (37) 0.6959	0/70 (40) 1.0000	0/70 (42) 1.0000
	Fibrosarcoma	0/76 (45) 0.7273	1/70 (38) 0.4578	0/70 (40) NC	0/70 (42) NC
	Fibrosarcoma, Pleomorphic	1/76 (45) 1.0000	0/70 (37) 1.0000	0/70 (40) 1.0000	0/70 (42) 1.0000
	Hemangiosarcoma	0/76 (45) 0.7273	1/70 (38) 0.4578	0/70 (40) NC	0/70 (42) NC
	Lipoma	0/76 (45) 0.7273	1/70 (38) 0.4578	0/70 (40) NC	0/70 (42) NC
	Schwannoma	0/76 (45) 0.1571	1/70 (38) 0.4578	3/70 (41) 0.1042	2/70 (43) 0.2359
Small Intestine, Duodenum	Leiomyoma	1/76 (45) 1.0000	0/70 (37) 1.0000	0/70 (40) 1.0000	0/70 (42) 1.0000
	Sarcoma, Histiocytic	0/76 (45) 0.5000	0/70 (37) NC	1/70 (40) 0.4706	0/70 (42) NC
Spleen	Lymphoma	1/76 (45) 1.0000	0/70 (37) 1.0000	0/70 (40) 1.0000	0/70 (42) 1.0000
Thymus	Sarcoma, Histiocytic	0/76 (45) 0.5000	0/70 (37) NC	1/70 (40) 0.4706	0/70 (42) NC
	Thymoma	0/76 (45) 0.8004	2/70 (38) 0.2066	0/70 (40) NC	0/70 (42) NC
Thyroid Gland	Adenoma, C-Cell	3/76 (45) 0.0524	2/70 (38) 0.7629	6/70 (41) 0.1973	7/70 (44) 0.1482
	Adenoma, Follicular Cell	1/76 (45) 0.5521	1/70 (38) 0.7091	0/70 (40) 1.0000	1/70 (43) 0.7414
	Carcinoma, C-Cell	1/76 (45) 0.4041	0/70 (37) 1.0000	1/70 (40) 0.7227	1/70 (43) 0.7414
	Carcinoma, Follicular Cell	0/76 (45) 0.5000	0/70 (37) NC	1/70 (40) 0.4706	0/70 (42) NC
	Adenoma/Carcinoma C-Cell	4/76 (45) 0.0499	2/70 (38) 0.8554	7/70 (41) 0.2087	8/70 (44) 0.1655
	Adenoma/Carcinoma Follicular Cell	1/76 (45) 0.5201	1/70 (38) 0.7091	1/70 (40) 0.7227	1/70 (43) 0.7414

Female Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	35 mg Low (N=70) P - C vs. L	80 mg Med (N=70) P - C vs. M	200 mg High (N=70) P - C vs. H
Tongue	Carcinoma, Squamous Cell	0/76 (45) 0.1939	0/70 (37) NC	1/70 (40) 0.4706	1/70 (43) 0.4886
Urinary Bladder	Papilloma, Transitional Cell	0/76 (45) 0.7256	1/70 (37) 0.4512	0/70 (40) NC	0/70 (42) NC
Uterus with Cervix	Adenocarcinoma	0/76 (45) 0.5000	0/70 (37) NC	1/70 (40) 0.4706	0/70 (42) NC
	Granular Cell Tumor	5/76 (46) 0.8028	2/70 (38) 0.9096	4/70 (41) 0.6968	2/70 (43) 0.9338
	Hemangiosarcoma	0/76 (45) 0.2606	0/70 (37) NC	0/70 (40) NC	1/70 (43) 0.4886
	Leiomyoma	0/76 (45) 0.2606	0/70 (37) NC	0/70 (40) NC	1/70 (43) 0.4886
	Lymphoma	1/76 (45) 1.0000	0/70 (37) 1.0000	0/70 (40) 1.0000	0/70 (42) 1.0000
	Polyp, Endometrial Stromal	1/76 (46) 0.4003	0/70 (37) 1.0000	1/70 (40) 0.7168	1/70 (43) 0.7357
	Polyp, Stromal	5/76 (46) 0.6379	2/70 (38) 0.9096	5/70 (42) 0.5707	3/70 (43) 0.8440
	Sarcoma, Histiocytic	0/76 (45) 0.5000	0/70 (37) NC	1/70 (40) 0.4706	0/70 (42) NC
	Sarcoma, Stromal	0/76 (45) 0.0659	0/70 (37) NC	1/70 (41) 0.4767	2/70 (43) 0.2359
	Polyp, Endometrial Stromal /Sarcoma Stromal	5/76 (46) 0.3385	2/70 (38) 0.9096	6/70 (43) 0.4516	5/70 (44) 0.6015
Vagina	Granular Cell Tumor	3/76 (45) 0.7401	8/70 (39) 0.0599	8/70 (44) 0.0914	3/70 (43) 0.6398
	Sarcoma, Stromal	0/76 (45) 0.5030	0/70 (37) NC	1/70 (41) 0.4767	0/70 (42) NC
Uterus/Vagina	Sarcoma, Stromal	0/76 (45) 0.0659	0/70 (37) NC	1/70 (41) 0.4767	2/70 (43) 0.2359
Zymbal`S Gland	Carcinoma, Zymbals Gland	1/76 (45) 1.0000	0/70 (37) 1.0000	0/70 (40) 1.0000	0/70 (42) 1.0000
	Fibrosarcoma	0/76 (45) 0.5000	0/70 (37) NC	1/70 (40) 0.4706	0/70 (42) NC

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

NC = Not calculable

*: Statistically significant at 0 005 and 0 025 for common and rare tumors, respectively in dose response relationship or 0 01 and 0 05 for common and rare tumors, respectively in pairwise comparisons

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

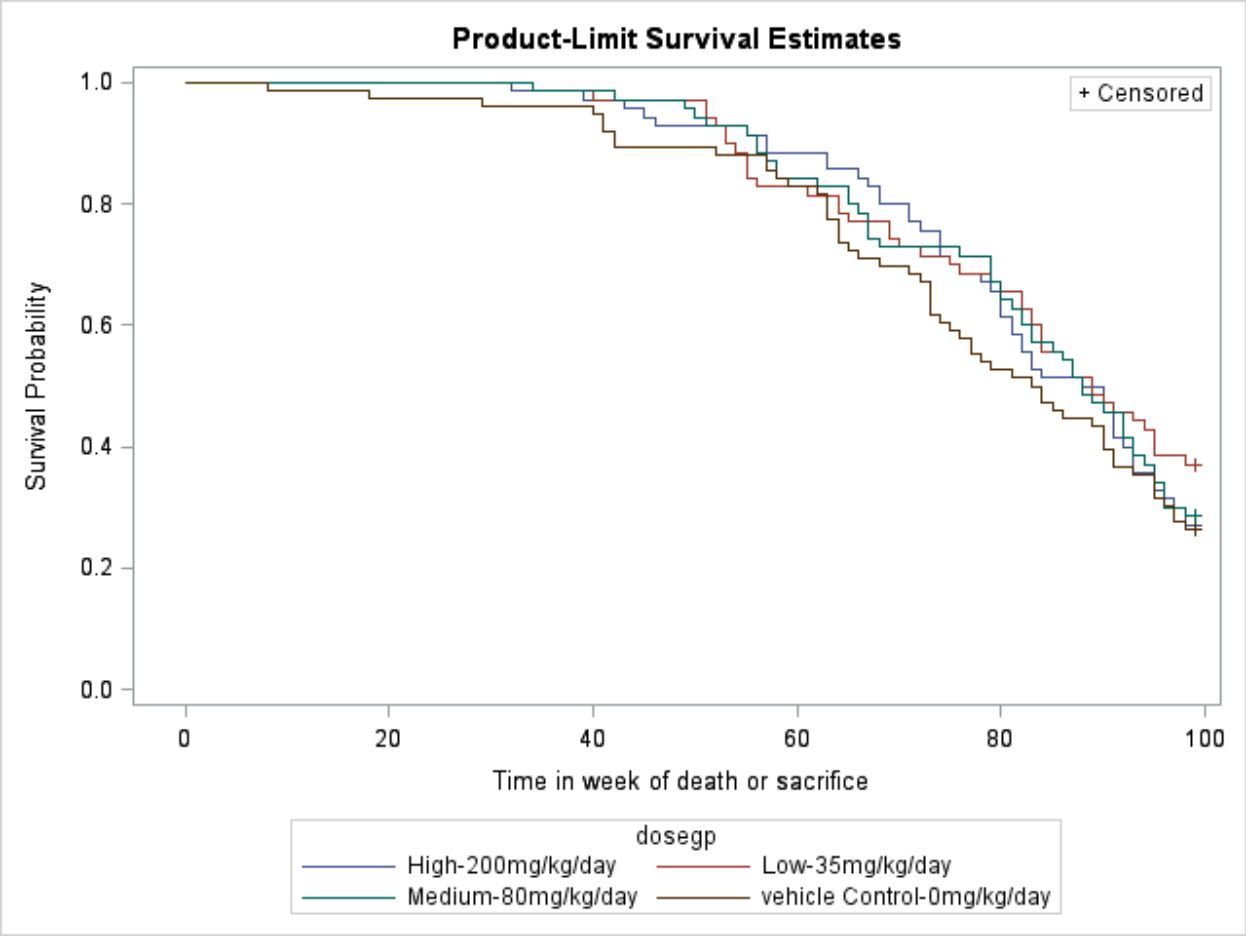


Figure 1B: Kaplan-Meier Survival Curves **for Female Rats**

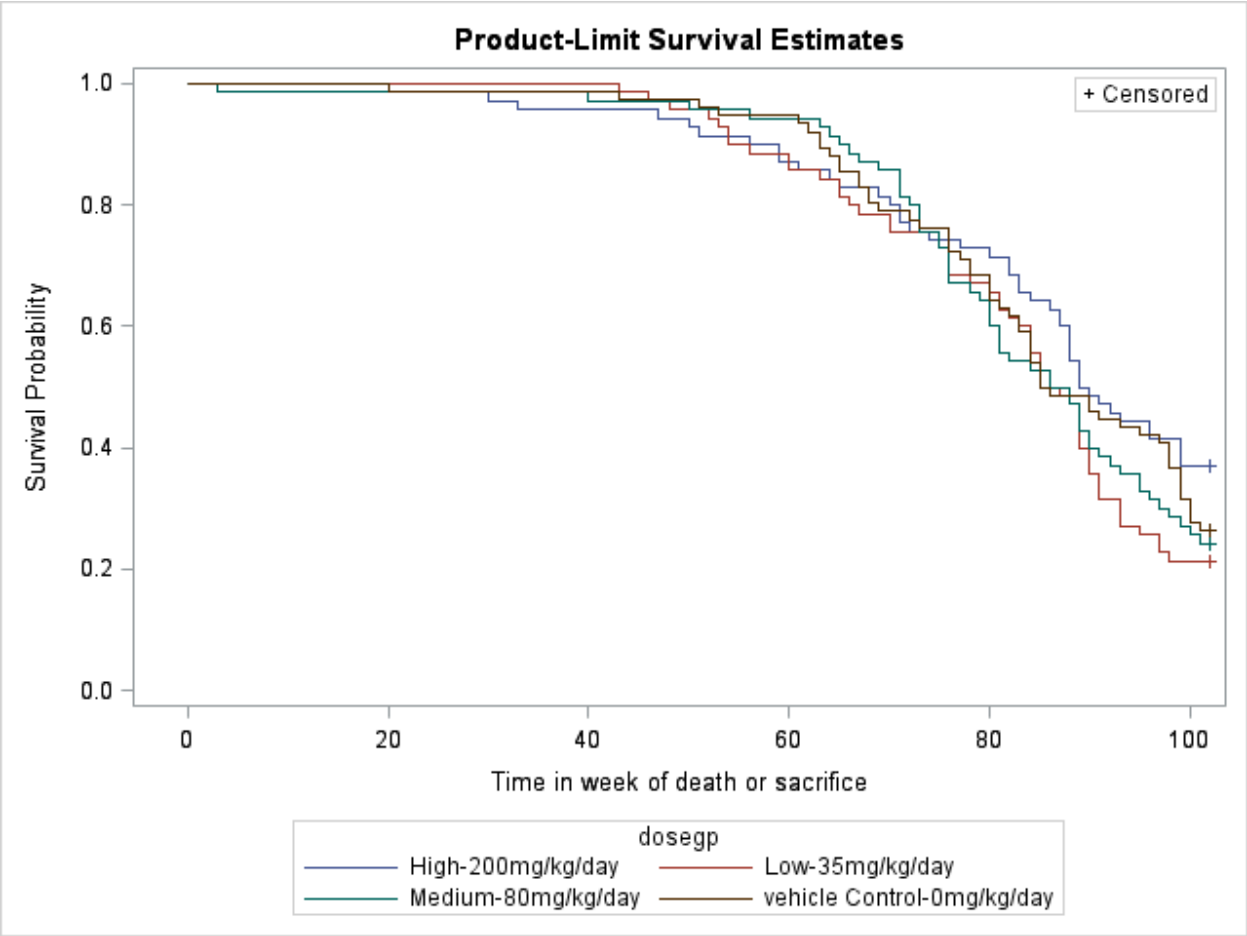


Table4A: Intercurrent Mortality Rate
Male Mice

	0 mg|kg|day		20 mg|kg|day		65 mg|kg|day		200 mg|kg|day	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
1 - 13	.	.	.	.	.	.	2	3.33
14 - 26	2	3.33	1	1.67	1	1.67	2	6.67
27 - 39	1	5.00	1	3.33	4	8.33	.	.
40 - 52	3	10.00	2	6.67	3	13.33	.	.
53 - 65	3	15.00	3	11.67	6	23.33	2	10.00
66 - 78	8	28.33	8	25.00	5	31.67	10	26.67
79 - 91	6	38.33	8	38.33	12	51.67	8	40.00
92 - 105	12	58.33	15	63.33	9	66.67	12	60.00
Ter. Sac.	41	68.33	22	36.67	20	33.33	24	40.00
Total	76	100.00	60	100.00	60	100.00	60	100.00

Table4B: Intercurrent Mortality Rate
Female Mice

	0 mg|kg|day		20 mg|kg|day		65 mg|kg|day		200 mg|kg|day	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
1 - 13	.	.	1	1.67	1	1.67	3	5.00
14 - 26	2	3.33	.	.	.	.	1	6.67
27 - 39	1	5.00	.	.	1	3.33	1	8.33
40 - 52	1	6.67	3	6.67	2	6.67	2	11.67
53 - 65	5	15.00	5	15.00	6	16.67	5	20.00
66 - 78	6	25.00	8	28.33	9	31.67	7	31.67
79 - 91	13	46.67	6	38.33	14	55.00	9	46.67
92 - 105	21	81.67	12	58.33	11	73.33	12	66.67
Ter. Sac.	27	45.00	25	41.67	16	26.67	20	33.33
Total	76	100.00	60	100.00	60	100.00	60	100.00

Table 5A: Intercurrent Mortality Comparison for
Male Mice

Test Statistics	**P-value for Vehicle Cont. Low, Med, high**	**P-value for Vehicle Cont. vs Low**	**P-value for Vehicle Cont. vs Med**	**P-value for Vehicle Cont. vs High**
Dose-Response (Likelihood Ratio)	0.3051	0.0677	0.0087*	0.1028
Homogeneity (Log-Rank)	0.0503	0.0636	0.0074*	0.0973

Table 5B: Intercurrent Mortality Comparison for
Female Mice

Test Statistics	**P-value for Vehicle Cont. Low, Med, high**	**P-value for Vehicle Cont. vs Low**	**P-value for Vehicle Cont. vs Med**	**P-value for Vehicle Cont. vs High**
Dose-Response (Likelihood Ratio)	0.3835	0.7919	0.0991	0.4645
Homogeneity (Log-Rank)	0.2790	0.7904	0.0923	0.4582

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

Male Mice Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	20 mg Low (N=60) P - C vs. L	65 mg Med (N=60) P - C vs. M	200 mg High (N=60) P - C vs. H
Adrenal Glands	Adenoma, Cortical	1/76 (59) 0.4132	0/60 (42) 1.0000	0/60 (37) 1.0000	1/60 (42) 0.6612
	Adenoma, Subcapsular Cell	2/76 (58) 0.8376	1/60 (42) 0.8092	2/60 (38) 0.5193	0/60 (42) 1.0000
	Leukemia, Granulocytic	0/76 (58) 0.2346	0/60 (42) NC	0/60 (37) NC	1/60 (42) 0.4200
	Lymphoma	0/76 (58) 0.4440	3/60 (44) 0.0771	0/60 (37) NC	1/60 (42) 0.4200
Aorta	Lymphoma	0/76 (58) 0.2346	0/60 (42) NC	0/60 (37) NC	1/60 (42) 0.4200
Bone Marrow, Femur	Hemangiosarcoma	0/76 (58) 0.2346	0/60 (42) NC	0/60 (37) NC	1/60 (42) 0.4200
	Leukemia, Granulocytic	1/76 (59) 0.0787	1/60 (42) 0.6612	0/60 (37) 1.0000	3/60 (43) 0.2004
	Lymphoma	2/76 (60) 0.6293	6/60 (47) 0.0708	1/60 (37) 0.7679	2/60 (43) 0.5569
Bone Marrow, Sternum	Hemangiosarcoma	0/76 (58) 0.2346	0/60 (42) NC	0/60 (37) NC	1/60 (42) 0.4200
	Leukemia, Granulocytic	1/76 (59) 0.0787	1/60 (42) 0.6612	0/60 (37) 1.0000	3/60 (43) 0.2004
	Lymphoma	2/76 (60) 0.6485	6/60 (47) 0.0708	0/60 (37) 1.0000	2/60 (43) 0.5569
Bone, Mandible	Hemangiosarcoma	1/76 (58) 1.0000	0/60 (42) 1.0000	0/60 (37) 1.0000	0/60 (42) 1.0000
Brain	Lymphoma	1/76 (59) 0.5602	2/60 (44) 0.3905	0/60 (37) 1.0000	1/60 (42) 0.6612
Bulbourethral Gland	Adenoma	1/76 (58) 1.0000	0/60 (42) 1.0000	0/60 (37) 1.0000	0/60 (42) 1.0000
Cavity, Abdominal	Leukemia, Granulocytic	0/76 (58) 0.2346	0/60 (42) NC	0/60 (37) NC	1/60 (42) 0.4200
	Lymphoma	3/76 (60) 0.8956	7/60 (47) 0.0796	1/60 (37) 0.8593	1/60 (42) 0.8853
Cavity, Thoracic	Carcinoma, Bronchiolar Alveol	1/76 (59) 0.7594	1/60 (42) 0.6612	1/60 (37) 0.6248	0/60 (42) 1.0000
	Leukemia, Granulocytic	0/76 (58) 0.2346	0/60 (42) NC	0/60 (37) NC	1/60 (42) 0.4200
	Lymphoma	3/76 (60) 0.7723	8/60 (48) 0.0472	2/60 (37) 0.6353	2/60 (43) 0.6981
Coagulating Glands	Adenoma	1/76 (58) 1.0000	0/60 (42) 1.0000	0/60 (37) 1.0000	0/60 (42) 1.0000

Male Mice Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	20 mg Low (N=60) P - C vs. L	65 mg Med (N=60) P - C vs. M	200 mg High (N=60) P - C vs. H
	Leukemia, Granulocytic	1/76 (59) 0.4132	0/60 (42) 1.0000	0/60 (37) 1.0000	1/60 (42) 0.6612
	Lymphoma	0/76 (58) 0.4301	3/60 (44) 0.0771	1/60 (37) 0.3895	1/60 (42) 0.4200
Diaphragm	Carcinoma, Bronchiolar Alveol	1/76 (58) 1.0000	0/60 (42) 1.0000	0/60 (37) 1.0000	0/60 (42) 1.0000
Epididymides	Leukemia, Granulocytic	0/76 (58) 0.2346	0/60 (42) NC	0/60 (37) NC	1/60 (42) 0.4200
	Lymphoma	0/76 (58) 0.2726	4/60 (45) 0.0337*	0/60 (37) NC	2/60 (42) 0.1739
Eyes	Leukemia, Granulocytic	0/76 (58) 0.2346	0/60 (42) NC	0/60 (37) NC	1/60 (42) 0.4200
	Lymphoma	0/76 (58) 0.3677	2/60 (44) 0.1837	0/60 (37) NC	1/60 (42) 0.4200
Gallbladder	Lymphoma	0/76 (58) 0.5174	4/60 (46) 0.0355*	0/60 (37) NC	1/60 (42) 0.4200
Galt	Leukemia, Granulocytic	0/76 (58) 0.2346	0/60 (42) NC	0/60 (37) NC	1/60 (42) 0.4200
	Lymphoma	3/76 (59) 0.6561	4/60 (45) 0.3512	1/60 (37) 0.8630	2/60 (43) 0.7049
Harderian Glands	Adenocarcinoma	0/76 (58) 0.3713	2/60 (42) 0.1739	0/60 (37) NC	1/60 (42) 0.4200
	Adenoma	13/76 (60) 0.6981	10/60 (44) 0.5411	5/60 (38) 0.9101	8/60 (43) 0.7330
	Adenoma/Adenocarcinoma	13/76 (60) 0.6437	12/60 (44) 0.3325	5/60 (38) 0.9101	9/60 (43) 0.6277
	Leukemia, Granulocytic	1/76 (59) 0.4132	0/60 (42) 1.0000	0/60 (37) 1.0000	1/60 (42) 0.6612
	Lymphoma	2/76 (60) 0.8373	6/60 (47) 0.0708	0/60 (37) 1.0000	1/60 (42) 0.8007
	Adenoma/Adenocarcinoma	13/76 (60) 0.6437	12/60 (44) 0.3325	5/60 (38) 0.9101	9/60 (43) 0.6277
Heart	Carcinoma, Bronchiolar Alveol	1/76 (59) 1.0000	0/60 (42) 1.0000	0/60 (37) 1.0000	0/60 (42) 1.0000
	Leukemia, Granulocytic	1/76 (59) 0.0422	0/60 (42) 1.0000	0/60 (37) 1.0000	3/60 (43) 0.2004
	Lymphoma	2/76 (60) 0.7480	3/60 (44) 0.3553	0/60 (37) 1.0000	1/60 (42) 0.8007
Kidneys	Adenoma, Tubular Cell	0/76 (58) 0.0461	0/60 (42) NC	1/60 (37) 0.3895	2/60 (42) 0.1739
	Leukemia, Granulocytic	1/76 (59) 0.0422	0/60 (42) 1.0000	0/60 (37) 1.0000	3/60 (43) 0.2004

Male Mice Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	20 mg Low (N=60) P - C vs. L	65 mg Med (N=60) P - C vs. M	200 mg High (N=60) P - C vs. H
	Lymphoma	4/76 (61) 0.8015	6/60 (47) 0.2203	1/60 (37) 0.9124	2/60 (43) 0.7948
Lacrimal Glands, Exorbital	Leukemia, Granulocytic	1/76 (59) 0.0787	1/60 (42) 0.6612	0/60 (37) 1.0000	3/60 (43) 0.2004
	Lymphoma	2/76 (59) 0.8415	6/60 (47) 0.0743	0/60 (37) 1.0000	1/60 (42) 0.8049
Large Intestine, Cecum	Lymphoma	1/76 (59) 0.6189	3/60 (44) 0.2074	0/60 (37) 1.0000	1/60 (42) 0.6612
Large Intestine, Colon	Adenocarcinoma	1/76 (58) 1.0000	0/60 (42) 1.0000	0/60 (37) 1.0000	0/60 (42) 1.0000
	Lymphoma	0/76 (58) 0.2620	1/60 (43) 0.4257	0/60 (37) NC	1/60 (42) 0.4200
Large Intestine, Rectum	Lymphoma	0/76 (58) 0.2346	0/60 (42) NC	0/60 (37) NC	1/60 (42) 0.4200
Larynx	Lymphoma	0/76 (58) 0.7419	2/60 (44) 0.1837	0/60 (37) NC	0/60 (42) NC
Liver	Adenoma, Hepatocellular	13/76 (60) 0.8237	8/60 (44) 0.7515	6/60 (38) 0.8360	6/60 (42) 0.8862
	Carcinoma, Bronchiolar Alveol	1/76 (59) 1.0000	0/60 (42) 1.0000	0/60 (37) 1.0000	0/60 (42) 1.0000
	Carcinoma, Hepatocellular	2/76 (58) 0.3359	1/60 (42) 0.8092	1/60 (37) 0.7771	2/60 (42) 0.5613
	Adenoma/Carcinom Hepatocellular	15/76 (60) 0.7611	9/60 (44) 0.7810	7/60 (38) 0.8435	8/60 (43) 0.8434
	Hemangioma	0/76 (58) 0.6778	1/60 (43) 0.4257	0/60 (37) NC	0/60 (42) NC
	Hemangiosarcoma	3/76 (59) 0.5604	4/60 (43) 0.3277	6/60 (38) 0.0800	2/60 (42) 0.6955
	Leukemia, Granulocytic	1/76 (59) 0.0787	1/60 (42) 0.6612	0/60 (37) 1.0000	3/60 (43) 0.2004
	Lymphoma	3/76 (60) 0.5684	7/60 (47) 0.0796	2/60 (37) 0.6353	3/60 (43) 0.4928
Lung	Adenoma, Bronchiolar Alveolar	19/76 (61) 0.7097	16/60 (44) 0.3622	17/60 (43) 0.2490	12/60 (44) 0.7398
	Carcinoma, Bronchiolar Alveol	6/76 (60) 0.2969	5/60 (43) 0.5178	4/60 (38) 0.5935	6/60 (44) 0.3924
	Adenoma/Carcinoma Bronchiolar Alveol	25/76 (62) 0.6203	21/60 (45) 0.3237	20/60 (44) 0.3712	18/60 (46) 0.6262
	Fibrosarcoma	2/76 (60) 0.9654	1/60 (43) 0.8065	0/60 (37) 1.0000	0/60 (42) 1.0000
	Leukemia, Granulocytic	0/76 (58) 0.0561	0/60 (42) NC	0/60 (37) NC	2/60 (43) 0.1788

Male Mice Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	20 mg Low (N=60) P - C vs. L	65 mg Med (N=60) P - C vs. M	200 mg High (N=60) P - C vs. H
	Lymphoma	3/76 (60) 0.5969	7/60 (47) 0.0796	0/60 (37) 1.0000	3/60 (43) 0.4928
Lymph Node	Lymphoma	0/76 (58) 0.6778	1/60 (43) 0.4257	0/60 (37) NC	0/60 (42) NC
Lymph Node, Hepatic	Lymphoma	2/76 (58) 0.5044	3/60 (44) 0.3704	0/60 (37) 1.0000	2/60 (43) 0.5711
Lymph Node, Inguinal	Leukemia, Granulocytic	1/76 (59) 0.4132	0/60 (42) 1.0000	0/60 (37) 1.0000	1/60 (42) 0.6612
Lymph Node, Mandibular	Leukemia, Granulocytic	1/76 (59) 0.0787	1/60 (42) 0.6612	0/60 (37) 1.0000	3/60 (43) 0.2004
	Lymphoma	3/76 (60) 0.7278	6/60 (47) 0.1392	1/60 (37) 0.8593	2/60 (43) 0.6981
Lymph Node, Mediastinal	Carcinoma, Bronchiolar Alveol	0/76 (58) 0.1516	0/60 (42) NC	1/60 (37) 0.3895	1/60 (42) 0.4200
	Leukemia, Granulocytic	0/76 (58) 0.2346	0/60 (42) NC	0/60 (37) NC	1/60 (42) 0.4200
	Lymphoma	1/76 (58) 0.1423	0/60 (42) 1.0000	0/60 (37) 1.0000	2/60 (43) 0.3883
Lymph Node, Mesenteric	Leukemia, Granulocytic	1/76 (59) 0.0787	1/60 (42) 0.6612	0/60 (37) 1.0000	3/60 (43) 0.2004
	Lymphoma	5/76 (60) 0.9360	11/60 (49) 0.0359	1/60 (37) 0.9493	2/60 (43) 0.8719
	Sarcoma, Histiocytic	1/76 (58) 1.0000	0/60 (42) 1.0000	0/60 (37) 1.0000	0/60 (42) 1.0000
Lymph Node, Renal	Lymphoma	1/76 (58) 0.7629	1/60 (42) 0.6661	1/60 (37) 0.6298	0/60 (42) 1.0000
Lymph Node, Tracheobronchial	Lymphoma	0/76 (58) 0.6778	1/60 (43) 0.4257	0/60 (37) NC	0/60 (42) NC
Multicentric Neoplasm	Hemangioma	1/76 (58) 0.8934	2/60 (43) 0.3883	0/60 (37) 1.0000	0/60 (42) 1.0000
	Hemangiosarcoma	5/76 (59) 0.5235	6/60 (44) 0.3004	7/60 (39) 0.1392	4/60 (44) 0.5898
	Hemangiosarcoma/Hemangioma	6/76 (59) 0.6809	8/60 (44) 0.1882	7/60 (39) 0.2087	4/60 (44) 0.6935
	Leukemia, Granulocytic	1/76 (59) 0.0787	1/60 (42) 0.6612	0/60 (37) 1.0000	3/60 (43) 0.2004
	Lymphoma	10/76 (62) 0.9396	12/60 (49) 0.1953	3/60 (37) 0.9310	4/60 (44) 0.9133
	Sarcoma, Histiocytic	1/76 (58) 1.0000	0/60 (42) 1.0000	0/60 (37) 1.0000	0/60 (42) 1.0000
Nerve, Sciatic	Lymphoma	0/76 (58) 0.2620	1/60 (43) 0.4257	0/60 (37) NC	1/60 (42) 0.4200

Male Mice Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	20 mg Low (N=60) P - C vs. L	65 mg Med (N=60) P - C vs. M	200 mg High (N=60) P - C vs. H
Nose, Level A	Lymphoma	1/76 (59) 0.5602	2/60 (44) 0.3905	0/60 (37) 1.0000	1/60 (42) 0.6612
Nose, Level B	Lymphoma	1/76 (59) 0.5602	2/60 (44) 0.3905	0/60 (37) 1.0000	1/60 (42) 0.6612
Nose, Level C	Lymphoma	1/76 (59) 0.5602	2/60 (44) 0.3905	0/60 (37) 1.0000	1/60 (42) 0.6612
Nose, Level D	Lymphoma	1/76 (59) 0.5602	2/60 (44) 0.3905	0/60 (37) 1.0000	1/60 (42) 0.6612
Pancreas	Adenoma, Islet Cell	0/76 (58) 0.2346	0/60 (42) NC	0/60 (37) NC	1/60 (42) 0.4200
	Leukemia, Granulocytic	0/76 (58) 0.0129*	0/60 (42) NC	0/60 (37) NC	3/60 (43) 0.0741
	Lymphoma	4/76 (61) 0.9459	7/60 (46) 0.1278	0/60 (37) 1.0000	1/60 (42) 0.9320
Pituitary Gland	Adenoma, Pars Distalis	1/76 (58) 0.8962	1/60 (42) 0.6661	0/60 (37) 1.0000	0/60 (42) 1.0000
	Lymphoma	0/76 (58) 0.2620	1/60 (43) 0.4257	0/60 (37) NC	1/60 (42) 0.4200
Preputial Glands	Leukemia, Granulocytic	1/76 (59) 0.4846	1/60 (42) 0.6612	0/60 (37) 1.0000	1/60 (42) 0.6612
	Lymphoma	0/76 (58) 0.2072	3/60 (44) 0.0771	0/60 (37) NC	2/60 (42) 0.1739
Prostate Gland	Adenoma	0/76 (58) 0.5920	1/60 (42) 0.4200	2/60 (37) 0.1492	0/60 (42) NC
	Leukemia, Granulocytic	0/76 (58) 0.0561	0/60 (42) NC	0/60 (37) NC	2/60 (43) 0.1788
	Lymphoma	1/76 (59) 0.7322	6/60 (46) 0.0266	1/60 (37) 0.6248	1/60 (42) 0.6612
Salivary Gland, Mandibular	Leukemia, Granulocytic	0/76 (58) 0.2346	0/60 (42) NC	0/60 (37) NC	1/60 (42) 0.4200
	Lymphoma	2/76 (59) 0.7069	2/60 (44) 0.5735	0/60 (37) 1.0000	1/60 (42) 0.8049
Salivary Gland, Parotid	Leukemia, Granulocytic	0/76 (58) 0.2346	0/60 (42) NC	0/60 (37) NC	1/60 (42) 0.4200
	Lymphoma	1/76 (58) 0.5645	2/60 (44) 0.3967	0/60 (37) 1.0000	1/60 (42) 0.6661
Salivary Gland, Sublingual	Lymphoma	1/76 (59) 0.4132	0/60 (42) 1.0000	0/60 (37) 1.0000	1/60 (42) 0.6612
Seminal Vesicles	Fibrosarcoma	0/76 (58) 0.2346	0/60 (42) NC	0/60 (37) NC	1/60 (42) 0.4200
	Leukemia, Granulocytic	0/76 (58) 0.2346	0/60 (42) NC	0/60 (37) NC	1/60 (42) 0.4200

Male Mice Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	20 mg Low (N=60) P - C vs. L	65 mg Med (N=60) P - C vs. M	200 mg High (N=60) P - C vs. H
	Lymphoma	0/76 (58) 0.5195	4/60 (45) 0.0337*	0/60 (37) NC	1/60 (42) 0.4200
Skeletal Muscle, Biceps Femoris	Lymphoma	0/76 (58) 0.6778	1/60 (43) 0.4257	0/60 (37) NC	0/60 (42) NC
Skin	Keratoacanthoma	1/76 (59) 0.4132	0/60 (42) 1.0000	0/60 (37) 1.0000	1/60 (42) 0.6612
	Lymphoma	1/76 (59) 0.2039	1/60 (43) 0.6678	0/60 (37) 1.0000	2/60 (42) 0.3737
Skin, Subcutis	Fibrosarcoma	5/76 (60) 0.9248	3/60 (44) 0.7402	1/60 (37) 0.9493	1/60 (42) 0.9628
	Hemangiosarcoma	0/76 (58) 0.2346	0/60 (42) NC	0/60 (37) NC	1/60 (42) 0.4200
	Leukemia, Granulocytic	0/76 (58) 0.2346	0/60 (42) NC	0/60 (37) NC	1/60 (42) 0.4200
	Lymphoma	0/76 (58) 0.7740	3/60 (44) 0.0771	0/60 (37) NC	0/60 (42) NC
	Sarcoma, Undifferentiated	1/76 (59) 1.0000	0/60 (42) 1.0000	0/60 (37) 1.0000	0/60 (42) 1.0000
Small Intestine, Duodenum	Lymphoma	0/76 (58) 0.7407	3/60 (44) 0.0771	1/60 (37) 0.3895	0/60 (42) NC
Small Intestine, Ileum	Lymphoma	0/76 (58) 0.7740	3/60 (44) 0.0771	0/60 (37) NC	0/60 (42) NC
Small Intestine, Jejunum	Lymphoma	0/76 (58) 0.6778	1/60 (43) 0.4257	0/60 (37) NC	0/60 (42) NC
Spleen	Hemangioma	1/76 (58) 0.8962	1/60 (42) 0.6661	0/60 (37) 1.0000	0/60 (42) 1.0000
	Hemangiosarcoma	2/76 (59) 0.4067	2/60 (43) 0.5640	1/60 (37) 0.7725	2/60 (42) 0.5541
	Leukemia, Granulocytic	1/76 (59) 0.0787	1/60 (42) 0.6612	0/60 (37) 1.0000	3/60 (43) 0.2004
	Lymphoma	2/76 (58) 0.6294	10/60 (48) 0.0055*	1/60 (37) 0.7771	3/60 (43) 0.3601
	Sarcoma, Histiocytic	1/76 (58) 1.0000	0/60 (42) 1.0000	0/60 (37) 1.0000	0/60 (42) 1.0000
Stomach, Glandular	Adenoma	0/76 (58) 0.0461	0/60 (42) NC	1/60 (37) 0.3895	2/60 (42) 0.1739
	Leukemia, Granulocytic	0/76 (58) 0.2346	0/60 (42) NC	0/60 (37) NC	1/60 (42) 0.4200
	Lymphoma	0/76 (58) 0.5195	4/60 (45) 0.0337*	0/60 (37) NC	1/60 (42) 0.4200
Stomach, Nonglandular	Lymphoma	0/76 (58) 0.2620	1/60 (43) 0.4257	0/60 (37) NC	1/60 (42) 0.4200

Male Mice Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	20 mg Low (N=60) P - C vs. L	65 mg Med (N=60) P - C vs. M	200 mg High (N=60) P - C vs. H
	Papilloma, Squamous Cell	0/76 (58) 0.4413	0/60 (42) NC	1/60 (37) 0.3895	0/60 (42) NC
Tail	Fibrous Histiocytoma	0/76 (58) 0.4413	0/60 (42) NC	1/60 (37) 0.3895	0/60 (42) NC
Testes	Adenoma, Interstitial Cell	2/76 (59) 0.6784	0/60 (42) 1.0000	4/60 (37) 0.1521	0/60 (42) 1.0000
	Lymphoma	0/76 (58) 0.2620	1/60 (43) 0.4257	0/60 (37) NC	1/60 (42) 0.4200
	Papilloma	1/76 (58) 1.0000	0/60 (42) 1.0000	0/60 (37) 1.0000	0/60 (42) 1.0000
Thymus	Carcinoma, Bronchiolar Alveol	1/76 (59) 1.0000	0/60 (42) 1.0000	0/60 (37) 1.0000	0/60 (42) 1.0000
	Leukemia, Granulocytic	1/76 (59) 0.2116	1/60 (42) 0.6612	0/60 (37) 1.0000	2/60 (43) 0.3822
	Lymphoma	8/76 (62) 0.9205	9/60 (47) 0.2652	2/60 (37) 0.9449	3/60 (43) 0.9059
	Thymoma	1/76 (58) 1.0000	0/60 (42) 1.0000	0/60 (37) 1.0000	0/60 (42) 1.0000
Tongue	Lymphoma	1/76 (59) 0.8950	1/60 (43) 0.6678	0/60 (37) 1.0000	0/60 (42) 1.0000
Ureters	Lymphoma	1/76 (59) 0.8950	1/60 (43) 0.6678	0/60 (37) 1.0000	0/60 (42) 1.0000
Urinary Bladder	Leukemia, Granulocytic	0/76 (58) 0.2346	0/60 (42) NC	0/60 (37) NC	1/60 (42) 0.4200
	Lymphoma	0/76 (58) 0.3677	2/60 (44) 0.1837	0/60 (37) NC	1/60 (42) 0.4200
Zymbal`S Gland	Leukemia, Granulocytic	1/76 (59) 0.4846	1/60 (42) 0.6612	0/60 (37) 1.0000	1/60 (42) 0.6612
	Lymphoma	0/76 (58) 0.1467	2/60 (44) 0.1837	0/60 (37) NC	2/60 (42) 0.1739

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

NC = Not calculable

*: Statistically significant at 0 005 and 0 025 for common and rare tumors, respectively in dose response relationship or 0 01 and 0 05 for common and rare tumors, respectively in pairwise comparisons

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

Female Mice Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	20 mg Low (N=60) P - C vs. L	65 mg Med (N=60) P - C vs. M	200 mg High (N=60) P - C vs. H
Adipose Tissue	Lymphoma	3/76 (56) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
Adrenal Glands	Adenocarcinoma	0/76 (55) 0.4386	0/60 (41) NC	1/60 (37) 0.4022	0/60 (38) NC
	Adenoma, Subcapsular Cell	3/76 (55) 0.5213	2/60 (41) 0.7143	1/60 (37) 0.8779	2/60 (38) 0.6837
	Lymphoma	2/76 (56) 0.6173	2/60 (42) 0.5760	2/60 (38) 0.5341	1/60 (38) 0.7932
	Pheochromocytoma	1/76 (55) 0.7584	1/60 (41) 0.6743	1/60 (37) 0.6452	0/60 (38) 1.0000
Bone Marrow, Femur	Hemangioma	1/76 (55) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
	Leukemia, Granulocytic	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149
	Lymphoma	6/76 (57) 0.8604	5/60 (43) 0.5539	3/60 (39) 0.7923	2/60 (39) 0.9098
	Sarcoma, Histiocytic	1/76 (55) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
Bone Marrow, Sternum	Leukemia, Granulocytic	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149
	Lymphoma	8/76 (57) 0.9249	5/60 (43) 0.7409	4/60 (39) 0.8045	2/60 (39) 0.9651
	Sarcoma, Histiocytic	1/76 (55) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
Bone, Femur	Osteoma	0/76 (55) 0.4386	0/60 (41) NC	1/60 (37) 0.4022	0/60 (38) NC
Bone, Sternum	Lymphoma	0/76 (55) 0.2222	0/60 (41) NC	0/60 (37) NC	1/60 (38) 0.4086
Bone, Tibia	Osteosarcoma	0/76 (55) 0.6784	1/60 (41) 0.4271	0/60 (37) NC	0/60 (38) NC
Brain	Astrocytoma	1/76 (55) 0.6863	0/60 (41) 1.0000	1/60 (37) 0.6452	0/60 (38) 1.0000
	Lymphoma	4/76 (56) 0.9568	2/60 (42) 0.8167	2/60 (38) 0.7818	0/60 (38) 1.0000
Cavity, Abdominal	Leukemia, Granulocytic	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149
	Lymphoma	13/76 (60) 0.8673	6/60 (44) 0.9053	4/60 (39) 0.9630	5/60 (40) 0.9268
	Sarcoma, Histiocytic	3/76 (56) 0.6816	0/60 (41) 1.0000	0/60 (37) 1.0000	1/60 (39) 0.8846

Female Mice Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	20 mg Low (N=60) P - C vs. L	65 mg Med (N=60) P - C vs. M	200 mg High (N=60) P - C vs. H
Cavity, Thoracic	Carcinoma, Bronchiolar Alveol	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149
	Lymphoma	13/76 (59) 0.7436	5/60 (43) 0.9504	5/60 (40) 0.9321	6/60 (40) 0.8720
	Sarcoma, Histiocytic	1/76 (55) 0.8978	1/60 (41) 0.6743	0/60 (37) 1.0000	0/60 (38) 1.0000
Clitoral Glands	Adenoma	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149
	Lymphoma	4/76 (56) 0.8551	3/60 (43) 0.6589	2/60 (38) 0.7818	1/60 (39) 0.9341
Diaphragm	Sarcoma, Histiocytic	1/76 (55) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
Esophagus	Lymphoma	0/76 (55) 0.6802	1/60 (42) 0.4330	0/60 (37) NC	0/60 (38) NC
Eyes	Lymphoma	5/76 (56) 0.9631	0/60 (41) 1.0000	2/60 (38) 0.8568	0/60 (38) 1.0000
Gallbladder	Leukemia, Granulocytic	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149
	Lymphoma	6/76 (57) 0.8012	2/60 (42) 0.9255	1/60 (37) 0.9742	2/60 (38) 0.9038
	Sarcoma, Histiocytic	1/76 (55) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
Galt	Leukemia, Granulocytic	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149
	Lymphoma	5/76 (56) 0.1694	4/60 (43) 0.6079	0/60 (37) 1.0000	6/60 (40) 0.2734
Harderian Glands	Adenocarcinoma	1/76 (55) 0.8978	1/60 (41) 0.6743	0/60 (37) 1.0000	0/60 (38) 1.0000
	Adenoma	6/76 (55) 0.0847	2/60 (42) 0.9326	2/60 (37) 0.9063	7/60 (40) 0.2657
	Lymphoma	8/76 (58) 0.8127	4/60 (43) 0.8413	3/60 (39) 0.8979	3/60 (39) 0.8979
	Sarcoma, Histiocytic	1/76 (55) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
Heart	Hemangiosarcoma	1/76 (55) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
	Lymphoma	13/76 (60) 0.9832	3/60 (42) 0.9909	5/60 (40) 0.9268	2/60 (39) 0.9966
	Sarcoma, Histiocytic	1/76 (55) 0.4031	0/60 (41) 1.0000	0/60 (37) 1.0000	1/60 (39) 0.6603
Kidneys	Leukemia, Granulocytic	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149

Female Mice Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	20 mg Low (N=60) P - C vs. L	65 mg Med (N=60) P - C vs. M	200 mg High (N=60) P - C vs. H
	Lymphoma	14/76 (60) 0.9330	10/60 (45) 0.6416	5/60 (40) 0.9495	5/60 (39) 0.9434
	Sarcoma, Histiocytic	2/76 (56) 0.3205	1/60 (41) 0.8120	1/60 (38) 0.7932	2/60 (39) 0.5450
Lacrimal Glands, Exorbital	Leukemia, Granulocytic	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149
	Lymphoma	15/76 (60) 0.9909	5/60 (43) 0.9766	2/60 (38) 0.9987	3/60 (39) 0.9950
Large Intestine, Cecum	Lymphoma	1/76 (55) 0.8990	1/60 (42) 0.6811	0/60 (37) 1.0000	0/60 (38) 1.0000
Large Intestine, Colon	Lymphoma	1/76 (55) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
Larynx	Lymphoma	6/76 (57) 0.9082	1/60 (42) 0.9822	2/60 (38) 0.9038	1/60 (39) 0.9778
Liver	Adenocarcinoma	0/76 (55) 0.4386	0/60 (41) NC	1/60 (37) 0.4022	0/60 (38) NC
	Adenoma, Hepatocellular	1/76 (55) 0.5064	2/60 (41) 0.3903	1/60 (37) 0.6452	1/60 (38) 0.6529
	Hemangiosarcoma	3/76 (56) 0.7484	1/60 (41) 0.8940	0/60 (37) 1.0000	1/60 (38) 0.8796
	Leukemia, Granulocytic	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149
	Lymphoma	13/76 (60) 0.8529	8/60 (44) 0.7515	8/60 (40) 0.6707	5/60 (39) 0.9189
	Sarcoma, Histiocytic	2/76 (56) 0.4635	3/60 (42) 0.3652	1/60 (38) 0.7932	2/60 (39) 0.5450
Lung	Adenocarcinoma	1/76 (55) 0.6863	0/60 (41) 1.0000	1/60 (37) 0.6452	0/60 (38) 1.0000
	Adenoma, Bronchiolar Alveolar	9/76 (57) 0.2154	6/60 (43) 0.7015	10/60 (40) 0.1930	8/60 (39) 0.3699
	Carcinoma, Bronchiolar Alveol	8/76 (56) 0.2585	4/60 (43) 0.8565	5/60 (38) 0.6722	7/60 (41) 0.4599
	Leukemia, Granulocytic	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149
	Lymphoma	16/76 (61) 0.9647	11/60 (45) 0.6659	6/60 (40) 0.9458	5/60 (39) 0.9713
	Osteosarcoma (Primary Site Un	1/76 (55) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
	Sarcoma, Histiocytic	2/76 (56) 0.4987	0/60 (41) 1.0000	1/60 (38) 0.7932	1/60 (39) 0.7997
Lymph Node, Axillary	Lymphoma	0/76 (55) 0.6802	1/60 (42) 0.4330	0/60 (37) NC	0/60 (38) NC

Female Mice Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	20 mg Low (N=60) P - C vs. L	65 mg Med (N=60) P - C vs. M	200 mg High (N=60) P - C vs. H
Lymph Node, Hepatic	Lymphoma	0/76 (55) 0.5719	1/60 (42) 0.4330	2/60 (38) 0.1643	0/60 (38) NC
Lymph Node, Iliac	Lymphoma	1/76 (55) 0.8937	2/60 (42) 0.3990	0/60 (37) 1.0000	0/60 (38) 1.0000
	Sarcoma, Histiocytic	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149
Lymph Node, Inguinal	Leukemia, Granulocytic	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149
	Lymphoma	1/76 (55) 0.5508	2/60 (42) 0.3990	0/60 (37) 1.0000	1/60 (38) 0.6529
Lymph Node, Mandibular	Leukemia, Granulocytic	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149
	Lymphoma	17/76 (62) 0.9686	10/60 (45) 0.7978	6/60 (40) 0.9588	5/60 (39) 0.9788
	Sarcoma, Histiocytic	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149
Lymph Node, Mediastinal	Lymphoma	5/76 (56) 0.6619	1/60 (42) 0.9692	2/60 (38) 0.8568	2/60 (39) 0.8644
Lymph Node, Mesenteric	Fibrous Histiocytoma	1/76 (55) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
	Leukemia, Granulocytic	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149
	Lymphoma	14/76 (60) 0.6891	10/60 (45) 0.6416	5/60 (39) 0.9434	8/60 (40) 0.7369
	Sarcoma, Histiocytic	1/76 (55) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
Lymph Node, Renal	Leukemia, Granulocytic	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149
	Lymphoma	0/76 (55) 0.6802	1/60 (42) 0.4330	0/60 (37) NC	0/60 (38) NC
Mammary Gland	Adenoacanthoma	0/76 (55) 0.6784	1/60 (41) 0.4271	0/60 (37) NC	0/60 (38) NC
	Adenocarcinoma	3/76 (56) 0.9627	4/60 (42) 0.3422	1/60 (37) 0.8742	0/60 (38) 1.0000
	Adenoma	1/76 (55) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
	Lymphoma	7/76 (57) 0.5098	2/60 (42) 0.9547	2/60 (38) 0.9389	4/60 (39) 0.7320
	Adenoacanthoma/Adenocarcinoma /Adenoma	4/76 (56) 0.9835	5/60 (42) 0.3218	1/60 (37) 0.9265	0/60 (38) 1.0000
Multicentric Neoplasm	Hemangioma	2/76 (55) 0.8781	1/60 (41) 0.8164	1/60 (37) 0.7911	0/60 (38) 1.0000

Female Mice Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	20 mg Low (N=60) P - C vs. L	65 mg Med (N=60) P - C vs. M	200 mg High (N=60) P - C vs. H
	Hemangiosarcoma	5/76 (57) 0.3785	3/60 (42) 0.7430	3/60 (38) 0.6939	4/60 (40) 0.5523
	Hemangioma/Hemangiosarcoma	7/76 (57) 0.5979	4/60 (42) 0.7722	4/60 (38) 0.7171	4/60 (40) 0.7461
	Leukemia, Granulocytic	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149
	Lymphoma	27/76 (63) 0.8448	13/60 (45) 0.9548	12/60 (42) 0.9555	13/60 (42) 0.9252
	Sarcoma, Histiocytic	4/76 (56) 0.7189	4/60 (42) 0.4728	2/60 (38) 0.7818	2/60 (39) 0.7912
Nerve, Sciatic	Lymphoma	4/76 (56) 0.9793	3/60 (42) 0.6469	1/60 (37) 0.9265	0/60 (38) 1.0000
Nose, Level A	Lymphoma	2/76 (56) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
Nose, Level B	Lymphoma	2/76 (56) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
	Schwannoma	0/76 (55) 0.6802	1/60 (42) 0.4330	0/60 (37) NC	0/60 (38) NC
Nose, Level C	Lymphoma	1/76 (56) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
Nose, Level D	Lymphoma	1/76 (56) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
Ovaries	Cystadenoma	1/76 (55) 0.8936	2/60 (41) 0.3903	0/60 (37) 1.0000	0/60 (38) 1.0000
	Fibrous Histiocytoma	1/76 (55) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
	Luteoma	0/76 (55) 0.4386	0/60 (41) NC	1/60 (37) 0.4022	0/60 (38) NC
	Lymphoma	10/76 (59) 0.7484	6/60 (44) 0.7667	2/60 (38) 0.9835	5/60 (40) 0.8125
	Sarcoma, Histiocytic	2/76 (56) 0.5924	1/60 (41) 0.8120	1/60 (38) 0.7932	1/60 (39) 0.7997
	Sex-Cord/Stromal Tumor	1/76 (55) 0.5527	2/60 (41) 0.3903	0/60 (37) 1.0000	1/60 (38) 0.6529
Oviducts	Lymphoma	6/76 (58) 0.1798	3/60 (43) 0.8254	2/60 (38) 0.8994	6/60 (40) 0.3489
	Sarcoma, Histiocytic	2/76 (56) 0.8775	1/60 (41) 0.8120	1/60 (38) 0.7932	0/60 (38) 1.0000
Pancreas	Fibrous Histiocytoma	1/76 (55) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
	Leukemia, Granulocytic	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149

Female Mice Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	20 mg Low (N=60) P - C vs. L	65 mg Med (N=60) P - C vs. M	200 mg High (N=60) P - C vs. H
	Lymphoma	14/76 (60) 0.9471	11/60 (45) 0.5371	5/60 (39) 0.9434	5/60 (40) 0.9495
	Sarcoma, Histiocytic	2/76 (56) 0.5924	1/60 (41) 0.8120	1/60 (38) 0.7932	1/60 (39) 0.7997
Parathyroid Glands	Lymphoma	3/76 (56) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
Pharynx	Lymphoma	6/76 (57) 0.9082	1/60 (42) 0.9822	2/60 (38) 0.9038	1/60 (39) 0.9778
Pituitary Gland	Adenoma, Pars Distalis	3/76 (55) 0.2762	2/60 (42) 0.7238	5/60 (38) 0.1769	3/60 (39) 0.4874
Salivary Gland, Mandibular	Lymphoma	15/76 (60) 0.9909	5/60 (43) 0.9766	2/60 (38) 0.9987	3/60 (39) 0.9950
Salivary Gland, Parotid	Lymphoma	12/76 (59) 0.9074	4/60 (42) 0.9627	2/60 (38) 0.9940	4/60 (40) 0.9539
Salivary Gland, Sublingual	Lymphoma	8/76 (57) 0.9967	1/60 (42) 0.9948	2/60 (38) 0.9619	0/60 (38) 1.0000
Skeletal Muscle, Biceps Femoris	Lymphoma	9/76 (58) 0.9545	3/60 (42) 0.9473	1/60 (37) 0.9948	2/60 (39) 0.9773
Skin	Adenoma, Sebaceous Cell	1/76 (55) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
	Fibrosarcoma	0/76 (55) 0.6784	1/60 (41) 0.4271	0/60 (37) NC	0/60 (38) NC
	Hair Follicle Tumor	0/76 (55) 0.1364	2/60 (42) 0.1849	0/60 (37) NC	2/60 (38) 0.1643
	Lymphoma	7/76 (57) 0.9636	3/60 (43) 0.8890	2/60 (38) 0.9389	1/60 (39) 0.9875
Skin, Subcutis	Chondrosarcoma	1/76 (55) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
	Fibrosarcoma	2/76 (55) 0.6571	2/60 (41) 0.5735	1/60 (37) 0.7911	1/60 (38) 0.7978
	Fibrous Histiocytoma	2/76 (56) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
	Lymphoma	3/76 (57) 0.9609	4/60 (43) 0.3453	1/60 (37) 0.8705	0/60 (38) 1.0000
Small Intestine, Duodenum	Adenoma	0/76 (55) 0.6784	1/60 (41) 0.4271	0/60 (37) NC	0/60 (38) NC
	Lymphoma	1/76 (55) 0.6171	3/60 (43) 0.2221	0/60 (37) 1.0000	1/60 (39) 0.6603
Spinal Cord, Cervical	Lymphoma	1/76 (55) 0.6206	0/60 (41) 1.0000	2/60 (38) 0.3630	0/60 (38) 1.0000
Spinal Cord, Lumbar	Lymphoma	4/76 (56) 0.9260	0/60 (41) 1.0000	2/60 (38) 0.7818	0/60 (38) 1.0000

Female Mice Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	20 mg Low (N=60) P - C vs. L	65 mg Med (N=60) P - C vs. M	200 mg High (N=60) P - C vs. H
Spinal Cord, Thoracic	Lymphoma	3/76 (56) 0.8614	0/60 (41) 1.0000	2/60 (38) 0.6761	0/60 (38) 1.0000
Spleen	Hemangioma	0/76 (55) 0.4386	0/60 (41) NC	1/60 (37) 0.4022	0/60 (38) NC
	Hemangiosarcoma	0/76 (55) 0.6784	1/60 (41) 0.4271	0/60 (37) NC	0/60 (38) NC
	Leukemia, Granulocytic	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149
	Lymphoma	13/76 (59) 0.6930	10/60 (45) 0.5828	9/60 (40) 0.5724	7/60 (39) 0.7707
Stomach, Glandular	Lymphoma	1/76 (55) 0.4091	1/60 (42) 0.6811	2/60 (37) 0.3536	1/60 (39) 0.6603
Stomach, Nonglandular	Papilloma, Squamous Cell	0/76 (55) 0.2523	1/60 (41) 0.4271	0/60 (37) NC	1/60 (38) 0.4086
Thymus	Leukemia, Granulocytic	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149
	Lymphoma	24/76 (62) 0.7444	13/60 (45) 0.8967	11/60 (41) 0.9287	13/60 (42) 0.8460
	Sarcoma, Histiocytic	1/76 (55) 0.4031	0/60 (41) 1.0000	0/60 (37) 1.0000	1/60 (39) 0.6603
	Thymoma	0/76 (55) 0.4386	0/60 (41) NC	1/60 (37) 0.4022	0/60 (38) NC
Thyroid Gland	Adenoma, C-Cell	1/76 (55) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
	Adenoma, Follicular Cell	2/76 (55) 0.9680	1/60 (41) 0.8164	0/60 (37) 1.0000	0/60 (38) 1.0000
	Lymphoma	8/76 (58) 0.9965	1/60 (42) 0.9944	2/60 (38) 0.9595	0/60 (38) 1.0000
Tongue	Lymphoma	5/76 (56) 0.9878	1/60 (42) 0.9692	1/60 (38) 0.9601	0/60 (38) 1.0000
Tooth/Teeth	Lymphoma	1/76 (56) 1.0000	0/60 (41) 1.0000	0/60 (37) 1.0000	0/60 (38) 1.0000
Trachea	Lymphoma	1/76 (55) 0.7596	1/60 (42) 0.6811	1/60 (38) 0.6529	0/60 (38) 1.0000
Urinary Bladder	Leukemia, Granulocytic	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149
	Lymphoma	11/76 (59) 0.7566	5/60 (43) 0.8935	4/60 (39) 0.9245	5/60 (40) 0.8634
	Sarcoma, Histiocytic	1/76 (55) 0.6899	0/60 (41) 1.0000	1/60 (38) 0.6529	0/60 (38) 1.0000
Uterus with Cervix	Hemangioma	1/76 (55) 0.8978	1/60 (41) 0.6743	0/60 (37) 1.0000	0/60 (38) 1.0000

Female Mice Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=76) P - Trend	20 mg Low (N=60) P - C vs. L	65 mg Med (N=60) P - C vs. M	200 mg High (N=60) P - C vs. H
	Hemangiosarcoma	1/76 (55) 0.1295	2/60 (42) 0.3990	3/60 (38) 0.1842	3/60 (40) 0.1994
	Leiomyoma	2/76 (55) 0.8278	1/60 (41) 0.8164	2/60 (37) 0.5305	0/60 (38) 1.0000
	Leiomyosarcoma	0/76 (55) 0.6784	1/60 (41) 0.4271	0/60 (37) NC	0/60 (38) NC
	Leiomyoma/Leiomyosarcoma	2/76 (55) 0.8667	2/60 (41) 0.5735	2/60 (37) 0.5305	0/60 (38) 1.0000
	Lymphoma	13/76 (60) 0.8481	5/60 (44) 0.9515	3/60 (39) 0.9867	5/60 (39) 0.9189
	Polyp, Stromal	2/76 (56) 0.1020	0/60 (41) 1.0000	5/60 (38) 0.0919	3/60 (39) 0.3323
	Sarcoma, Endometrial Stromal	0/76 (55) 0.1602	0/60 (41) NC	2/60 (38) 0.1643	1/60 (39) 0.4149
	Sarcoma, Histiocytic	3/76 (56) 0.5679	3/60 (42) 0.5163	2/60 (38) 0.6761	2/60 (39) 0.6868
Vagina	Lymphoma	8/76 (59) 0.8751	1/60 (42) 0.9940	2/60 (38) 0.9570	2/60 (39) 0.9605
	Sarcoma, Endometrial Stromal	0/76 (55) 0.2267	0/60 (41) NC	0/60 (37) NC	1/60 (39) 0.4149
Vagina/uterus	Sarcoma Endometrial Stromal	0/76 (55) 0.1602	0/60 (41) NC	2/60 (38) 0.1643	1/60 (39) 0.4149
Zymbal`S Gland	Lymphoma	3/76 (57) 0.7669	2/60 (42) 0.7095	1/60 (37) 0.8705	1/60 (39) 0.8811

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

NC = Not calculable

*: Statistically significant at 0 005 and 0 025 for common and rare tumors, respectively in dose response relationship or 0 01 and 0 05 for common and rare tumors, respectively in pairwise comparisons

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

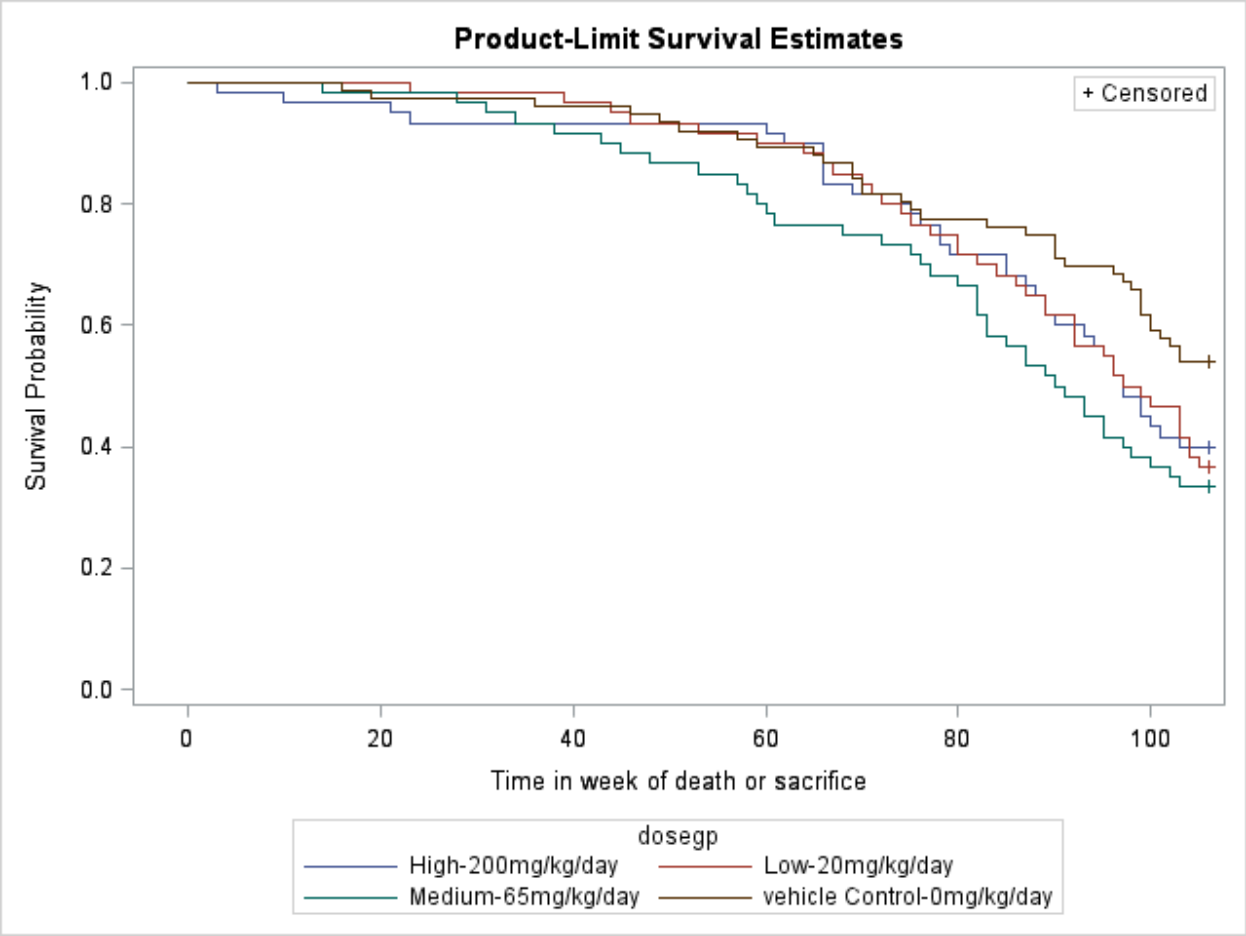
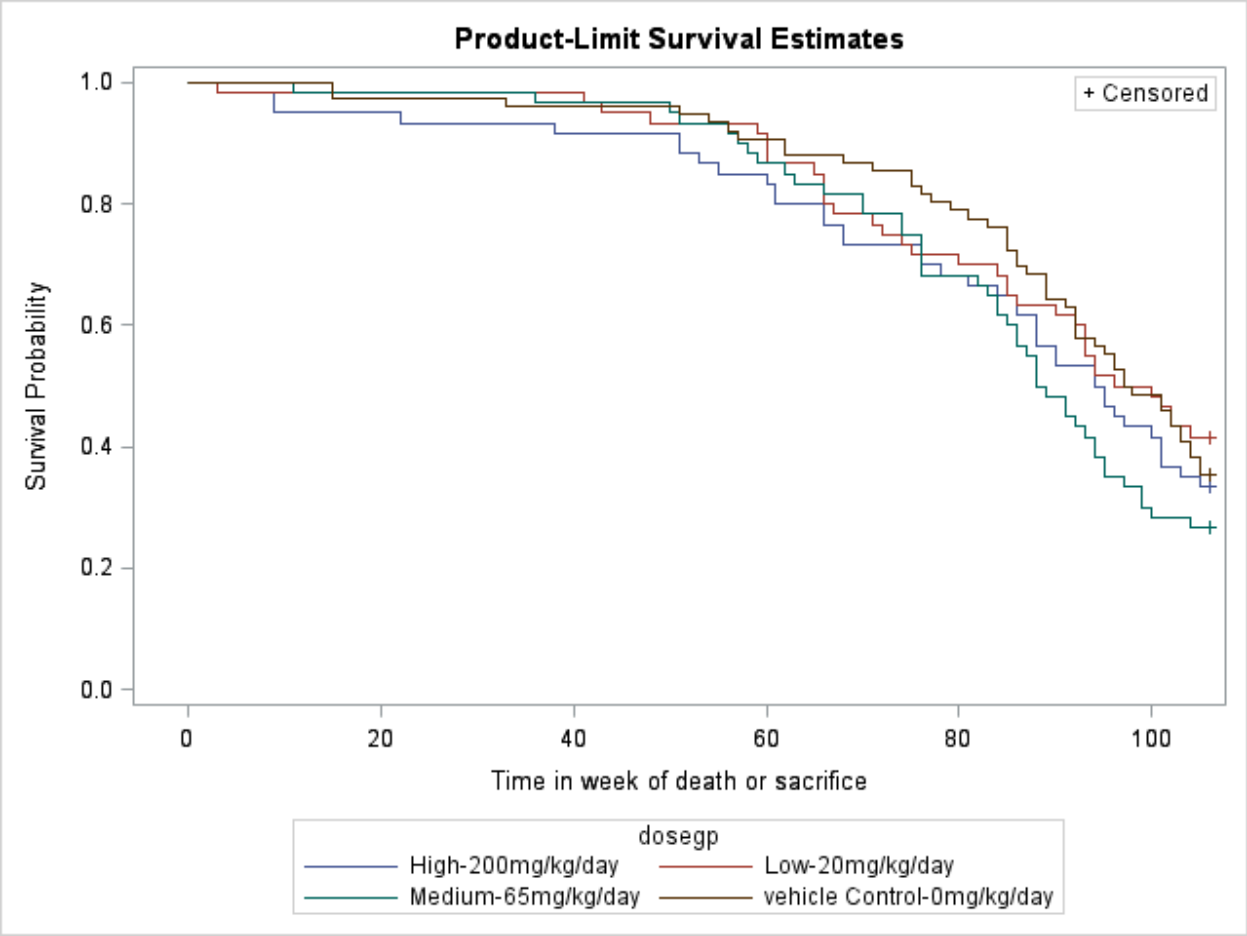


Figure 2B: Kaplan-Meier Survival Curves for
Female Mice



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/s/

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06/26/2018
Concur with review.