

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206940Orig1s000**

**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: 206940/000  
Drug Name: (b) (4) (eluxadoline) Tablets  
Indication: Treatment of adults with diarrhea predominant irritable bowel syndrome (IBS-d)  
Applicant: Furiex Pharmaceuticals  
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## 1. EXECUTIVE SUMMARY

The sponsor submitted two phase 3 studies to demonstrate the efficacy of eluxadoline as a treatment for abdominal pain and diarrhea in adult patients with diarrhea predominant irritable bowel syndrome (IBS-d). For both studies, the 75 mg and 100 mg doses of eluxadoline showed a statistically significant difference in the primary endpoint, composite response, compared with placebo at 12 weeks.

Components of the primary endpoint, abdominal pain response and stool consistency response were specified as secondary endpoints. For both studies and both doses, only stool consistency response indicated a significant difference compared to placebo at 12 weeks; no statistical differences were shown for abdominal pain response. As the sponsor did not pre-specify a multiplicity adjustment procedure for type I error control for secondary endpoints, formal hypothesis testing would not be appropriate. However, the pain and stool consistency responder results and/or scores may be clinically informative and can augment labeling provided these results are presented with descriptive statistics only.

To further assess eluxadoline's effect on reducing patients' abdominal pain, the statistical reviewer performed a mixed effects model for repeated measures (MMRM) analysis on patients' pain scores directly. Based on this exploratory analysis, both doses of eluxadoline appeared to show treatment benefit in treating patients' diarrhea and in reducing their abdominal pain.

## 2. INTRODUCTION

### 2.1 OVERVIEW

The sponsor submitted this NDA for the study drug, eluxadoline (also known as JNJ-27018966), with a proposed indication for the treatment of abdominal pain and diarrhea in adult patients with diarrhea predominant irritable bowel syndrome (IBS-d). Eluxadoline is claimed to be a locally active, mixed mu opioid receptor ( $\mu$ OR) agonist/delta opioid receptor ( $\delta$ OR) antagonist with low oral bioavailability.

Pharmacologic treatment options for patients with IBS-d are limited. Presently there are no unrestricted prescription products on the market that are indicated to provide relief to patients who are suffering from IBS-d. There are approved drugs in treating IBS-d, such as alosetron and loperamide; however alosetron was approved in women with severe symptoms refractory to other therapies and loperamide allegedly showed limited effectiveness in treating abdominal pain and global symptoms of IBS-d and both drugs may be associated with constipation, which can pose a serious problem for IBS-d patients. Therefore, the sponsor claims that a new agent is needed with favorable safety and tolerability profiles that is effective in providing sustained relief of abdominal discomfort, abdominal pain, and bowel urgency associated with IBS-d.

The sponsor's clinical program for eluxadoline comprises a total of 11 phase 1 clinical trials, one phase 2 dose-ranging clinical trial (IBS-2001) and two phase 3 clinical trials (IBS-3001 and IBS-3002).

On March 16, 2010, the sponsor had an End-of-Phase 1 (EOP1) meeting with the FDA to discuss the clinical development program and the proposed phase 2 proof-of-concept (POC) study. Before the phase 3 trials were initiated, an End of Phase 2 (EOP2) meeting was held to reach the agreement on the overall phase 3 study design including primary endpoint, responder definitions and associated analyses, and the overall safety exposures on September 27, 2011.

At the pre-NDA meeting held on April 22, 2014, FDA confirmed the appropriateness of the sponsor's strategy to submit the NDA with the two completed phase 3 studies but all available safety data from the ongoing Study IBS-3001 then had January 24, 2014 as cut-off date. It was agreed that all remaining safety data from Study IBS-3001 be provided as a major safety amendment to the NDA via an updated integrated summary of safety (ISS) and associated statistical output no later than 120 days after the NDA submission.

The efficacy of eluxadoline for the treatment of IBS-d was initially evaluated in the phase 2 study (IBS-2001), which contained four different doses (5 mg twice daily [BID], 25 mg BID, 100 mg BID, and 200 mg BID) and it was titled "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-27018966 in Treatment of Patients with Irritable Bowel Syndrome with Diarrhea". The two phase 3 studies were both titled as "A Randomized, Double-Blind, Placebo-Controlled, phase 3 Study to Evaluate the Efficacy, Safety and Tolerability of JNJ-27018966 in the Treatment of Patients with Diarrhea-Predominant Irritable Bowel Syndrome".

The primary responder definition of the phase 2 study IBS-2001 data was based the Bristol Stool Scale (BSS) different from FDA's recommended overall responder definition based on both stool consistency and abdominal pain. So the dose selected for the phase 3 studies was based on the sponsor's post hoc analysis with the FDA recommended endpoint. The sponsor concluded that the study demonstrated that patients with IBS-d who were treated with 100 mg BID and 200 mg BID eluxadoline were twice as likely as placebo patients to achieve study response (simultaneous improvement in pain and stool consistency). The sponsor further claimed that even though the 200-mg BID dose also demonstrated statistically significant superiority over placebo from multiple analyses, such as those for the percentage of patients reporting adequate relief and BSS response rate, increasing the dose did not improve the post hoc response rates over the 100-mg BID dose and it resulted in more adverse events (AEs) at 200 mg BID, particularly gastrointestinal AEs. Therefore, the sponsor decided to choose 100 mg BID as the top dose from the phase 2 study to carry into the phase 3 program; although the efficacy of 75 mg BID was not specifically explored in the phase 2 study, this dose was included as one of the therapeutic arms in the phase 3 studies. Of note, for this phase 2 study although four doses were included, due to its exploratory nature, no alpha adjustment were made for adjusting multiple dose comparisons and the missing data were simply imputed by the baseline observation carried forward (BOCF) method.

For both IBS-3001 and IBS-3002 studies, the primary endpoint for FDA approval was the proportion of composite responders over the interval from Weeks 1-12 while for the EU approval was the proportion of composite responders over the interval from Weeks 1-26. A patient was counted as a composite responder if he/she met the daily response criteria for at least 50% of the days with diary entries during the interval of interest (Weeks 1-12 or Weeks 1-26). The primary analysis assessed treatment effect via pair-wise comparisons using a two-sided Cochran-Mantel-Haenszel (CMH) test for eluxadoline (75 mg BID or 100 mg BID) versus placebo. The proportions of composite responders in the eluxadoline groups (75 mg BID and 100 mg BID) were compared to the proportion of composite responders in the placebo group. With the significant findings for Studies IBS-3001 and IBS-3002, the sponsor concludes that the effectiveness of eluxadoline has been demonstrated.

## **2.2 DATA SOURCES**

The original NDA submission including clinical study reports and data sets are stored in [\\CDSESUB1\evsprod\NDA206940\0000](#). During the review cycle, the statistical reviewer encountered some difficulty in duplicating the sponsor's final analysis results in terms of the study raw data and thus an information request was sent to the sponsor for clarification. The sponsor's response is stored in [\\CDSESUB1\evsprod\NDA206940\0009](#).

For both studies, there were more than 50 patients who failed to meet the inclusion and exclusion criteria but were randomized. The studies also had many patients with protocol violations but no per-protocol analyses were performed and submitted. Therefore, the sponsor was asked to perform the re-analysis for the primary endpoint by removing those patients. Their re-analysis results are included in [\\CDSESUB1\evsprod\NDA206940\0013](#) and [\\CDSESUB1\evsprod\NDA206940\0019](#).

## **3. STATISTICAL EVALUATION**

### **3.1 DATA AND ANALYSIS QUALITY**

The statistical reviewer has successfully confirmed the sponsor's analysis results from the raw data submitted in this application. The efficacy data included in this application were carefully examined and the quality was determined to be acceptable.

### **3.2 EVALUATION OF EFFICACY**

#### **3.2.1 Description of Studies 3001 and 3002**

Studies 3001 and 3002 have the same design, but different durations after the double-blind period of 26 weeks. They were both titled as "A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ 27018966 in the Treatment of Patients with Diarrhea-Predominant Irritable Bowel Syndrome (IBS-d)".

Study 3001 was conducted from May 29, 2012 to July 25, 2014 but Study 302 from May 29, 2012 to January 09, 2014. Both studies were conducted in the US, Canada, and the UK, where Study 3001 included 295 sites and Study 3002 included 261 sites.

### **3.2.1.1 Study Design and Objectives**

Study 3001 consisted of a pretreatment period (consisting of a prescreening period up to 1-week and a screening period up to 3-weeks), a 52-week double-blind treatment period, and a 2-week post-treatment follow-up period. Efficacy assessments for the determination of clinical response were conducted through the first 26 weeks of double-blind treatment.

Study 3002, however, consisted of a pretreatment period (consisting of a prescreening period up to 1-week and a screening period up to 3-weeks), a 26-week double-blind treatment period, and a 4-week single-blinded withdrawal period, at which time patients received single-blinded placebo. The total planned duration of Study 3002, including the pretreatment period, was not more than 34 weeks for each patient.

For both studies, approximately 1125 patients were planned for randomization (in a 1:1:1 ratio) to 1 of 3 treatment groups as follows, with the overall randomization stratified by country (i.e., US, Canada, and UK);

- Group 1: eluxadoline oral tablets at a dose of 75 mg BID
- Group 2: eluxadoline oral tablets at a dose of 100 mg BID
- Group 3: matching placebo oral tablets BID

After prescreening procedures were performed, eligible patients entered a screening period of up to 3 weeks. Patients who met the study entry were randomized into the double-blind treatment period. Following randomization, patients returned to the clinic at Weeks 2, 4, 8, 12, 18, 26, 36, 44, and 52 (Note: Weeks 36, 44 and 52 are for Study 3001 only.). A post-treatment follow-up visit occurred at Week 54 for Study 3001 but at Week 30 for Study 3002 for patients who completed the study. Patients who discontinued from the study drug before their follow-up visit were instructed to return to the study center to complete the early withdrawal assessments as soon as possible after stopping the study drug.

The primary objectives of both studies were the following:

- To evaluate the clinical response of patients with IBS-d to eluxadoline, relative to placebo
- To evaluate the overall safety and tolerability of eluxadoline in the treatment of IBS-d

The secondary objective of this study was to further evaluate the treatment effect of eluxadoline relative to placebo based on patient reports of IBS-d symptoms (abdominal pain, abdominal discomfort, abdominal bloating, stool consistency, global symptom scores, adequate relief), bowel functioning and quality of life.

### 3.2.1.2 Efficacy Endpoints and Analyses

While the FDA and EMA now both recommend using a primary efficacy endpoint based upon a composite of improvement in worst abdominal pain and stool consistency, the two regulatory agencies differed in the suggested length of treatment time over which to evaluate the primary efficacy endpoint. For the FDA, this period is 12 weeks while the EMA evaluation period is defined as 26 weeks.

#### **Primary endpoint**

The primary efficacy endpoint was the composite responder proportion evaluated over the initial 12 weeks of double-blind treatment for the FDA and over 26 weeks of treatment for the EMA. A patient was counted as a composite responder if he or she met the daily response criteria for at least 50% of the days with diary entries during the interval of interest (Weeks 1-12 or Weeks 1-26). A patient must have met both of the following criteria on a given day to be a daily responder:

- **Daily pain response:** worst abdominal pain scores in the past 24 hours improved by  $\geq 30\%$  compared to baseline (average of daily worst abdominal pain the week prior to randomization).
- **Daily stool consistency response:** Bristol Stool Scale (BSS) score  $< 5$  (i.e., score of 1, 2, 3, or 4) or the absence of a bowel movement if accompanied by  $\geq 30\%$  improvement in worst abdominal pain compared to baseline pain.

To be eligible to be a composite responder, a patient must have had a minimum of 60 days of diary entries over the 12-week interval and a minimum of 110 days of diary entries over the 26-week interval. Any patient with fewer than the minimum number of days of diary entries was considered a non-responder for that interval, including patients in the intent to treat (ITT) analysis who had not yet recorded post-baseline diary data.

#### **Secondary endpoints**

Secondary efficacy endpoints include the following:

- **Pain responders:** defined as those patients who met the daily pain response criteria (i.e., the worst abdominal pain score in the past 24 hours improved by  $\geq 30\%$  compared to baseline) for at least 50% of days with diary entries during each interval over the 12-week interval (Weeks 1-12), 26-week interval (Weeks 1-26), and each 4-week interval (Weeks 1-4, 5-8, 9-12, 13-16, 17-20 and 21-24).
- **Stool consistency responders:** defined as those patients who met the daily stool consistency response criteria (i.e., BSS score  $< 5$  [i.e., score of 1, 2, 3, or 4]) or the absence of a bowel movement if accompanied by  $\geq 30\%$  improvement in worst abdominal pain compared to baseline pain) for at least 50% of days with diary entries during each interval for the 12-week interval (Weeks 1-12), 26-

week interval (Weeks 1-26), and each 4-week interval (Weeks 1-4, 5-8, 9-12, 13-16, 17-20, and 21-24).

- **IBS-d global symptom responders**: defined as those patients who met the daily IBS-d global symptom response criteria (i.e., IBS-d global symptom score of 0 [none] or 1 [mild]; or a daily IBS-d global symptom score improved by  $\geq 2.0$  compared to the baseline average) for at least 50% of days with diary entries during each interval over the 12-week interval (Weeks 1-12), 26-week interval (Weeks 1-26), and each 4-week interval (Weeks 1-4, 5-8, 9-12, 13-16, 17-20 and 21-24).

For the above listed responder endpoints, a patient must have had a minimum of 20 days of diary entries over any 4-week interval, a minimum of 60 days of diary entries over the 12-week interval, and a minimum of 110 days of diary entries over the 26-week interval to be a responder.

Other secondary efficacy endpoints include the following. Due to the exploratory nature of these endpoints, including the global symptom responder endpoint listed above, this review does not include nor discuss the sponsor's findings.

- **IBS-QoL responders**: defined as patients who achieved at least a 14-point improvement in IBS-QoL total score from baseline to the applicable visit. The “lowest possible score” and “possible raw score change” were based on the questions answered rather than all 34 questions.
- **IBS-AR responders**: defined as those patients with a weekly response of “Yes” to adequate relief of their IBS symptoms for at least 50% of the total weeks during the interval over the intervals from Weeks 1-12 and Weeks 1-26. A patient must have had a positive response on  $\geq 6$  weeks for the 12-week interval and  $\geq 13$  weeks for the 26-week interval, regardless of diary compliance, to be a responder. If a patient did not respond to the question for that week it was considered missing, no imputation was applied.
- Discomfort: changes from baseline in daily abdominal discomfort scores
- Bloating: changes from baseline in daily abdominal bloating scores
- Frequency: number of bowel movements per day Incontinence: number of bowel incontinence episodes per day and number of incontinence-free days
- Urgency: number of urgency episodes per day
- IBS-QoL: total score and scores compared to baseline

**Reviewer's Note:** The sponsor also conducted sensitivity analysis for the primary endpoint and important secondary endpoints, which include patients' daily pain score and daily stool consistency scores directly. In particular, these analyses were based on longitudinal models and are mainly for the purpose of exploration. Since both studies' results for the abdominal pain response are not significant, the sponsor's longitudinal analysis results for the pain and stool consistency scores are displayed in this review.

The sponsor's analysis results for the pain scores were compared with the statistical reviewer's using the MMRM analysis.

### **Analysis Populations**

The ITT Analysis Set was defined as all patients randomly assigned to treatment and is the primary set for all efficacy analysis. The MITT Analysis Set was defined as all patients randomly assigned to treatment who received at least one dose of study drug and who had a baseline and at least one post-randomization diary entry, which was used to assess durability based on analyses over the 4-week intervals for multiple responder definitions (i.e., composite responder, pain responder, stool consistency responder, and IBS-d global symptom responder).

### **Primary Analysis**

The primary analysis was to evaluate treatment effect for the ITT Analysis Set based on composite responders. Treatment effect was assessed via pair-wise comparison using a two-sided Cochran- Mantel-Haenszel (CMH) test for active treatment (eluxadoline 75 mg BID or 100 mg BID) versus placebo. The primary (alternative) hypothesis was that the composite response rate for the active treatment group ( $\pi_{\text{Active}}$ ) was greater than that of the placebo group ( $\pi_{\text{placebo}}$ ). Because there were two active groups compared to placebo, the Bonferroni adjustment was used to preserve the family-wise type I error rate.

**Reviewer's note:** For secondary endpoints, the sponsor did not clearly define a multiplicity adjustment procedure that would control the study-wise type I error rate. Consequently, formal testing for statistical significance is not appropriate. However, the pain and stool consistency responder results and/or scores may be clinically informative and can augment labeling provided these are presented in descriptive fashion only (b) (4)

### **Sensitivity analyses**

To assess the robustness of the efficacy findings, sensitivity analyses that the sponsor conducted included the worst-case scenario (included missing data), a weekly composite responder defined by two methods, described below, and for a subset of patients who did not have any dose interruptions due to possible or confirmed constipation.

#### **Method 1:**

Composite responder = a patient who met the weekly pain response AND the weekly stool consistency response criteria for more than 50% of weeks (i.e., 6 or more weeks) over the interval from Weeks 1-12

Weekly pain response = at least a 30% improvement in the weekly average of worst abdominal pain scores compared to baseline abdominal pain

Weekly stool consistency response = a weekly average BSS of 5 or less, if the baseline average BSS was 6 or greater; or a reduction in weekly average BSS scores of at least 1 point for those with a baseline average BSS greater than or equal to 5.5 and less than 6

Additionally, a patient must have had no more than 2 missed reporting days over the past 7 days for an individual week to qualify as a responder.

**Method 2:**

Composite responder = a patient who met the weekly pain response AND the weekly stool consistency response criteria for more than 50% of weeks (i.e., 6 or more weeks) over the interval from Weeks 1-12

Weekly pain response = at least a 30% improvement in the weekly average of worst abdominal pain scores compared to baseline abdominal pain

Weekly stool consistency response = at least a 50% decrease in the number of days in a week where BSS was 6 or greater as compared to the number of days in the baseline week (Week -1) where BSS is 6 or greater

Additionally, a patient must have had no more than 2 missed reporting days over the past 7 days for an individual week to qualify as a responder.

**Reviewer's Note:** The methods 1 and 2 are different in terms of patients' weekly stool consistency response.

### 3.2.2 Patient Disposition and Demographic and Baseline Characteristics

#### 3.2.2.1 Study 3001

A total of 3825 patients were prescreened and entered into the interactive voice response system/interactive web response system (IVRS/IWRS). Table 3.1 presents the disposition of patients for Study 3001. Overall, 1282 patients were randomized or received at least one dose of study drug and comprised the Enrolled Set. One patient (#057/0001) received eluxadoline but was never randomized

Table 3.1 Disposition of Patients for Study 3001 (Based on ITT)

<i>Reported are N (%)</i>	<i>Eluxadoline 75 mg BID (N=429)</i>	<i>Eluxadoline 100 mg BID (N=426)</i>	<i>Placebo BID (N=427)</i>	<i>Total (N=1282)</i>
Total Number of Patients				
Randomized	428 (99.8)	426 (100.0)	427 (100.0)	1281 (99.9)
ITT Analysis Set	427 (99.5)	426 (100.0)	427 (100.0)	1280 (99.8)
Modified ITT Analysis Set	422 (98.4)	421 (98.8)	424 (99.3)	1276 (99.5)
Attended Week 12 Visit	341 (79.5)	330 (77.5)	342 (80.1)	1013 (79.0)
Attended Week 26 Visit	289 (67.4)	291 (68.3)	289 (67.7)	869 (67.8)
Ongoing*	183 (42.7)	193 (45.3)	186 (43.6)	562 (43.8)
Complete Study	91 (21.2)	79 (18.5)	94 (22.0)	264 (20.6)
Discontinued Study	155 (36.1)	154 (36.2)	147 (34.4)	456 (35.6)
IVRS Misallocation	53 (12.4)	0	0	53 (4.1)
Reason of Discontinuation				
Voluntarily Withdrew	85 (19.8)	75 (17.6)	91 (21.3)	251 (19.6)
Adverse Event or SAE	32 (7.5)	41 (9.6)	15 (3.5)	88 (6.9)
Lost to follow-up	24 (5.6)	20 (4.7)	12 (2.8)	56 (4.4)
Physician Decision: Other	8 (1.9)	11 (2.6)	15 (3.5)	34 (2.7)
Physician Decision: Lack of Efficacy	2 (0.5)	3 (0.7)	7 (1.6)	12 (0.9)
Protocol Violation	3 (0.7)	4 (0.9)	4 (0.9)	11 (0.9)
Sponsor Decision	1 (0.2)	0 (0)	3 (0.7)	4 (0.3)

\*As of the data cut for the interim safety analysis (24 January 2014)

Source: Tables 14.1.1 & 11-1 of CSR

Table 3.2 summarizes patient demographic characteristics for the Enrolled Set. As shown in the table, demographic characteristics were similar across treatment groups, except for the proportion of patients who were  $\geq 65$  years of age, which was lowest in the 75 mg group (6.8%) and highest in the placebo group (11.9%). The overall mean age of patients were 44.9 years (median: 45 years) and ranged from 18 to 80 years. Most patients in the study were white (86.7%) and 65.4% of patients were female. Mean overall BMI was 30.85 kg/m<sup>2</sup> and was similar across treatment groups.

Table 3.2 Patient Demographic Characteristics for Study 3001 (Based on Enrolled Set)

	<i>Eluxadoline 75 mg BID (N=429)</i>	<i>Eluxadoline 100 mg BID (N=426)</i>	<i>Placebo BID (N=427)</i>	<i>Total (N=1282)</i>
Age (years)				
Mean (SD)	44.5 (13.18)	44.4 (13.91)	45.8 (14.10)	44.9 (13.74)
Median	44.0	45.0	45.0	45.0
Min, Max	18, 80	18, 79	18, 79	18, 80
Age categories (years), n (%)				
18-40	173 (40.3)	166 (39.0)	159 (37.2)	498 (38.8)
41-64	227 (52.9)	225 (52.8)	217 (50.8)	669 (52.2)
$\geq 65$	29 (6.8)	35 (8.2)	51 (11.9)	115 (9.0)
Gender, n (%)				
Male	151 (35.2)	143 (33.6)	150 (35.1)	444 (34.6)
Female	278 (64.8)	283 (66.4)	277 (64.9)	838 (65.4)
Race				
White	374 (87.2)	368 (86.4)	370 (86.7)	1112 (86.7)
Black	46 (10.7)	48 (11.3)	46 (10.8)	140 (10.9)
Asian	3 (0.7)	3 (0.7)	4 (0.9)	10 (0.8)
American Indian or Alaska Native	1 (0.2)	2 (0.5)	1 (0.2)	4 (0.3)
Native Hawaiian or Other Pacific Islander	0	1 (0.2)	0	1 (0.1)
Other	5 (1.2)	4 (0.9)	6 (1.4)	15 (1.2)
Ethnicity, n (%)				
Hispanic or Latino	119 (27.7)	117 (27.5)	125 (29.3)	361 (28.2)
Not Hispanic or Latino	310 (72.3)	309 (72.5)	302 (70.7)	921 (71.8)
BMI (kg/m <sup>2</sup> )				
N	428	424	425	1277
Mean (SD)	30.7 (7.4)	31.22 (7.9)	30.63 (7.3)	30.85 (7.5)
Median	29.45	30.30	29.80	29.80
Min, Max	17.8, 54.6	16.7, 60.9	16.9, 72.3	16.7, 72.3

Source: Table 11-2 of CSR

Table 3.3 presents patients' baseline IBS characteristics for the Enrolled Set. According to the table, overall, patients' baseline IBS symptoms were similar across treatment groups. Patients in the Enrolled Set had an average daily worst abdominal pain score of 6.19 and an average daily BSS of 6.27 (scale from 1-7, where 1 is hard stool and 7 is watery diarrhea). The average IBS-d global symptom score was 2.85 (scale from 0-4, where 0 = no symptoms and 4 = very severe symptoms).

Table 3.3 Baseline IBS Characteristics For Study 3001 (Based on Enrolled Set)

<i>Mean (SD)</i>	<i>Eluxadoline 75 mg BID (N=428)</i>	<i>Eluxadoline 100 mg BID (N=426)</i>	<i>Placebo BID (N=427)</i>	<i>Total (N=1281)</i>
Worst abdominal pain	6.13 (1.55)	6.19 (1.51)	6.24 (1.57)	6.19 (1.54)
Abdominal bloating* (*Note Ns are different)	5.89 (2.02) N=364	5.83 (2.1) N=359	6.08 (2.02) N=351	5.93 (2.05) N=1074
Abdominal discomfort	6.33 (1.52)	6.33 (1.52)	6.41 (1.55)	6.36 (1.53)
Stool consistency (BSS)	6.25 (0.41)	6.28 (0.42)	6.26 (0.41)	6.27 (0.42)
Bowel movement frequency	4.85 (2.70)	4.96 (3.0)	5.0 (2.74)	4.93 (2.8)
Urgency episodes	3.48 (2.22)	3.47 (2.11)	3.67 (2.71)	3.54 (2.36)
Incontinence episodes	1.35 (2.02)	1.28 (1.86)	1.47 (2.18)	1.37 (2.02)
Incontinence free days	3.73 (2.92)	3.87 (2.88)	3.64 (2.95)	3.75 (2.92)
IBS-d global symptoms score	2.80 (0.55)	2.87 (0.54)	2.88 (0.55)	2.85 (0.55)

Source: Table 11-3 of CSR

### 3.2.2.2 Study 3002

There were total 2521 patients who entered into the screening phase of the study. Of these, Only 2385 patients were screened at sites that randomized at least one patient but only 1146 patients were randomized in this study. One patient was unintentionally randomized twice and was assigned two different patient identification numbers (502/0004 and 545/0001) due to the patient trying to participate at more than on study center at once. Table 3.4 summarizes disposition for all patients enrolled in the study. As seen from the table, of the 1146 patients randomized in the study, most (79.3%) attended the Week 12 visit, 70.5% Attended the Week 26 visit, and 68.7 completed the study (i.e., through Week 30). In addition, the discontinuation rate was slightly higher in the 75-mg (34.4%) and 100-mg (31.1%) treatment groups compared with placebo (28.5%). The most common reason for discontinuation was voluntary withdrawal and was comparable among the placebo group.

Table 3.4 Disposition of Patients for Study 3002 (Based on ITT)

<i>Reported are N (%)</i>	<i>Eluxadoline 75 mg BID (N=381)</i>	<i>Eluxadoline 100 mg BID (N=383)</i>	<i>Placebo BID (N=382)</i>	<i>Total (N=1146)</i>
Total Number of Patients				
Randomized	381 (100.0)	383 (100.0)	382 (100.0)	1146 (100.0)
ITT Analysis Set	381 (100.0)	382 (99.7)	382 (100.0)	1145 (99.9)
Modified ITT Analysis Set	376 (98.7)	376 (98.2)	379 (99.2)	1131 (98.7)
Attended Week 12 Visit	296 (77.7)	301 (78.6)	312 (81.7)	909 (79.3)
Attended Week 26 Visit	259 (68.0)	271 (70.8)	278 (72.8)	808 (70.5)
Complete Study	250 (65.6)	264 (68.9)	273 (71.5)	787 (68.7)
Discontinued Study	131 (34.4)	119 (31.1)	109 (28.5)	359 (31.3)
IVRS Misallocation	12 (3.1)	13 (3.4)	0	25 (2.2)
Reason of Discontinuation				
Voluntarily Withdrew	70 (18.4)	66 (17.2)	74 (19.4)	210 (18.3)
Adverse Event or SAE	32 (8.4)	28 (7.3)	19 (5.0)	79 (6.9)
Lost to follow-up	11 (2.9)	5 (1.3)	6 (1.6)	22 (1.9)
Physician Decision: Other	10 (2.6)	8 (2.1)	7 (1.8)	25 (2.2)
Physician Decision: Lack of Efficacy	1 (0.3)	5 (1.3)	3 (0.8)	9 (0.8)
Protocol Violation	0	2 (0.5)	0	2 (0.2)
Sponsor Decision	7 (1.8)	5 (1.3)	0	12 (1.0)

Source: Tables 14.1.1 & 11-1 of CSR

The sponsor's summary for patient demographic characteristics for the Enrolled Set is displayed in Table 3.5. As seen from the table, demographic characteristics were similar across treatment groups, except those for the proportion of patients who were  $\geq 65$  years of age, which was lowest in the 75-mg group (9.4%) and highest in the placebo group (13.4%). The overall patients' mean age was 45.9 years, where most patients were white (85%) and 67% of patients were female. Patients' BMI was similar across treatment groups and the overall average was 30.34 kg/m<sup>2</sup>.

Table 3.5 Patient Demographic Characteristics for Study 3002 (Based on Enrolled Set)

	<i>Eluxadoline 75 mg BID (N=381)</i>	<i>Eluxadoline 100 mg BID (N=383)</i>	<i>Placebo BID (N=382)</i>	<i>Total (N=1146)</i>
Age (years)				
Mean (SD)	45.0 (13.17)	45.7 (13.31)	47.1 (13.82)	45.9 (13.45)
Median	45.0	45.0	47.5	45.5
Min, Max	18, 77	19, 75	19, 77	18, 77
Age categories (years), n (%)				
18-40	139 (36.5)	146 (38.1)	133 (34.8)	418 (36.5)
41-64	206 (54.1)	198 (51.7)	198 (51.8)	602 (52.5)
$\geq 65$	36 (9.4)	39 (10.2)	51 (13.4)	126 (11.0)
Gender, n (%)				
Male	120 (31.5)	126 (32.9)	132 (34.6)	378 (33.0)
Female	261 (68.5)	257 (67.1)	250 (65.4)	768 (67.0)
Race				
White	327 (85.8)	318 (83.0)	329 (86.1)	974 (85.0)
Black	46 (12.1)	51 (13.3)	43 (11.3)	140 (12.2)
Asian	2 (0.5)	7 (1.8)	6 (1.6)	15 (1.3)
American Indian or Alaska Native	3 (0.8)	3 (0.8)	1 (0.3)	7 (0.6)
Native Hawaiian or Other Pacific Islander	0	1 (0.3)	2 (0.5)	3 (0.3)
Other	3 (0.8)	3 (0.8)	1 (0.3)	7 (0.6)
Ethnicity, n (%)				
Hispanic or Latino	98 (25.7)	99 (25.8)	101 (26.4)	298 (26.0)
Not Hispanic or Latino	283 (74.3)	284 (74.2)	281 (73.6)	848 (74.0)
BMI (kg/m <sup>2</sup> )				
Mean (SD)	30.79 (8.17)	30.45 (7.74)	29.79 (6.87)	30.34 (7.61)
Median	29.30	28.90	29.00	29.05
Min, Max	15.5, 65.8	16.0, 63.5	14.8, 69.6	14.8, 69.6

Source: Table 11-2 of CSR

Patients' baseline IBS characteristics for the Enrolled Set are presented in Table 3.6. Based on the sponsor's results, they concluded that patients' baseline IBS symptoms were similar across treatment groups, where their average daily worst abdominal pain score was 6.00 and their average daily BSS score and IBS-d global symptom score were 6.22 and 2.79, respectively.

Table 3.6 Baseline IBS Characteristics For Study 3002 (Based on Enrolled Set)

<i>Mean (SD)</i>	<i>Eluxadoline 75 mg BID (N=381)</i>	<i>Eluxadoline 100 mg BID (N=383)</i>	<i>Placebo BID (N=382)</i>	<i>Total (N=1146)</i>
Worst abdominal pain	6.00 (1.50)	5.95 (1.51)	6.04 (1.49)	6.00 (1.50)
Abdominal bloating* (*Note Ns are different)	5.72 (2.02) N=324	5.62 (2.03) N=335	5.70 (2.14) N=319	5.68 (2.06) N=978
Abdominal discomfort	6.23 (1.53)	6.10 (1.49)	6.24 (1.43)	6.19 (1.48)
Stool consistency (BSS)	6.24 (0.39)	6.20 (0.41)	6.22 (0.41)	6.22 (0.40)
Bowel movement frequency	4.71 (2.32)	4.94 (4.16)	4.69 (2.25)	4.78 (3.04)
Urgency episodes	3.42 (2.20)	3.55 (4.15)	3.44 (1.99)	3.47 (2.94)
Incontinence episodes	0.97 (1.69)	0.93 (1.52)	0.99 (1.68)	0.96 (1.63)
Incontinence free days	4.42 (2.76)	4.24 (2.72)	4.38 (2.85)	4.35 (2.78)
IBS-d global symptoms score	2.76 (0.54)	2.79 (0.51)	2.81 (0.54)	2.79 (0.53)

Source: Table 11-3 of CSR

### 3.2.3 Sponsor's Efficacy Results and Conclusions for Study 3001

#### 3.2.3.1 Primary Analysis for Composite Responders

The sponsor's analysis results for the primary endpoint are shown in Table 3.7. Based on the Bonferroni adjustment, the proportions of composite responders for both the 75 mg and 100-mg treatment groups were statistically superior to placebo for Weeks 1-12. For Weeks 1-26, only the 100-mg dose was statistically superior to placebo.

Table 3.7 Sponsor's CMH Analysis for Composite Responders for Study 3001 (Based on ITT)

<i>Interval Treatment</i>	<i>Number (%)</i>		<i>P-value</i>
	<i>Responder</i>	<i>Non-Responder</i>	
Weeks 1-12 (FDA primary endpoint)			
Eluxadoline 75 mg BID (N=427)	102 (23.9)	325 (76.1)	0.014
Eluxadoline 100 mg BID (N=426)	107 (25.1)	319 (74.9)	0.004
Placebo BID (N=427)	73 (17.1)	354 (82.9)	
Weeks 1-26 (EMA primary endpoint)			
Eluxadoline 75 mg BID (N=427)	100 (23.4)	327 (76.6)	0.112
Eluxadoline 100 mg BID (N=426)	125 (29.3)	301 (70.7)	<0.001
Placebo BID (N=427)	81 (19.0)	346 (81.0)	

Source: Table 11-6 of CSR

#### 3.2.3.2 Sensitivity Analyses for Composite Responders

##### Composite Responder Endpoint by Worst-Case Scenario

The sponsor conducted a worst-case scenario sensitivity analysis to determine if the allowance of missing data based on patients' non-compliance with the daily diary had an impact on the analysis of composite response. The composite responder definition for this analysis required 42 of 84 days to be positive days for the assessment over Weeks 1-12 and 91 of 182 days to be positive response days for the assessment over Weeks 1-26, irrespective of diary compliance. Patients with missing diary data were non-responders for that day.

The sponsor’s analysis results from the CMH analysis for the aforementioned worst-case scenario are displayed in Table 3.8. Since the proportion of composite responders from both the 75-mg and 100 mg treatment groups was statistically superior to placebo over the 3-month interval (Weeks 1-12) and the 6-month interval (Weeks 1-26) using the worst-case scenario, the sponsor concluded that the data handling conventions for missing data did not have an impact on the overall findings.

Table 3.8 Sponsor’s CMH Analysis for Worst-Case Composite Responders for Study 3001 (Based on ITT)

<i>Interval Treatment</i>	<i>Number (%)</i>		<i>P-value</i>
	Responder	Non-Responder	
<b>Weeks 1-12</b>			
Eluxadoline 75 mg BID (N=427)	100 (23.4)	327 (76.6)	0.013
Eluxadoline 100 mg BID (N=426)	103 (24.2)	323 (75.8)	0.006
Placebo BID (N=427)	71 (16.6)	356 (83.4)	
<b>Weeks 1-26</b>			
Eluxadoline 75 mg BID (N=427)	97 (22.7)	330 (77.3)	0.012
Eluxadoline 100 mg BID (N=426)	112 (26.3)	314 (73.7)	<0.001
Placebo BID (N=427)	68 (15.9)	359 (84.1)	

Source: Table 11-8 of CSR

**Reviewer’s Note:** Even though the sponsor concluded that the data handling conventions for missing data did not have an impact on the overall findings, we noted that for the 75 mg BID of eluxadoline, when compared with placebo at Weeks 1 to 26, the above results by the CMH analysis for the worst-case scenario had larger treatment difference with a smaller p-value than that shown on Table 3.7.

#### Weekly Evaluated Sensitivity of the Composite Responder Endpoint (Weeks 1-12)

The sponsor’s analysis results, using the weekly evaluated data, by the aforementioned Method 1 and Method 2 (see Section 3.2.3), are shown in Table 3.9. For this analysis, patients were required to meet the weekly composite responder definitions for at least 6 weeks over the interval from Weeks 1-12. Based on the nominal p-values without considering the alpha adjustment due to multiple doses, when the weekly composite responder definitions were used, the proportion of responders for the 75-mg and 100-mg treatment groups still showed statistical superiority to placebo over the 3-month interval (Weeks 1-12) for both methods.

The sponsor also performed exploratory analysis of daily composite responders using a longitudinal model (evaluated at Weeks 4, 8, 12, 16, 20, 24 and 26) and their results are displayed in Table 3.10. Based on the nominal p-values without considering the alpha adjustment, the sponsor concluded that when the proportion of daily composite responders was analyzed using this model, the 75-mg and 100-mg treatment groups showed significance compared to placebo at each time point evaluated.

Table 3.9 Sponsor's CMH Analysis for Alternative Composite Responders for Study 3001  
(Based on ITT)

<i>Interval Treatment (Weeks 1-12)</i>	<i>Number (%)</i>		<i>P-value</i>
	<i>Responder</i>	<i>Non-Responder</i>	
<b>Method 1</b>			
Eluxadoline 75 mg BID (N=427)	143 (33.5)	284 (66.5)	0.013
Eluxadoline 100 mg BID (N=426)	154 (36.2)	272 (63.8)	0.001
Placebo BID (N=427)	110 (25.8)	317 (74.2)	
<b>Method 2</b>			
Eluxadoline 75 mg BID (N=427)	164 (38.4)	263 (61.6)	0.026
Eluxadoline 100 mg BID (N=426)	178 (41.8)	248 (58.2)	<0.001
Placebo BID (N=427)	133 (31.1)	294 (68.9)	

Source: Table 11-10 of CSR

Table 3.10 Sponsor's Longitudinal Analysis for Composite Responders for Study 3001  
(Based on ITT)

	<i>Incidence</i>	<i>Odds ratio (95% C.I.)</i>	<i>P-Value</i>
<b>Weeks 4</b>			
Eluxadoline 75 mg BID	0.13	1.51 (1.05, 2.17)	0.025
Eluxadoline 100 mg BID	0.15	1.76 (1.23, 2.53)	0.002
Placebo BID	0.09		
<b>Weeks 8</b>			
Eluxadoline 75 mg BID	0.15	1.5 (1.05, 2.16)	0.026
Eluxadoline 100 mg BID	0.17	1.75 (1.22, 2.50)	0.002
Placebo BID	0.11		
<b>Weeks 12</b>			
Eluxadoline 75 mg BID	0.18	1.5 (1.05, 2.15)	0.027
Eluxadoline 100 mg BID	0.21	1.73 (1.21, 2.48)	0.003
Placebo BID	0.13		
<b>Weeks 16</b>			
Eluxadoline 75 mg BID	0.22	1.49 (1.04, 2.14)	0.029
Eluxadoline 100 mg BID	0.24	1.72 (1.20, 2.47)	0.003
Placebo BID	0.16		
<b>Weeks 20</b>			
Eluxadoline 75 mg BID	0.26	1.49 (1.04, 2.14)	0.031
Eluxadoline 100 mg BID	0.28	1.71 (1.19, 2.45)	0.004
Placebo BID	0.19		
<b>Weeks 24</b>			
Eluxadoline 75 mg BID	0.30	1.48 (1.03, 2.13)	0.034
Eluxadoline 100 mg BID	0.33	1.69 (1.18, 2.44)	0.005
Placebo BID	0.22		
<b>Weeks 26</b>			
Eluxadoline 75 mg BID	0.32	1.48 (1.03, 2.13)	0.036
Eluxadoline 100 mg BID	0.35	1.69 (1.17, 2.43)	0.005
Placebo BID	0.24		

Source: Table 14.2.2.3.15 of CSR

### 3.2.3.3 Analyses of Secondary Endpoints - Pain Responders and Pain Scores

#### **Pain Responders:**

The sponsor's CMH analysis results for pain responders (individual pain component of the daily composite responder definition) over the intervals from Weeks 1-12 and Weeks 1-26 are shown in Table 3.11. Based on the results, the proportion of pain responders for the 75 mg and 100 mg treatment groups was higher than placebo over the 3-month interval and the 6-month interval; however, these difference were not statistically significant at the significance level of 0.05. The sponsor also analyzed the data using the logistic regression model and conducted the worst case scenario analysis defined similarly for the composite responder endpoint. Their results for both intervals were consistent with the findings from the above CMH analysis.

Table 3.11 Sponsor's CMH Analysis for Pain Responders for Study 3001 (Based on ITT)

<i>Interval Treatment</i>	<i>Number (%)</i>		<i>P-value</i>
	<i>Responder</i>	<i>Non-Responder</i>	
Weeks 1-12			
Eluxadoline 75 mg BID (N=427)	181 (42.4)	246 (57.6)	0.404
Eluxadoline 100 mg BID (N=426)	184 (43.2)	242 (56.8)	0.284
Placebo BID (N=427)	169 (39.6)	258 (60.4)	
Weeks 1-26			
Eluxadoline 75 mg BID (N=427)	193 (45.2)	234 (54.8)	0.582
Eluxadoline 100 mg BID (N=426)	198 (46.5)	228 (53.5)	0.355
Placebo BID (N=427)	185 (43.3)	242 (56.7)	

Source: Table 11-11 of CSR

#### **Pain Scores:**

Table 3.12 presents the sponsor's exploratory analysis results for patients' daily pain scores using a longitudinal generalized linear model. Based on the results, scores were significantly lower than placebo for the 100-mg treatment group for each time point evaluated. For the 75-mg group, while the mean daily pain scores were lower than placebo from Week 4 to Week 26, the differences only appeared to reach nominal statistical significance at Weeks 16, 20, 24 and 26 when we consider a significance level of 0.05 without any alpha adjustment for multiplicity.

**Reviewer's Note:** For dealing with missing data, the statistical reviewer has performed the commonly used mixed effect model for repeated measures (i.e., MMRM) to perform the analysis for patients' average daily pain scores with their baseline pain scores as a covariate for Weeks 4, 8, 12, 16, 20, 24 and 26 data. The statistical reviewer's analysis results are shown in Table 3.26 in the Appendix.

As seen from Table 3.26, the mean differences between the eluxadoline and placebo resulting from the MMRM are larger at most time-points than those from the sponsor's longitudinal analysis except for the 75 mg at Weeks 12 and 26. When determined by nominal p-values at a significance level of 0.05, eluxadoline, especially 100 mg, appears to be effective in improving patients' daily pain scores.

Table 3.12 Sponsor’s Longitudinal Analysis for Daily Pain Scores for Study 3001  
(Based on ITT)

	<i>LS Mean</i>	<i>LS Mean Difference (95% C.I.)</i>	<i>P Value</i>
<b>Weeks 4</b>			
Eluxadoline 75 mg BID	4.04	-0.19 (-0.46, 0.07)	0.152
Eluxadoline 100 mg BID	3.90	-0.34 (-0.61, -0.07)	0.012
Placebo BID	4.24		
<b>Weeks 8</b>			
Eluxadoline 75 mg BID	3.79	-0.22 (-0.48, 0.05)	0.104
Eluxadoline 100 mg BID	3.67	-0.34 (-0.60, -0.07)	0.013
Placebo BID	4.01		
<b>Weeks 12</b>			
Eluxadoline 75 mg BID	3.53	-0.25 (-0.51, 0.02)	0.069
Eluxadoline 100 mg BID	3.45	-0.33 (-0.60, -0.07)	0.015
Placebo BID	3.78		
<b>Weeks 16</b>			
Eluxadoline 75 mg BID	3.27	-0.27 (-0.54, -0.01)	0.045
Eluxadoline 100 mg BID	3.22	-0.33 (-0.59, -0.06)	0.016
Placebo BID	3.55		
<b>Weeks 20</b>			
Eluxadoline 75 mg BID	3.02	-0.30 (-0.56, -0.03)	0.028
Eluxadoline 100 mg BID	3.00	-0.32 (-0.59, -0.05)	0.018
Placebo BID	3.32		
<b>Weeks 24</b>			
Eluxadoline 75 mg BID	2.76	-0.32 (-0.59, -0.06)	0.018
Eluxadoline 100 mg BID	2.77	-0.32 (-0.58, -0.05)	0.021
Placebo BID	3.09		
<b>Weeks 26</b>			
Eluxadoline 75 mg BID	2.64	-0.34 (-0.60, -0.07)	0.014
Eluxadoline 100 mg BID	2.66	-0.31 (-0.58, -0.05)	0.022
Placebo BID	2.97		

Source: Table 11-14 of CSR

### 3.2.3.4 Analysis of Secondary Endpoints - Stool Consistency Responders and Stool Consistency Scores

Table 3.13 presents the sponsor’s CMH analysis results for stool consistency responders over the intervals from Weeks 1-12 and Weeks 1-26. As shown in the table, based on daily response criteria, both 75 mg and 100-mg treatment group results were superior to placebo for over the 3-month interval and the 6-month interval using a nominal significance level of 0.05, but the 75-mg treatment was not significantly higher than placebo over the 6-month interval. According to two methods stated earlier in Section 3.2.3, both 75 mg and 100 mg’s efficacy over Weeks 1-12 were supported by Method 1 but not Method 2. The sponsor has also analyzed the data using the logistic regression model and results are consistent with the findings from CMH.

Table 3.13 Sponsor's CMH Analysis for Stool consistency Responders for Study 3001  
(Based on ITT)

<i>Interval Treatment (Daily Response Criteria)</i>	<i>Number (%)</i>		<i>P-value</i>
	<i>Responder</i>	<i>Non-Responder</i>	
<b>Weeks 1-12</b>			
Eluxadoline 75 mg BID (N=427)	128 (30.0)	299 (70.0)	0.008
Eluxadoline 100 mg BID (N=426)	146 (34.3)	280 (65.7)	<0.001
Placebo BID (N=427)	94 (22.0)	333 (78.0)	
<b>Weeks 1-26</b>			
Eluxadoline 75 mg BID (N=427)	120 (28.1)	307 (71.9)	0.186
Eluxadoline 100 mg BID (N=426)	145 (34.0)	281 (66.0)	0.001
Placebo BID (N=427)	103 (24.1)	324 (75.9)	
<b>(Method 1)</b>			
<b>Weeks 1-12</b>			
Eluxadoline 75 mg BID (N=427)	177 (41.5)	250 (58.5)	0.009
Eluxadoline 100 mg BID (N=426)	184 (43.2)	242 (56.8)	0.002
Placebo BID (N=427)	140 (32.8)	287 (67.2)	
<b>(Method 2)</b>			
<b>Weeks 1-12</b>			
Eluxadoline 75 mg BID (N=427)	213 (49.9)	214 (50.1)	0.193
Eluxadoline 100 mg BID (N=426)	228 (53.5)	198 (46.5)	0.018
Placebo BID (N=427)	194 (45.4)	233 (54.6)	

Source: Tables 11-15 and 11-17 of CSR

Table 3.14 presents the sponsor's analysis for daily stool consistency scores (evaluated at Weeks 4, 8, 12, 16, 20, 24 and 26) using a longitudinal generalized linear model. As shown in the table, scores were lower than placebo for the 75-mg and 100-mg treatment groups for each time point evaluated.

Table 3.14 Sponsor's Longitudinal Analysis for Stool Consistency Scores for Study 3001  
(Based on ITT)

	<i>LS Mean</i>	<i>LS Mean Difference</i>	<i>P Value</i>
		<i>(95% C.I.)</i>	
<b>Weeks 4</b>			
Eluxadoline 75 mg BID	4.96	-0.28 (-0.42, -0.14)	<0.001
Eluxadoline 100 mg BID	4.91	-0.33 (-0.46, -0.19)	<0.001
Placebo BID	5.24		
<b>Weeks 8</b>			
Eluxadoline 75 mg BID	4.89	-0.26 (-0.40, -0.13)	<0.001
Eluxadoline 100 mg BID	4.84	-0.32 (-0.45, -0.18)	<0.001
Placebo BID	5.15		
<b>Weeks 12</b>			
Eluxadoline 75 mg BID	4.82	-0.25 (-0.39, -0.12)	<0.001
Eluxadoline 100 mg BID	4.76	-0.31 (-0.44, -0.17)	<0.001
Placebo BID	5.07		
<b>Weeks 16</b>			
Eluxadoline 75 mg BID	4.74	-0.24 (-0.38, -0.10)	<0.001
Eluxadoline 100 mg BID	4.69	-0.29 (-0.43, -0.16)	<0.001
Placebo BID	4.98		

	<i>LS Mean</i>	<i>LS Mean Difference (95% C.I.)</i>	<i>P Value</i>
<b>Weeks 20</b>			
Eluxadoline 75 mg BID	4.67	-0.23 (-0.36, -0.09)	0.001
Eluxadoline 100 mg BID	4.61	-0.28 (-0.42, -0.15)	<0.001
Placebo BID	4.90		
<b>Weeks 24</b>			
Eluxadoline 75 mg BID	4.60	-0.21 (-0.35, -0.07)	0.003
Eluxadoline 100 mg BID	4.54	-0.27 (-0.41, -0.13)	<0.001
Placebo BID	4.81		
<b>Weeks 26</b>			
Eluxadoline 75 mg BID	4.56	-0.21 (-0.35, -0.07)	0.004
Eluxadoline 100 mg BID	4.50	-0.27 (-0.41, -0.13)	<0.001
Placebo BID	4.77		

Source: Table 11-18 of CSR

### 3.2.4 Sponsor's Efficacy Results and Conclusions for Study 3002

#### 3.2.4.1 Primary Analysis for Composite Responders

As mentioned earlier, the primary endpoint for the purpose of the FDA review is the proportion of composite responders over the interval from Weeks 1-12. The EMA endpoint (composite response over the interval from Weeks 1-26) is shown for completeness only.

Table 3.15 presents the sponsor's results from the CMH analysis of composite responders over the intervals from Weeks 1-12 and Weeks 1-26. After applying the pre-specified Bonferroni adjustment for multiple comparisons, the proportion of composite responders for both 75-mg and 100-mg treatment groups was statistically superior to placebo for both Weeks 1-12 and Weeks 1-26.

Table 3.15 Sponsor's CMH Analysis for Composite Responders for Study 3002  
(Based on ITT)

<i>Interval Treatment</i>	<i>Number (%)</i>		<i>P-value</i>
	<i>Responder</i>	<i>Non-Responder</i>	
<b>Weeks 1-12 (FDA primary endpoint)</b>			
Eluxadoline 75 mg BID (N=381)	110 (28.9)	271 (71.1)	<0.001
Eluxadoline 100 mg BID (N=382)	113 (29.6)	269 (70.4)	<0.001
Placebo BID (N=382)	62 (16.2)	320 (83.8)	
<b>Weeks 1-26 (EMA primary endpoint)</b>			
Eluxadoline 75 mg BID (N=381)	116 (30.4)	265 (69.6)	0.001
Eluxadoline 100 mg BID (N=382)	125 (32.7)	257 (67.3)	<0.001
Placebo BID (N=382)	77 (20.2)	305 (79.8)	

Source: Table 11-6 of CSR

The sponsor also performed the exploratory analyses of composite responders using the logistic regression model over Weeks 1-12 and Weeks 1-26 and results were consistent with the findings from the CMH analysis.

### 3.2.4.2 Sensitivity Analyses for Composite Responders

#### Composite Responder Endpoint by Worst-Case Scenario

As done for Study 3001, the sponsor also performed sensitivity analyses for the composite responder endpoint using a worst-case scenario (including missing data), a weekly composite responder definition (Method 1 and Method 2), and for a subset of patients who did not have any dose interruptions. Table 3.16 presents their results from the CMH analysis by the worst-case scenario for composite responders. As seen in the table below, the proportion of composite responders for both the 75-mg and 100-mg treatment groups was statistically superior to placebo over both the 3-month and 6-month intervals, and thus the sponsor concluded that the data handling conventions for missing data did not have an impact on the overall efficacy findings.

Table 3.16 Sponsor’s CMH Analysis for Worst-Case Composite Responders for Study 3002 (Based on ITT)

<i>Interval Treatment</i>	<i>Number (%)</i>		<i>P-value</i>
	<i>Responder</i>	<i>Non-Responder</i>	
<i>Weeks 1-12</i>			
Eluxadoline 75 mg BID (N=381)	108 (28.3)	273 (71.7)	<0.001
Eluxadoline 100 mg BID (N=382)	108 (28.3)	274 (71.7)	<0.001
Placebo BID (N=382)	53 (13.9)	329 (86.1)	
<i>Weeks 1-26</i>			
Eluxadoline 75 mg BID (N=381)	110 (28.9)	271 (71.1)	<0.001
Eluxadoline 100 mg BID (N=382)	117 (30.6)	265 (69.4)	<0.001
Placebo BID (N=382)	60 (15.7)	322 (84.3)	

Source: Table 11-8 of CSR

#### Weekly Evaluated Sensitivity of the Composite Responder Endpoint (Weeks 1-12)

As was done for Study 3001, the sponsor also performed sensitivity analyses using the weekly evaluated data, by the aforementioned Method 1 and Method 2 over the 12-week interval and the interval from Weeks 1-12. Their results only for the interval of Weeks 1-12 weeks are shown in Table 3.17. When the weekly composite responder definitions were used, the proportion of responders for the 75-mg and 100-mg treatment groups still showed statistical significance compared to placebo over the 3-month interval (Weeks 1-12) using the Method 1 responder definitions. Using Method 2, the results appeared to be nominally significant only for the 100mg dose group.

The sponsor also performed exploratory analysis of daily composite responders using a longitudinal model (evaluated at Weeks 4, 8, 12, 16, 20, 24 and 26) and their results are displayed in Table 3.18. Based on the results, the sponsor concluded that when the proportion of daily composite responders was analyzed using this model, the 75-mg and 100-mg treatment groups were both statistically superior to placebo at each time point evaluated.

Table 3.17 Sponsor's CMH Analysis for Alternative Composite Responders for Study 3002  
(Based on ITT)

<i>Interval Treatment (Weeks 1-12)</i>	<i>Number (%)</i>		<i>P-value</i>
	<i>Responder</i>	<i>Non-Responder</i>	
<b>Method 1</b>			
Eluxadoline 75 mg BID (N=381)	138 (36.2)	243 (63.8)	0.004
Eluxadoline 100 mg BID (N=382)	144 (37.7)	238 (62.3)	<0.001
Placebo BID (N=382)	101 (26.4)	281 (73.6)	
<b>Method 2</b>			
Eluxadoline 75 mg BID (N=381)	147 (38.6)	234 (61.4)	0.091
Eluxadoline 100 mg BID (N=382)	172 (45.0)	210 (55.0)	<0.001
Placebo BID (N=382)	125 (32.7)	257 (67.3)	

Source: Table 11-10 of CSR

Table 3.18 Sponsor's Longitudinal Analysis for Composite Responders for Study 3002  
(Based on ITT)

	<i>Incidence</i>	<i>Odds ratio (95% C.I.)</i>	<i>P Value</i>
<b>Weeks 4</b>			
Eluxadoline 75 mg BID	0.18	2.64 (1.79, 3.90)	<0.001
Eluxadoline 100 mg BID	0.19	2.71 (1.84, 4.00)	<0.001
Placebo BID	0.08		
<b>Weeks 8</b>			
Eluxadoline 75 mg BID	0.21	2.60 (1.76, 3.83)	<0.001
Eluxadoline 100 mg BID	0.22	2.74 (1.86, 4.04)	<0.001
Placebo BID	0.09		
<b>Weeks 12</b>			
Eluxadoline 75 mg BID	0.24	2.55 (1.73, 3.76)	<0.001
Eluxadoline 100 mg BID	0.26	2.77 (1.88, 4.08)	<0.001
Placebo BID	0.11		
<b>Weeks 16</b>			
Eluxadoline 75 mg BID	0.28	2.50 (1.70, 3.69)	<0.001
Eluxadoline 100 mg BID	0.30	2.80 (1.90, 4.13)	<0.001
Placebo BID	0.13		
<b>Weeks 20</b>			
Eluxadoline 75 mg BID	0.32	2.46 (1.66, 3.63)	<0.001
Eluxadoline 100 mg BID	0.35	2.83 (1.92, 4.18)	<0.001
Placebo BID	0.16		
<b>Weeks 24</b>			
Eluxadoline 75 mg BID	0.36	2.41 (1.63, 3.57)	<0.001
Eluxadoline 100 mg BID	0.40	2.86 (1.93, 4.24)	<0.001
Placebo BID	0.19		
<b>Weeks 26</b>			
Eluxadoline 75 mg BID	0.38	2.39 (1.61, 3.55)	<0.001
Eluxadoline 100 mg BID	0.43	2.88 (1.94, 4.27)	<0.001
Placebo BID	0.21		

Source: Table 14.2.2.3.15 of CSR

### 3.2.4.3 Analyses of Secondary endpoints - Pain Responders and Pain Scores

#### **Pain Responders:**

The sponsor’s CMH analysis results for pain responders (individual pain component of the daily composite responder definition) over the intervals from Weeks 1-12 and Weeks 1-26 are shown in Table 3.19. Similar to Study 3001, the proportion of pain responders for the 75 mg and 100 mg treatment groups was higher than placebo over the 3-month interval and the 6-month interval; however, these differences were not statistically significant at the nominal significance level of 0.05 . For assessing the robustness of the results, the sponsor also analyzed the data using the logistic regression model and conducted the worst case scenario analysis defined similarly for the composite responder endpoint. Their results for both intervals were consistent with the findings from the above CMH analysis.

Table 3.19 Sponsor’s CMH Analysis for Pain Responders for Study 3002 (Based on ITT)

<i>Interval Treatment</i>	<i>Number (%)</i>		<i>P-value</i>
	Responder	Non-Responder	
<b>Weeks 1-12</b>			
Eluxadoline 75 mg BID (N=381)	183 (48.0)	198 (52.0)	0.448
Eluxadoline 100 mg BID (N=382)	195 (51.0)	187 (49.0)	0.111
Placebo BID (N=382)	173 (45.3)	209 (54.7)	
<b>Weeks 1-26</b>			
Eluxadoline 75 mg BID (N=381)	181 (47.5)	200 (52.5)	0.448
Eluxadoline 100 mg BID (N=382)	191 (50.0)	191 (50.0)	0.148
Placebo BID (N=382)	171 (44.8)	211 (55.2)	

Source: Table 11-11 of CSR

#### **Pain Scores:**

Table 3.20 presents the sponsor’s results for patients’ daily pain scores using a longitudinal generalized linear model. Similar to Study 3001, based on these exploratory results, scores were significantly lower than placebo for the 100-mg treatment group for each time point evaluated. For the 75-mg group, while the mean daily pain scores were lower than placebo from Week 4 to Week 26, the differences only appeared to reach statistical significance at Weeks 4 and 8 at the significance level of 0.05.

**Reviewer’s Note:** Similar to Study 3001, the statistical reviewer’s also performed the MMRM analysis for patients’ average daily pain data for Study 3002 and the results are shown in Table 3.26 of the Appendix. The LS mean differences between eluxadoline and placebo from the MMRM analysis are, for most time points, larger than those from the sponsor’s longitudinal analysis and the nominal p-values are less than the significance level of 0.05. This implies that eluxadoline may have an effect in improving patients’ daily pain scores.

Table 3.20 Sponsor’s Longitudinal Analysis for Daily Pain Scores for Study 3002  
(Based on ITT)

	<i>LS Mean</i>	<i>LS Mean Difference (95% C.I.)</i>	<i>P Value</i>
<b>Weeks 4</b>			
Eluxadoline 75 mg BID	3.67	-0.29 (-0.57, -0.01)	0.039
Eluxadoline 100 mg BID	3.71	-0.25 (-0.53, 0.02)	0.071
Placebo BID	3.97		
<b>Weeks 8</b>			
Eluxadoline 75 mg BID	3.49	-0.28 (-0.56, -0.01)	0.044
Eluxadoline 100 mg BID	3.49	-0.29 (-0.56, -0.01)	0.042
Placebo BID	3.78		
<b>Weeks 12</b>			
Eluxadoline 75 mg BID	3.31	-0.28 (-0.55, 0.00)	0.050
Eluxadoline 100 mg BID	3.27	-0.32 (-0.59, -0.04)	0.024
Placebo BID	3.59		
<b>Weeks 16</b>			
Eluxadoline 75 mg BID	3.13	-0.27 (-0.54, 0.01)	0.058
Eluxadoline 100 mg BID	3.05	-0.35 (-0.63, -0.07)	0.013
Placebo BID	3.40		
<b>Weeks 20</b>			
Eluxadoline 75 mg BID	2.95	-0.26 (-0.54, 0.02)	0.066
Eluxadoline 100 mg BID	2.83	-0.38 (-0.66, -0.10)	0.007
Placebo BID	3.21		
<b>Weeks 24</b>			
Eluxadoline 75 mg BID	2.77	-0.25 (-0.53, 0.03)	0.076
Eluxadoline 100 mg BID	2.61	-0.41 (-0.69, -0.13)	0.004
Placebo BID	3.03		
<b>Weeks 26</b>			
Eluxadoline 75 mg BID	2.68	-0.25 (-0.53, 0.03)	0.081
Eluxadoline 100 mg BID	2.50	-0.43 (-0.71, -0.15)	0.003
Placebo BID	2.93		

Source: Table 11-14 of CSR

#### 3.2.4.4 Analysis of Secondary Endpoints - Stool Consistency Responders and Stool Consistency Scores

Table 3.21 presents the sponsor’s CMH analysis results for stool consistency responders over the intervals from Weeks 1-12 and Weeks 1-26. As shown in the table, based on daily response criteria, both 75-mg and 100-mg treatment group were nominally significantly superior to placebo for over the 3-month interval and the 6-month interval at the significance level of 0.05 . According to two methods stated earlier in Section 3.2.3, both 75 mg and 100 mg’s efficacy over Weeks 1-12 were demonstrated. The sponsor has also analyzed the data using the logistic regression model and results are consistent with the findings from CMH.

Table 3.21 Sponsor's CMH Analysis for Stool consistency Responders for Study 3002  
(Based on ITT)

<i>Interval Treatment (Daily Response Criteria)</i>	<i>Number (%)</i>		<i>P-value</i>
	<i>Responder</i>	<i>Non-Responder</i>	
<i>Weeks 1-12</i>			
Eluxadoline 75 mg BID (N=381)	141 (37.0)	240 (63.0)	<0.001
Eluxadoline 100 mg BID (N=382)	136 (35.6)	246 (64.4)	<0.001
Placebo BID (N=382)	80 (20.9)	302 (79.1)	
<i>Weeks 1-26</i>			
Eluxadoline 75 mg BID (N=381)	131 (34.4)	250 (65.6)	<0.001
Eluxadoline 100 mg BID (N=382)	152 (39.8)	230 (60.2)	<0.001
Placebo BID (N=382)	90 (23.6)	292 (76.4)	
<i>(Method 1)</i>			
<i>Weeks 1-12</i>			
Eluxadoline 75 mg BID (N=381)	181 (47.5)	200 (52.5)	0.002
Eluxadoline 100 mg BID (N=382)	184 (48.2)	198 (51.8)	<0.001
Placebo BID (N=382)	139 (36.4)	243 (63.6)	
<i>(Method 2)</i>			
<i>Weeks 1-12</i>			
Eluxadoline 75 mg BID (N=381)	210 (55.1)	171 (44.9)	0.023
Eluxadoline 100 mg BID (N=382)	227 (59.4)	155 (40.6)	<0.001
Placebo BID (N=382)	179 (46.9)	203 (53.1)	

Source: Tables 11-15 and 11-17 of CSR

Table 3.22 presents the sponsor's analysis for daily stool consistency scores (evaluated at Weeks 4, 8, 12, 16, 20, 24 and 26) using a longitudinal generalized linear model. As shown in the table, scores were consistently lower than placebo for the 75-mg and 100-mg treatment groups for each time point evaluated.

Table 3.22 Sponsor's Longitudinal Analysis for Stool Consistency Scores for Study 3002  
(Based on ITT)

	<i>LS Mean</i>	<i>LS Mean Difference (95% C.I.)</i>	<i>P Value</i>
<i>Weeks 4</i>			
Eluxadoline 75 mg BID	4.76	-0.52 (-0.68, -0.37)	<0.001
Eluxadoline 100 mg BID	4.76	-0.52 (-0.68, -0.37)	<0.001
Placebo BID	5.28		
<i>Weeks 8</i>			
Eluxadoline 75 mg BID	4.69	-0.52 (-0.68, -0.37)	<0.001
Eluxadoline 100 mg BID	4.68	-0.53 (-0.69, -0.38)	<0.001
Placebo BID	5.21		
<i>Weeks 12</i>			
Eluxadoline 75 mg BID	4.63	-0.52 (-0.67, -0.37)	<0.001
Eluxadoline 100 mg BID	4.60	-0.55 (-0.70, -0.39)	<0.001
Placebo BID	5.15		
<i>Weeks 16</i>			
Eluxadoline 75 mg BID	4.57	-0.52 (-0.67, -0.36)	<0.001
Eluxadoline 100 mg BID	4.52	-0.56 (-0.72, -0.41)	<0.001
Placebo BID	5.09		
<i>Weeks 20</i>			
Eluxadoline 75 mg BID	4.50	-0.52 (-0.67, -0.36)	0.001
Eluxadoline 100 mg BID	4.45	-0.57 (-0.73, -0.42)	<0.001
Placebo BID	5.02		

	<i>LS Mean</i>	<i>LS Mean Difference (95% C.I.)</i>	<i>P Value</i>
<b>Weeks 24</b>			
Eluxadoline 75 mg BID	4.44	-0.52 (-0.67, -0.36)	<0.001
Eluxadoline 100 mg BID	4.37	-0.59 (-0.74, -0.43)	<0.001
Placebo BID	4.96		
<b>Weeks 26</b>			
Eluxadoline 75 mg BID	4.41	-0.52 (-0.67, -0.36)	<0.001
Eluxadoline 100 mg BID	4.33	-0.59 (-0.75, -0.44)	<0.001
Placebo BID	4.92		

Source: Table 11-18 of CSR

### 3.2.5 Sponsor's Conclusion

The sponsor concluded that the positive treatment effects for eluxadoline over placebo were demonstrated in both studies 3001 and 3002 for the primary composite response endpoint of simultaneous improvement in both abdominal pain and BSS on the same day over the interval from Weeks 1-12 (FDA primary endpoint) and Weeks 1-26 (EMA primary endpoint) as well as for numerous secondary endpoints.

### 3.2.6 Statistical Reviewer's Findings and Comments

1. The statistical reviewer confirmed the sponsor's analysis results for the primary endpoint (composite response) based on the intent to treat population. The primary endpoints was also consistent across different subgroups, including age, gender and region. It is concluded that data from both phase 3 studies 3001 and 3002 indeed supported the efficacy of eluxadoline as a treatment for IBS-d. Although both studies showed positive findings on the composite primary endpoints for both patients' abdominal pain and stool consistency, when focusing on individual components of the composite endpoint, only the data for stool consistency indicated significant findings. A reason why the results of the abdominal pain endpoint were not statistically significant in both studies appears to be mainly due to the occurrence of high placebo response (See Tables 3.11 and 3.19).
2. (MMRM Analysis for Assessing Pain Response) To further assess eluxadoline's effect in improving patients' abdominal pain, the reviewer re-analyzed the sponsor's longitudinal data (See Tables 3.12 and 3.20) for patients' daily pain scores. For dealing with missing data, which commonly happens in subject response measurements, the statistical reviewer performed the commonly used mixed effect model for repeated measures analysis (i.e., MMRM) including the baseline values as a covariate to assess the eluxadoline's effect comparing with placebo in each visit.

This exploratory analysis is shown in Table 3.26 in the Appendix. It showed that except for eluxadoline 75 mg at Week 12 for Study 3001, the estimated eluxadoline's effects were larger than those obtained based on the sponsor's longitudinal analysis. The analysis suggests that although not statistically significant at an alpha level 0.025 for both doses, eluxadoline appears to have some effect in treating IBS-d patients' abdominal pain. In particular after Week 8, eluxadoline 100 mg indicated statistically significant results in both studies.

3. (Sponsor's Per-Protocol Analysis Results) The statistical reviewer noted that there were 348 patients (~27%) and 805 patients (~70%) with protocol violations for Studies 3001 and 3002, respectively, but the sponsor did not perform the per protocol analyses. Therefore, an information request was sent to the sponsor for a per protocol analyses by removing all patients with protocol violations.

Instead of removing all patients with protocol violations, the sponsor performed the per protocol analyses by only removing those patients with informed consent issues, inclusion/exclusion issues or excluded medication taken. The sponsor's analysis results are displayed in the Appendix, Table 3.27. The statistical reviewer agreed with the sponsor that the per protocol results are consistent with ITT analysis results.

4. (Comparable Efficacy Results for the 75 mg and 100 mg of eluxadoline) For both Studies 3001 and 3002, the 75 mg and 100 mg dose groups showed a statistically higher composite response rate compared to placebo at Week 12. Based on the primary endpoint, i.e., complete response. The statistical reviewer performed an exploratory chi-square test to compare patients' composite response rates between the 75 mg and 100 mg dose groups. Unsurprisingly, the test was not significant, and there was no difference indicated in dose groups' response.

Furthermore, the only non-significant finding in Study 3001 from Table 3.7 in the comparisons of the primary endpoint, i.e., composite responders, was shown for eluxadoline 75 mg from Week 1 to Week 26. The sponsor's worst case scenario results from Table 8 showed that by allowing patients to have missing data, i.e., regardless of their number of entries in the study period but only counting their sufficient number of days with satisfied response, the 75 mg eluxadoline group indeed had a response rate much closer to the 100 mg eluxadoline group. For Study 3002, the CR rate difference was only about 2% (30.4% vs. 32.7%) in the period of 26 weeks. These findings might support the efficacy of 75 mg in treating patients with IBS-d through 26 weeks.

### **3.3 EVALUATION OF SAFETY**

The evaluation of safety of eluxadoline is not performed in this statistical review. Please refer to the medical review for this evaluation.

## **4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS**

For both Studies 3001 and 3002, the sponsor conducted subgroup analyses by age categories (18-40, 41-64, and  $\geq 65$ ), gender subgroups as well as those by regions (US and non-US [Canada and UK]) for the composite endpoint (Weeks 1-12), abdominal pain (Weeks 1-12), stool consistency (Weeks 1-12), and IBS-d global symptom (Weeks 1-26) responder proportions. Since more than 85% of patients are white in both studies, the subgroup analyses for race were not performed. In addition, for the interest of US approval, only the results for 1 to 12 weeks are reported in this review. In other words, the subgroup analysis results for IBS-d global symptom responder proportions are omitted. The statistical reviewer has confirmed the sponsor's analysis results.

#### 4.1 GENDER, RACE AND AGE

Tables 3.23 and 3.24 display the sponsor's subgroup analysis for gender and age. Overall, more female than male patients were included in the ITT analysis set. As shown in the tables, for Study 3001, female patients in eluxadoline 100 mg BID significantly performed better than those in placebo for the primary endpoint, CR, and also stool consistency. However, similar findings were not observed for male patients or eluxadoline 75 mg BID. Different from Study 3001, for Study 3002, in male and female patients, both eluxadoline 100 mg BID and 75mg BID performed significantly better than placebo in a significance level of 0.05.

Regarding age subgroups, for both studies, it is interesting to note that the drug does not seem to show any effect on patients less than 40 years old. For Study 3001, eluxadoline 75 mg BID even showed smaller response rate than placebo on the primary endpoint and also abdominal pain response and stool consistency responders, respectively. For Study 3002, only eluxadoline 100 mg BID, not eluxadoline 75 mg, performed statistically better than placebo on CR and also stool consistency.

Table 3.23 Subgroup Analysis for Gender Based on ITT Analysis Set

<i>Study 3001 Gender Subgroup</i>	<i>Number (%)</i>		
	<i>Responder</i>	<i>Non-Responder</i>	<i>P Value</i>
<b>Composite Responders (Weeks 1-12)</b>			
Male (N=444)			
Eluxadoline 75 mg BID (N=151)	39 (25.8)	112 (74.2)	0.006
Eluxadoline 100 mg BID (N=143)	31 (21.7)	112 (78.3)	0.060
Placebo BID (N=150)	20 (13.3)	130 (86.7)	
Female (N=836)			
Eluxadoline 75 mg BID (N=276)	63 (22.8)	213 (77.2)	0.287
Eluxadoline 100 mg BID (N=283)	76 (26.9)	207 (73.1)	0.030
Placebo BID (N=277)	53 (19.1)	224 (80.9)	
<b>Abdominal Pain Responders (Weeks 1-12)</b>			
Male (N=444)			
Eluxadoline 75 mg BID (N=151)	63 (41.7)	88 (58.3)	0.105
Eluxadoline 100 mg BID (N=143)	58 (40.6)	85 (59.4)	0.161
Placebo BID (N=150)	49 (32.7)	101 (67.3)	
Female (N=836)			
Eluxadoline 75 mg BID (N=276)	118 (42.8)	158 (57.2)	0.893
Eluxadoline 100 mg BID (N=283)	126 (44.5)	157 (55.5)	0.775
Placebo BID (N=277)	120 (43.3)	157 (56.7)	
<b>Stool Consistency Responders (Weeks 1-12)</b>			
Male (N=444)			
Eluxadoline 75 mg BID (N=151)	47 (31.1)	104 (68.9)	0.019
Eluxadoline 100 mg BID (N=143)	48 (33.6)	95 (66.4)	0.006
Placebo BID (N=150)	29 (19.3)	121 (80.7)	
Female (N=836)			
Eluxadoline 75 mg BID (N=276)	81 (29.3)	195 (70.7)	0.117
Eluxadoline 100 mg BID (N=283)	98 (34.6)	185 (65.4)	0.004
Placebo BID (N=277)	65 (23.5)	212 (76.5)	

<i>Study 3002 Gender Subgroup</i>	<i>Number (%)</i>		
	<i>Responder</i>	<i>Non-Responder</i>	<i>P Value</i>
<b>Composite Responders (Weeks 1-12)</b>			
Male (N=378)			
Eluxadoline 75 mg BID (N=120)	35 (29.2)	85 (70.8)	0.027
Eluxadoline 100 mg BID (N=126)	40 (31.7)	86 (68.3)	0.008
Placebo BID (N=132)	23 (17.4)	109 (82.6)	
Female (N=767)			
Eluxadoline 75 mg BID (N=261)	75 (28.7)	186 (71.3)	<0.001
Eluxadoline 100 mg BID (N=256)	73 (28.5)	183 (71.5)	<0.001
Placebo BID (N=250)	39 (15.6)	211 (84.4)	
<b>Abdominal Pain Responders (Weeks 1-12)</b>			
Male (N=378)			
Eluxadoline 75 mg BID (N=120)	55 (45.8)	65 (54.2)	0.763
Eluxadoline 100 mg BID (N=126)	67 (53.2)	59 (46.8)	0.139
Placebo BID (N=132)	58 (43.9)	74 (56.1)	
Female (N=767)			
Eluxadoline 75 mg BID (N=261)	128 (49.0)	133 (51.0)	0.492
Eluxadoline 100 mg BID (N=256)	128 (50.0)	128 (50.0)	0.368
Placebo BID (N=250)	115 (46.0)	135 (54.0)	
<b>Stool Consistency Responders (Weeks 1-12)</b>			
Male (N=378)			
Eluxadoline 75 mg BID (N=120)	43 (35.8)	77 (64.2)	0.032
Eluxadoline 100 mg BID (N=126)	47 (37.3)	79 (62.7)	0.016
Placebo BID (N=132)	31 (23.5)	101 (76.5)	
Female (N=767)			
Eluxadoline 75 mg BID (N=261)	98 (37.5)	163 (62.5)	<0.001
Eluxadoline 100 mg BID (N=256)	89 (34.8)	167 (65.2)	<0.001
Placebo BID (N=250)	49 (19.6)	201 (80.4)	

Source: Sponsor's Table 11-27 of CSR

Table 3.24 Subgroup Analysis for Age Based on ITT Analysis Set

<i>Study 3001 Age Subgroup</i>	<i>Number (%)</i>		
	<i>Responder</i>	<i>Non-Responder</i>	<i>P Value</i>
<b>Composite Responders (Weeks 1-12)</b>			
18-40 years (N=497)			
Eluxadoline 75 mg BID (N=172)	27 (15.7)	145 (84.3)	0.753
Eluxadoline 100 mg BID (N=166)	34 (20.5)	132 (79.5)	0.420
Placebo BID (N=159)	27 (17.0)	132 (83.0)	
41-64 years (N=668)			
Eluxadoline 75 mg BID (N=226)	61 (27.0)	165 (73.0)	0.023
Eluxadoline 100 mg BID (N=225)	61 (27.1)	164 (72.9)	0.022
Placebo BID (N=217)	39 (18.0)	178 (82.0)	
>=65 years (N=115)			
Eluxadoline 75 mg BID (N=29)	14 (48.3)	15 (51.7)	<0.001
Eluxadoline 100 mg BID (N=35)	12 (34.3)	23 (65.7)	0.025
Placebo BID (N=51)	7 (13.7)	44 (86.3)	

<i>Study 3001 Age Subgroup</i>	<i>Number (%)</i>		
	<i>Responder</i>	<i>Non-Responder</i>	<i>P Value</i>
<b>Abdominal Pain Responders (Weeks 1-12)</b>			
18-40 years (N=497)			
Eluxadoline 75 mg BID (N=172)	54 (31.4)	118 (68.6)	0.894
Eluxadoline 100 mg BID (N=166)	66 (39.8)	100 (60.2)	0.150
Placebo BID (N=159)	51 (32.1)	108 (67.9)	
41-64 years (N=668)			
Eluxadoline 75 mg BID (N=226)	107 (47.3)	119 (52.7)	0.253
Eluxadoline 100 mg BID (N=225)	103 (45.8)	122 (54.2)	0.416
Placebo BID (N=217)	91 (41.9)	126 (58.1)	
>=65 years (N=115)			
Eluxadoline 75 mg BID (N=29)	20 (69.0)	9 (31.0)	0.164
Eluxadoline 100 mg BID (N=35)	15 (42.9)	20 (57.1)	0.361
Placebo BID (N=51)	27 (52.9)	24 (47.1)	
<b>Stool Consistency Responders (Weeks 1-12)</b>			
18-40 years (N=497)			
Eluxadoline 75 mg BID (N=172)	37 (21.5)	135 (78.5)	0.702
Eluxadoline 100 mg BID (N=166)	46 (27.7)	120 (72.3)	0.360
Placebo BID (N=159)	37 (23.3)	122 (76.7)	
41-64 years (N=668)			
Eluxadoline 75 mg BID (N=226)	76 (33.6)	150 (66.4)	0.007
Eluxadoline 100 mg BID (N=225)	88 (39.1)	137 (60.9)	<0.001
Placebo BID (N=217)	48 (22.1)	169 (77.9)	
>=65 years (N=115)			
Eluxadoline 75 mg BID (N=29)	15 (51.7)	14 (48.3)	0.001
Eluxadoline 100 mg BID (N=35)	12 (34.3)	23 (65.7)	0.079
Placebo BID (N=51)	9 (17.6)	42 (82.4)	
<i>Study 3002 Age Subgroup</i>			
<b>Composite Responders (Weeks 1-12)</b>			
18-40 years (N=418)			
Eluxadoline 75 mg BID (N=139)	28 (20.1)	111 (79.9)	0.147
Eluxadoline 100 mg BID (N=146)	34 (23.3)	112 (76.7)	0.037
Placebo BID (N=133)	18 (13.5)	115 (86.5)	
41-64 years (N=601)			
Eluxadoline 75 mg BID (N=206)	66 (32)	140 (68)	0.005
Eluxadoline 100 mg BID (N=197)	65 (33)	132 (67)	0.003
Placebo BID (N=198)	39 (19.7)	159 (80)	
>=65 years (N=126)			
Eluxadoline 75 mg BID (N=36)	16 (44.4)	20 (55.6)	<0.001
Eluxadoline 100 mg BID (N=39)	14 (35.9)	25 (64.1)	0.003
Placebo BID (N=51)	5 (9.8)	46 (90.2)	
<b>Abdominal Pain Responders (Weeks 1-12)</b>			
18-40 (N=418)			
Eluxadoline 75 mg BID (N=139)	60 (43.2)	79 (56.8)	0.234
Eluxadoline 100 mg BID (N=146)	61 (41.8)	85 (58.2)	0.332
Placebo BID (N=133)	48 (36.1)	85 (63.9)	
41-64 years (N=601)			
Eluxadoline 75 mg BID (N=206)	102 (49.5)	104 (50.5)	0.997
Eluxadoline 100 mg BID (N=197)	110 (55.8)	87 (44.2)	0.207
Placebo BID (N=198)	98 (49.5)	100 (50.4)	
>=65 years (N=126)			
Eluxadoline 75 mg BID (N=36)	21 (58.3)	15 (41.7)	0.620
Eluxadoline 100 mg BID (N=39)	24 (61.5)	15 (38.5)	0.417
Placebo BID (N=51)	27 (52.9)	24 (47.1)	

<i>Study 3002 Age Subgroup</i>	<i>Number (%)</i>		
	<i>Responder</i>	<i>Non-Responder</i>	<i>P Value</i>
<b>Stool Consistency Responders (Weeks 1-12)</b>			
18-40 years (N=418)			
Eluxadoline 75 mg BID (N=139)	38 (27.3)	101 (72.7)	0.032
Eluxadoline 100 mg BID (N=146)	38 (26.0)	108 (74.0)	0.055
Placebo BID (N=133)	22 (16.5)	111 (83.5)	
41-64 (N=601)			
Eluxadoline 75 mg BID (N=206)	83 (40.3)	123 (59.7)	<0.001
Eluxadoline 100 mg BID (N=197)	81 (41.1)	116 (58.9)	<0.001
Placebo BID (N=198)	49 (24.7)	149 (75.3)	
>=65 years (N=126)			
Eluxadoline 75 mg BID (N=36)	20 (55.6)	16 (44.4)	<0.001
Eluxadoline 100 mg BID (N=39)	17 (43.6)	22 (56.4)	0.007
Placebo BID (N=51)	9 (17.6)	42 (82.4)	

Source: Sponsor's Tables 14.2.2.3.13, 14.2.2.5.4 and 14.2.2.5.15 of CSR

**Reviewer's note:** (Age Subgroup Analysis) The sponsor conducted the age subgroup analysis by three subsets: 18-40 years, 41-64 years and >=65 years. It is noted that for Study 3001 in 18-40 years subset, eluxadoline 75 mg performed worse than placebo numerically for the primary endpoint, i.e. composite response as well as in abdominal pain and stool consistency response separately.

As this cut off of 40 years appeared to be arbitrary, after discussing with the medical division, it was decided that we should perform the age subgroup analysis by only considering the 65 years cut off. That is, we performed the same type of analysis but by combining 18-40 years and 41-64 years two subsets. The statistical reviewer's analysis results are shown in Table 3.28 of the Appendix. As seen in the table, for Study 3001, the reverse trend for eluxadoline no longer appears. For the 18-64 years subset, both 75 mg and 100 mg eluxadoline showed higher response rate than placebo in complete response and individual pain and stool components.

## 4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

### 4.2.1 Region

Table 3.25 Subgroup Analysis for Region based on the ITT Analysis Set

<i>Study 3001 Region Subgroup</i>	<i>Number (%)</i>		
	<i>Responder</i>	<i>Non-Responder</i>	<i>P Value</i>
<b>Composite Responders (Weeks 1-12)</b>			
US (N=1212)			
Eluxadoline 75 mg BID (N=403)	94 (23.3)	309 (76.7)	0.009
Eluxadoline 100 mg BID (N=404)	103 (25.5)	301 (74.5)	<0.001
Placebo BID (N=405)	65 (16.0)	340 (84.0)	
Non-US (N=68)			
Eluxadoline 75 mg BID (N=24)	8 (33.3)	16 (66.7)	0.831
Eluxadoline 100 mg BID (N=22)	4 (18.2)	18 (81.8)	0.181
Placebo BID (N=22)	8 (36.4)	14 (63.6)	

<i>Study 3001 Region Subgroup</i>	<i>Number (%)</i>		
	<i>Responder</i>	<i>Non-Responder</i>	<i>P Value</i>
<b>Abdominal Pain Responders (Weeks 1-12)</b>			
US (N=1212)			
Eluxadoline 75 mg BID (N=403)	164 (40.7)	239 (59.3)	0.481
Eluxadoline 100 mg BID (N=404)	170 (42.1)	234 (57.9)	0.270
Placebo BID (N=405)	155 (38.3)	250 (61.7)	
Non-US (N=68)			
Eluxadoline 75 mg BID (N=24)	17 (70.8)	7 (29.2)	0.607
Eluxadoline 100 mg BID (N=22)	14 (63.6)	8 (36.4)	>0.999
Placebo BID (N=22)	14 (63.6)	8 (36.4)	
<b>Stool Consistency Responders (Weeks 1-12)</b>			
US (N=1212)			
Eluxadoline 75 mg BID (N=403)	118 (29.3)	285 (70.7)	0.005
Eluxadoline 100 mg BID (N=404)	138 (34.2)	266 (65.8)	<0.001
Placebo BID (N=405)	84 (20.7)	321 (79.3)	
Non-US (N=68)			
Eluxadoline 75 mg BID (N=24)	10 (41.7)	14 (58.3)	0.798
Eluxadoline 100 mg BID (N=22)	8 (36.4)	14 (63.6)	0.544
Placebo BID (N=22)	10 (45.5)	12 (54.5)	
<i>Study 3002 Region Subgroup</i>			
<b>Composite Responders (Weeks 1-12)</b>			
US (N=1097)			
Eluxadoline 75 mg BID (N=366)	107 (29.2)	259 (70.8)	<0.001
Eluxadoline 100 mg BID (N=365)	106 (29.0)	259 (71.0)	<0.001
Placebo BID (N=366)	61 (16.7)	305 (83.3)	
Non-US (N=48)			
Eluxadoline 75 mg BID (N=15)	3 (20)	12 (80)	0.262
Eluxadoline 100 mg BID (N=17)	7 (41.2)	10 (58.8)	0.021
Placebo BID (N=16)	1 (6.3)	15 (93.8)	
<b>Abdominal Pain Responders (Weeks 1-12)</b>			
US (N=1097)			
Eluxadoline 75 mg BID (N=366)	179 (48.9)	187 (51.1)	0.416
Eluxadoline 100 mg BID (N=365)	185 (50.7)	180 (49.3)	0.196
Placebo BID (N=366)	168 (45.9)	198 (54.1)	
Non-US (N=48)			
Eluxadoline 75 mg BID (N=15)	4 (26.7)	11 (73.3)	0.782
Eluxadoline 100 mg BID (N=17)	10 (58.8)	7 (41.2)	0.117
Placebo BID (N=16)	5 (31.3)	11 (68.8)	
<b>Stool Consistency Responders (Weeks 1-12)</b>			
US (N=1097)			
Eluxadoline 75 mg BID (N=366)	134 (36.6)	232 (63.4)	<0.001
Eluxadoline 100 mg BID (N=365)	125 (34.2)	240 (65.8)	<0.001
Placebo BID (N=366)	76 (20.8)	290 (79.2)	
Non-US (N=48)			
Eluxadoline 75 mg BID (N=15)	7 (46.7)	8 (53.3)	<0.215
Eluxadoline 100 mg BID (N=17)	11 (64.7)	6 (35.3)	<0.024
Placebo BID (N=16)	4 (25.0)	12 (75.0)	

Source: Sponsor's Table 14.2.2.3.13, 14.2.2.5.4 and 14.2.2.5.15 of CSR

**Reviewer's Note:** As seen from the above regional subgroup analysis results, both 75 mg and 100 mg doses of eluxadoline appear to be superior to placebo in US but not in the non-US region. Due to the small number of patients in the non-US region, the findings need to be interpreted with caution.

## **5. SUMMARY AND CONCLUSIONS**

### **5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE**

The sponsor submitted two phase 3 studies to demonstrate the efficacy of eluxadoline as a treatment for abdominal pain and diarrhea in adult patients with diarrhea predominant irritable bowel syndrome (IBS-d). For both studies, both 75 mg and 100 mg doses of eluxadoline showed a statistically significant difference in the primary endpoint, composite response, compared with placebo at 12 weeks. Regarding secondary endpoints, for both studies and both doses, only stool consistency response showed a significant difference compared to placebo at 12 weeks; no statistical differences were shown for abdominal pain response. Since the sponsor did not pre-specify a multiplicity adjustment procedure that would control the study-wise type I error rate for secondary endpoints, formal testing for statistical significance is not appropriate. However, the pain and stool consistency responder results and/or scores may be clinically informative and can augment labeling provided these are presented in descriptive fashion only (b) (4)

To further assess the eluxadoline's effect on reducing patients' abdominal pain, the statistical reviewer performed the mixed effect model for repeated measure (MMRM) analysis on patients' pain scores. Based on this exploratory analysis, both doses of eluxadoline appeared to show a treatment benefit not only in treating patients' diarrhea but also in reducing their abdominal pain.

### **5.2 CONCLUSIONS AND RECOMMENDATIONS**

Data from both Studies 3001 and 3002 support the efficacy of 75 mg and 100 mg of eluxadoline as a treatment for adult patients with diarrhea predominant irritable bowel syndrome (IBS-d).

## 6. Appendix

Table 3.26 Statistical Reviewer's MMRM Analysis for Daily Pain Scores (Based on ITT)

<i>For Study 3001</i>	<i>LS Mean</i>	<i>LS Mean Difference (95% C.I.)</i>	<i>P Value</i>
<b>Weeks 4</b>			
Eluxadoline 75 mg BID	3.91	-0.25 (-0.56, 0.05)	0.102
Eluxadoline 100 mg BID	3.70	-0.46 (-0.77, -0.16)	0.003
Placebo BID	4.16		
<b>Weeks 8</b>			
Eluxadoline 75 mg BID	3.44	-0.44 (-0.76, -0.12)	0.0065
Eluxadoline 100 mg BID	3.35	-0.34 (-0.85, -0.21)	0.0012
Placebo BID	3.89		
<b>Weeks 12</b>			
Eluxadoline 75 mg BID	3.37	-0.20 (-0.53, 0.13)	0.247
Eluxadoline 100 mg BID	3.22	-0.34 (-0.67, -0.003)	0.048
Placebo BID	3.56		
<b>Weeks 16</b>			
Eluxadoline 75 mg BID	3.11	-0.39 (-0.73, -0.04)	0.028
Eluxadoline 100 mg BID	3.16	-0.34 (-0.69, 0.003)	0.052
Placebo BID	3.50		
<b>Weeks 20</b>			
Eluxadoline 75 mg BID	2.91	-0.40 (-0.75, -0.05)	0.024
Eluxadoline 100 mg BID	2.95	-0.37 (-0.72, -0.02)	0.04
Placebo BID	3.32		
<b>Weeks 24</b>			
Eluxadoline 75 mg BID	2.90	-0.39 (-0.74, -0.04)	0.031
Eluxadoline 100 mg BID	2.90	-0.39 (-0.74, -0.04)	0.029
Placebo BID	3.29		
<b>Weeks 26</b>			
Eluxadoline 75 mg BID	2.88	-0.35 (-0.71, 0.01)	0.058
Eluxadoline 100 mg BID	2.82	-0.42 (-0.78, -0.06)	0.024
Placebo BID	3.23		

<i>For Study 3002</i>			
	<i>LS Mean</i>	<i>LS Mean Difference (95% C.I.)</i>	<i>P Value</i>
<b>Weeks 4</b>			
Eluxadoline 75 mg BID	3.51	-0.31 (-0.61, -0.008)	0.044
Eluxadoline 100 mg BID	3.63	-0.19 (-0.494, 0.110)	<b>0.212</b>
Placebo BID	3.83		
<b>Weeks 8</b>			
Eluxadoline 75 mg BID	3.23	-0.36 (-0.678, -0.043)	0.026
Eluxadoline 100 mg BID	3.19	-0.40 (-0.72, -0.09)	0.013
Placebo BID	3.59		
<b>Weeks 12</b>			
Eluxadoline 75 mg BID	3.07	-0.36 (-0.699, -0.0254)	0.035
Eluxadoline 100 mg BID	2.99	-0.44 (-0.779, -0.107)	0.01
Placebo BID	3.43		
<b>Weeks 16</b>			
Eluxadoline 75 mg BID	2.89	-0.49 (-0.826, -0.145)	0.005
Eluxadoline 100 mg BID	2.88	-0.50 (-0.836, -0.156)	0.004
Placebo BID	3.38		
<b>Weeks 20</b>			
Eluxadoline 75 mg BID	2.81	-0.45 (-0.788, -0.102)	0.011
Eluxadoline 100 mg BID	2.85	-0.40 (-0.747, -0.062)	0.020
Placebo BID	3.25		
<b>Weeks 24</b>			
Eluxadoline 75 mg BID	2.85	-0.42 (-0.78, -0.069)	0.019
Eluxadoline 100 mg BID	2.75	-0.52 (-0.878, -0.169)	0.004
Placebo BID	3.27		
<b>Weeks 26</b>			
Eluxadoline 75 mg BID	2.76	-0.40 (-0.76, -0.046)	0.027
Eluxadoline 100 mg BID	2.71	-0.45 (-0.80, -0.094)	0.013
Placebo BID	3.16		

Table 3.27 Sponsor's Per Protocol Analysis Results

<i>For Study 3001</i>	<i>Responder Rate</i>	<i>Odds Ratio</i>	<i>P Value</i>
Complete Response			
Eluxadoline 75 mg BID (N=371)	95 (25.6%)	1.74	0.002
Eluxadoline 100 mg BID (N=360)	87 (24.2%)	1.61	0.010
Placebo BID (N=370)	61 (16.5%)		
Abdominal Pain			
Eluxadoline 75 mg BID (N=371)	164 (44.2%)	1.30	0.078
Eluxadoline 100 mg BID (N=360)	157 (43.6%)	1.27	0.113
Placebo BID (N=370)	140 (37.8%)		
Stool Consistency			
Eluxadoline 75 mg BID (N=371)	117 (31.5%)	1.72	0.001
Eluxadoline 100 mg BID (N=360)	123 (34.2%)	1.94	<0.001
Placebo BID (N=370)	78 (21.1%)		
<i>For Study 3002</i>	<i>Responder Rate</i>	<i>Odds Ratio</i>	<i>P Value</i>
Complete Response			
Eluxadoline 75 mg BID (N=351)	104 (29.6%)	2.16	<0.001
Eluxadoline 100 mg BID (N=345)	104 (30.1%)	2.21	<0.001
Placebo BID (N=349)	57 (16.3%)		
Abdominal Pain			
Eluxadoline 75 mg BID (N=351)	168 (47.9%)	1.14	0.402
Eluxadoline 100 mg BID (N=345)	176 (51.0%)	1.29	0.096
Placebo BID (N=349)	156 (44.7%)		
Stool Consistency			
Eluxadoline 75 mg BID (N=351)	130 (37.0%)	2.19	<0.001
Eluxadoline 100 mg BID (N=345)	126 (36.5%)	2.14	<0.001
Placebo BID (N=349)	74 (21.1%)		

Source: Sponsor's Tables 2.4.1, 2.37.1 and of IR response in SN19 Submission.

Table 3.28 Statistical Reviewer's Subgroup Analysis for Age Based on ITT Analysis Set

<i>Study 3001 Age Subgroup</i>	<i>Number (%)</i>		
	<i>Responder</i>	<i>Non-Responder</i>	<i>P Value</i>
<b>Composite Responders (Weeks 1-12)</b>			
18-64 years (N=1165)			
Eluxadoline 75 mg BID (N=398)	88 (21.1)	310 (77.9)	0.113
Eluxadoline 100 mg BID (N=391)	95 (24.3)	296 (75.7)	0.022
Placebo BID (N=376)	66 (17.6)	310 (82.5)	
>=65 years (N=115)			
Eluxadoline 75 mg BID (N=29)	14 (48.3)	15 (51.7)	<0.001
Eluxadoline 100 mg BID (N=35)	12 (34.3)	23 (65.7)	0.025
Placebo BID (N=51)	7 (13.7)	44 (86.3)	
<b>Abdominal Pain Responders (Weeks 1-12)</b>			
18-64 years (N=1165)			
Eluxadoline 75 mg BID (N=398)	161 (40.5)	237 (59.6)	0.444
Eluxadoline 100 mg BID (N=391)	169 (43.2)	222 (56.8)	0.124
Placebo BID (N=376)	142 (37.8)	234 (62.2)	
>=65 years (N=115)			
Eluxadoline 75 mg BID (N=29)	20 (69.0)	9 (31.0)	0.164
Eluxadoline 100 mg BID (N=35)	15 (42.9)	20 (57.1)	0.361
Placebo BID (N=51)	27 (52.9)	24 (47.1)	
<b>Stool Consistency Responders (Weeks 1-12)</b>			
18-64 years (N=1165)			
Eluxadoline 75 mg BID (N=398)	113 (28.4)	285 (71.6)	0.065
Eluxadoline 100 mg BID (N=391)	134 (34.3)	257 (65.7)	0.0004
Placebo BID (N=376)	85 (22.6)	291 (77.4)	
>=65 years (N=115)			
Eluxadoline 75 mg BID (N=29)	15 (51.7)	14 (48.3)	0.001
Eluxadoline 100 mg BID (N=35)	12 (34.3)	23 (65.7)	0.079
Placebo BID (N=51)	9 (17.6)	42 (82.4)	

<i>Study 3002 Age Subgroup</i>	<i>Number (%)</i>		
	<i>Responder</i>	<i>Non-Responder</i>	<i>P Value</i>
<b>Composite Responders (Weeks 1-12)</b>			
18-64 years (N=1019)			
Eluxadoline 75 mg BID (N=345)	94 (27.3)	251 (72.8)	0.002
Eluxadoline 100 mg BID (N=343)	99 (28.9)	244 (71.1)	0.0003
Placebo BID (N=331)	57 (17.2)	274 (82.8)	
>=65 years (N=126)			
Eluxadoline 75 mg BID (N=36)	16 (44.4)	20 (55.6)	<0.001
Eluxadoline 100 mg BID (N=39)	14 (35.9)	25 (64.1)	0.003
Placebo BID (N=51)	5 (9.8)	46 (90.2)	
<b>Abdominal Pain Responders (Weeks 1-12)</b>			
18-64 years (N=1019)			
Eluxadoline 75 mg BID (N=345)	162 (47.0)	183 (53)	0.458
Eluxadoline 100 mg BID (N=343)	171 (49.9)	172 (50.2)	0.136
Placebo BID (N=331)	146 (44.1)	185 (55.9)	
>=65 years (N=126)			
Eluxadoline 75 mg BID (N=36)	21 (58.3)	15 (41.7)	0.620
Eluxadoline 100 mg BID (N=39)	24 (61.5)	15 (38.5)	0.417
Placebo BID (N=51)	27 (52.9)	24 (47.1)	
<b>Stool Consistency Responders (Weeks 1-12)</b>			
18-64 (N=1019)			
Eluxadoline 75 mg BID (N=345)	121 (35.1)	224 (64.9)	<0.0001
Eluxadoline 100 mg BID (N=343)	119 (34.7)	224 (65.3)	0.0001
Placebo BID (N=331)	71 (21.5)	260 (78.6)	
>=65 years (N=126)			
Eluxadoline 75 mg BID (N=36)	20 (55.6)	16 (44.4)	<0.001
Eluxadoline 100 mg BID (N=39)	17 (43.6)	22 (56.4)	0.007
Placebo BID (N=51)	9 (17.6)	42 (82.4)	

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YEH FONG CHEN  
03/07/2015

MICHAEL E WELCH  
03/09/2015  
Concur with review.



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

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/BLA #:** NDA 206940/S000

**Drug Name:** Eluxadoline Tablets

**Indication(s):** Treatment of pain and diarrhea associated with diarrhea predominant Irritable Bowel Syndrome (IBS-d).

**Applicant:** Furiex Pharmaceuticals, Inc.

**Date(s):** Received 6/26/2014

**Review Priority:** Priority review

**Biometrics Division:** Division of Biometrics VI/Office of Biostatistics (DBVI)

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**Medical Division:** Division of Gastroenterology and Inborn Errors Products

**Keywords:** Clinical studies, NDA review, drug abuse

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## EXECUTIVE SUMMARY

The applicant, Furiex Pharmaceuticals (Furiex), submitted the results from two abuse potential studies CPS-1010 and CPS-1006 [REDACTED] (b) (4) of eluxadoline in both intranasal and oral administration routes. These two studies were performed using the methodologies recommended in the 2010 FDA Draft Guidance for Industry: Assessment of Abuse Potential of Drugs (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf>).

The design of the two studies was similar; they were randomized, blinded, placebo- and active-controlled studies. Study CPS-1010 was conducted to evaluate the abuse potential of two doses of crushed eluxadoline (100 mg: 824 total powder weight and 200 mg: 1648 mg total powder weight) compared to crushed oxycodone immediate-release (IR) tablets (15 and 30 mg), placebo lactose (weight-matched to oxycodone HC1 IR), and placebo to match eluxadoline 200 mg through intranasal administration route in healthy, recreational opioid users with a history of intranasal abuse. Study CPS-1006 was conducted to evaluate the abuse potential of single doses of eluxadoline (100, 300, and 1000 mg) compared to oxycodone HC1 IR tablets (30 and 60 mg), and placebo lactose through oral administration in healthy, recreational users with a history of opioid abuse.

In intranasal study, based on the primary endpoint, Emax of Drug Liking VAS, responses to crushed eluxadoline doses (100 and 200 mg) were similar to those to placebo and much lower than those to two oxycodone IR doses (15 and 30 mg). The percentage of dose insufflated was significantly smaller for both eluxadoline doses in comparison to oxycodone IR doses and placebo lactose. Percentage of dose insufflated for eluxadoline 200 mg was significantly smaller than placebo eluxadoline. In oral study based on the primary endpoint, responses to crushed eluxadoline 100 mg were similar to those to placebo and much lower than those to two doses of oxycodone IR. Responses to the eluxadoline 300 and 1000 mg doses were significantly higher than those to placebo based on the Wilcoxon signed-rank test on the within-subject differences. Both studies were validated by the comparison between each dose of the positive control and placebo.

Statistically significant decreases in pupil diameter were observed for eluxadoline 1000 mg in comparison to placebo in Study CPS-1006. Although the decreases in pupil diameter also were observed for eluxadoline 300 mg in the same study, the change in pupil diameter was not statistically significant compared to placebo. The results were replicated by the statistical significantly larger pupillary differences between each intranasal dose of eluxadoline and placebo in study CPS-1010. The clinical and the controlled substances staff (CSS) reviewers will decide the clinical importance for this finding.

# 1 INTRODUCTION

## 1.1 Overview

### 1.1.1 Background Information

The applicant, Furiex Pharmaceuticals (Furiex), has submitted a New Drug Application (NDA 206940) to the Division of Gastroenterology and Inborn Errors Products (DGI) for eluxadoline tablets. The proposed indication is the “treatment of abdominal pain and diarrhea in adult patients with diarrhea predominant irritable bowel syndrome (IBS-d)”.

Eluxadoline (also known as JNJ-27018966) is a locally active, mixed mu opioid receptor ( $\mu$ OR) agonist and delta opioid receptor ( $\delta$ OR) antagonist. The sponsor summarized the abuse liability of eluxadoline according to the 8-factor analysis of the Controlled Substances Act (CSA) <sup>(b) (4)</sup>

(b) (4)

### 1.1.2 Specific Studies Reviewed

The applicant submitted a list of preclinical and clinical study reports related to abuse potential assessment that were conducted and cited in the NDA submission. I will only focus on two human abuse potential studies CPS-1010 and CPS-1006 in my review after discussed with the CSS reviewer (Table 1). Throughout this review, eluxadoline will be referred to as eluxadoline in the text contents and elu in the figures and tables; Oxycodone will be referred to as oxycodone in the text contents and oxy in the figures and tables.

Table 1: List of Studies Included in this Review

Study ID (Period)	Location	Design	Primary Endpoints	Treatments	Number of Subjects
CPS-1010 (2/7/2013–6/11/2013)	1 site in the Canada	R, DB, AC, PC, MD, six-arms crossover to evaluate the abuse potential of intranasally administered drug	Emax for Drug L king VAS	Eluxadoline 100 mg Eluxadoline 200 mg Oxycodone HCl IR 15 mg Oxycodone HCl IR 30 mg Placebo lactose, weight matched to HCl IR Placebo to match eluxadoline 200 mg	36 randomized and 31 subjects completed all treatment periods
CPS-1006 (9/20/2013–1/7/2014)	1 site in the USA	R, DB, AC, PC, MD, six-arms crossover to evaluate the abuse potential of orally administered drug	Emax for Drug L king VAS	Eluxadoline 100 mg Eluxadoline 300 mg Eluxadoline 1000 mg Oxycodone HCl IR 30 mg Oxycodone HCl IR 60 mg Placebo	40 randomized and 33 subjects completed all treatment periods

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

## 1.2 Data Sources

All data was supplied by the applicant to the CDER electronic data room in SAS transport format. The data and final study report for the electronic submission were archived under the network path location <\\...\\206940.enx>. The information needed for this review was contained in submission modules 1.11.4, 2.7, 5.3.4 modules and datasets.

## 2 STATISTICAL EVALUATION

### 2.1 Data and Analysis Quality

In general, the data and analysis quality are acceptable.

### 2.2 Human Abuse Potential Stud CPS-1010

#### 2.2.1 Overview

CPS-1010 was a randomized, blinded, placebo-, and active-controlled study to evaluate the relative abuse potential of intranasally administered crushed eluxadoline tablets compared to placebo and crushed oxycodone HCl Immediate Release (IR) tablets in healthy recreational opioid users with a history of intranasal abuse.

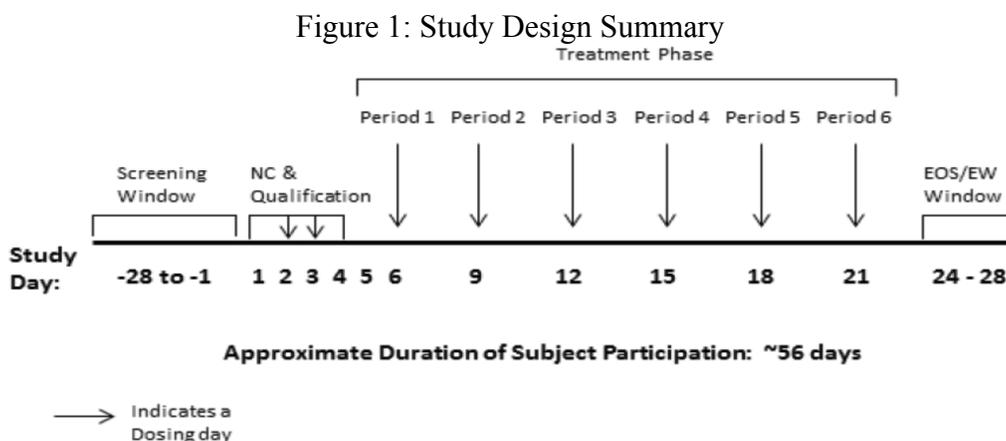
##### 2.2.1.1 Objectives of the Study

The primary objective was to evaluate the abuse potential of single doses of crushed eluxadoline (100 and 200 mg) compared to crushed oxycodone HCl IR tablets (15 and 30 mg), placebo lactose (weight-matched to oxycodone HCl IR), and placebo to match eluxadoline 200 mg in healthy, recreational opioid users with a history of intranasal abuse.

The secondary objectives were to confirm the safety and tolerability following single intranasal doses of eluxadoline (100 and 200 mg) and to assess the pharmacokinetics of eluxadoline in this population.

##### 2.2.1.2 Study Design

The study consisted of 3 phases: Pre-Treatment, Treatment, and Follow-up. The Pre-Treatment Phase included a standard medical screening visit followed by a Naloxone Challenge (NC)/Qualification visit. The Treatment Phase includes six 3-day inpatient visits. The Follow-up Phase includes a single End-of-Study/Early Withdrawal (EOS/EW) Visit. The approximate total duration for any subject will be approximately 56 days (Figure 1).



[Source: Figure 1 of study report CPS-1010-study-report.pdf, page 1392]

The Pre-Treatment Phase included 2 visits: a Screening visit (Visit 1), conducted with 28 days of the first study drug administration of the Naloxone Challenge (NC), and an NC/Qualification visit (Visit 2). The NC/Qualification visit lasted 4 days (3 overnight stays). All subjects completed the NC test on Day 1, at least 12 hours prior to drug administration in the Qualification, to confirm that subjects were not physically dependent to opioids. On the morning of Days 2 and 3, subjects self-administered crushed oxycodone HCl IR 20 mg or placebo in a randomized fashion (washout of 24 hours) to determine if they liked and tolerated the effects of oxycodone and could discriminate these from placebo. This visit also determined if each subject was suitable for entry into the study.

The following treatments were administered intranasally via insufflation:

- Oxycodone HCl IR 20 mg (2 × 10 mg tablets, crushed)
- Placebo (lactose tablets, crushed), weight matched to oxycodone HCl IR

The Treatment Phase included six 3-day (2-night) inpatient visits (Visits 3 to 8). The washout period from the last drug administration at the NC/Qualification visit and the first study drug administration in the Treatment Phase was at least 72 hours. Subjects received each of the intranasal treatments randomization sequence outlined in Table 2 in blinded fashion (one per Treatment visit):

- Treatment A: Eluxadoline 100 mg (1 × 100 mg tablet, crushed, weighted 824 mg)
- Treatment B: Eluxadoline 200 mg (2 × 100 mg tablets, crushed, weighted 1648 mg)
- Treatment C: Oxycodone HCl IR 15 mg (3 × 5 mg tablets, crushed)
- Treatment D: Oxycodone HCl IR 30 mg (3 × 10 mg tablets, crushed)
- Treatment E: Placebo (lactose tablets, crushed), weight matched to oxycodone HCl IR
- Treatment F: Placebo to match eluxadoline 200 mg (2 × placebo tablets, crushed, weighted 1648 mg)

Note that, in order to maintain subjects' blinding (and minimize investigator bias), 2 doses of placebo were administered that matched the weight of oxycodone HCl IR and eluxadoline (200 mg dose).

*Reviewer's comment* The sponsor did not use double dummy technique in the study. The double dummy now is not required for intranasal studies with large volume of the test drug. This study includes the placebo which matches the weight of 200 mg of the test drug in order to examine if the dislike of the test drug is due to large weight or the New Molecular Entity (NME) itself. Thus the main comparison of interest is between the test drug and placebo.

Table 2: Treatment Randomization Sequence

Treatment Sequence Group (n= 6 per group)	Treatment Period					
	1	2	3	4	5	6
1	A	B	F	C	E	D
2	B	C	A	D	F	E
3	C	D	B	E	A	F
4	D	E	C	F	B	A
5	E	F	D	A	C	B
6	F	A	E	B	D	C

[Source: Table 1 of study report CPS-1010-study-report.pdf, page 1392]

The Follow-up Phase included a single End-of-Study/ Early Withdrawal (EOS/EW) Visit (Visit 9). The EOS/EW visit was planned to occur between 3 and 7 days after the last study drug administration or at the time of early discontinuation.

The eligible subjects were male or female recreational opioid users, 18 to 55 years of age, who were not physically dependent on opioids, but had experience using opioids for non-therapeutic purposes (i.e., for psychoactive effects) on at least 10 occasions within the last year and at least once in the 8 weeks prior to screening. Subjects must have experienced at least 3 occasions of intranasal drug use in the last 12 months and at least 1 occasion of intranasal opioid drug use in the 3 months prior to screening. Approximately 36 subjects were planned for randomization to the treatment phase to ensure that at least 28 subjects completed all Treatment visits.

### 2.2.1.3 Abuse Potential Measures

Pharmacodynamic (PD), pharmacokinetic (PK), and safety assessments were conducted up to 24 hours post-dose. All subjects were discharged from each visit after completion of the final (i.e., 24 hours) post-dose procedures. Each study drug administration was separated by a minimum of 72 hours.

**The primary endpoint** was the peak score (Emax) for Drug Linking VAS. All other PD endpoints (Peak scores, Emax and/or Emin and time-averaged area under the effect curve [TA-AUE]) were secondary endpoints. Subjective and objective measures and corresponding endpoints are listed below:

Balance of effects:

- Drug Liking VAS (Emax, Emin and TA\_AUE)
- Overall Drug Liking VAS (Emax, Emin; end-of-day and next day scores)
- Take Drug Again VAS (Emax; end-of-day and next day scores)
- SDV (end-of-day and next day scores)

Positive effects:

- High VAS (Emax and TA\_AUE)
- Good Effects VAS (Emax and TA\_AUE)
- ARCI MBG scale (Emax and TA\_AUE)

Negative effects:

- Bad Effects VAS (Emax and TA\_AUE)
- ARCI LSD scale (Emax and TA\_AUE)

Other drug effects:

- Any Effects VAS (Emax and TA\_AUE)
- Alertness/Drowsiness VAS (Emax and TA\_AUE)
- ARCI PCAG scale
- Drug Similarity VAS (score at 12 hours)
- Subject-rated scale for nasal effects

Objective Measures:

- Pupillometry (maximum pupil constriction [MPC], time-averaged pupillometry area over the curve [PAOCavg])
- Observer-rated assessment of intranasal irritation
- Percentage of dose insufflated (mg %)

Note: Pupil diameters (mm) were collected at pre-dose, 5 min, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, and 6 hours. The MPC was the maximum pupil constriction (minimum pupil diameter vs. pre-dose) at each period; PAOCavg was the time-averaged pupillometry area over the curve.

#### 2.2.1.4 Analysis Population and Sample Size

The primary analysis was based on the PD Analysis Set which was defined as all enrolled subjects who received at least 1 dose of eluxadoline in the treatment phase and had sufficient PD samples to allow accurate calculation of PD parameters. Missing data for Plasma concentration, PD score or response to questionnaire were considered as non-informative missing. No imputation was performed for any missing observed value.

A total of 108 subjects were screened for enrollment. Of these subjects, 64 subjects passed Screening and were eligible for the Qualification Phase and 54 were dosed during the Qualification Phase. Of the 39 subjects passed qualification criteria, 36 subjects were randomized and 31 (86%) subjects completed all 6 treatment periods (Table 3).

The sponsor claimed that with a sample size of 28 subjects, yielded approximately 90% power (employing a paired T-test) to detect a significant difference in Drug Liking VAS (bipolar scale) between intranasally administered oxycodone IR and placebo (study validity) under the assumptions of a 15-point difference on the drug liking scale between oxycodone 30 mg and placebo, a common SD of 16.6 and a two-sided  $\alpha$  level of 0.05.

Table 3: Subject Disposition (Randomized Set)

Subject Disposition	Total n (%) <sup>a</sup>
Number of subjects randomized	36
Number (%) of completers	31 (86.1)
Eluxadoline 100 mg	32 (88.9)
Eluxadoline 200 mg	32 (88.9)
Oxycodone HCl IR 15 mg	32 (88.9)
Oxycodone HCl IR 30 mg	32 (88.9)
Placebo lactose	32 (88.9)
Placebo eluxadoline	34 (94.4)
Number (%) of subjects who withdrew early	5 (13.9)
Reason for withdrawal	
Adverse event or serious adverse event	4 (11.1)
Voluntarily withdrew	1 (2.8)

[Source: Table 5 of study report CPS-1010-study-report.pdf, page 59]

#### 2.2.1.5 Statistical Methodologies used in the Sponsor's Analyses

Pharmacodynamic data at each time point were summarized by descriptive statistics and presented graphically (where appropriate) for the Pharmacodynamic Population for the Treatment Phase; the primary measures, pertinent to qualification, were also summarized for the Qualification Phase. Derived parameters were summarized using descriptive statistics and boxplots. Pharmacodynamic parameters (Emax, Emin, and/or Time Weighted mean (TWmean), as appropriate) were analyzed using a mixed-effect model for a crossover study. The model included treatment, period, sequence, and first-order carryover effect as fixed effects, baseline (pre-dose) measurement as covariate where applicable, and subject nested within treatment sequence as random effect. A washout of at least 3 days was used in order to minimize the potential for carryover effects. If the carryover effect was found to be non-significant at the 25% level, then the term was dropped from the analysis model. Baseline and carryover were included as applicable. Least square means, standard errors (SE) and 95% two-sided confidence intervals for treatments and treatment differences were derived from the mixed-effects model. P values were provided

for the effects and the contrasts. The contrasts were presented only if there was an overall treatment effect.

### **Hypothesis testing:**

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

The contrasts to assess the abuse potential for eluxadoline included:

- Each dose of oxycodone HCl IR (15 and 30 mg) compared to placebo lactose – to validate the study sensitivity
- Each dose of eluxadoline (100 and 200 mg) compared to each dose of oxycodone HCl IR (15 and 30 mg)
- Each dose of eluxadoline (100 and 200 mg) compared to eluxadoline placebo and placebo lactose
- Eluxadoline placebo compared to placebo lactose

The primary endpoint, Emax for Drug Liking VAS, was compared between the positive control (oxycodone) and placebo to confirm the sensitivity of the study.

The abuse potential of eluxadoline was assessed through evaluation and integrative interpretation of the pattern of results across the various types of measures: measures of positive response (i.e., measures most predictive of the drug's abuse potential and reinforcing properties), measures of negative response (i.e., measures that potentially mitigate abuse potential), and measures of other effects. Measures of intranasal effects, and percentage of dose insufflated also provided information regarding the ease of intranasal administration of eluxadoline in comparison to oxycodone (measures how physical characteristics of eluxadoline may impede or limit intranasal abuse). The various planned comparisons helped to evaluate the importance of the steepness of the dose-response curves and the similarity of responses to eluxadoline, as compared to the responses to oxycodone.

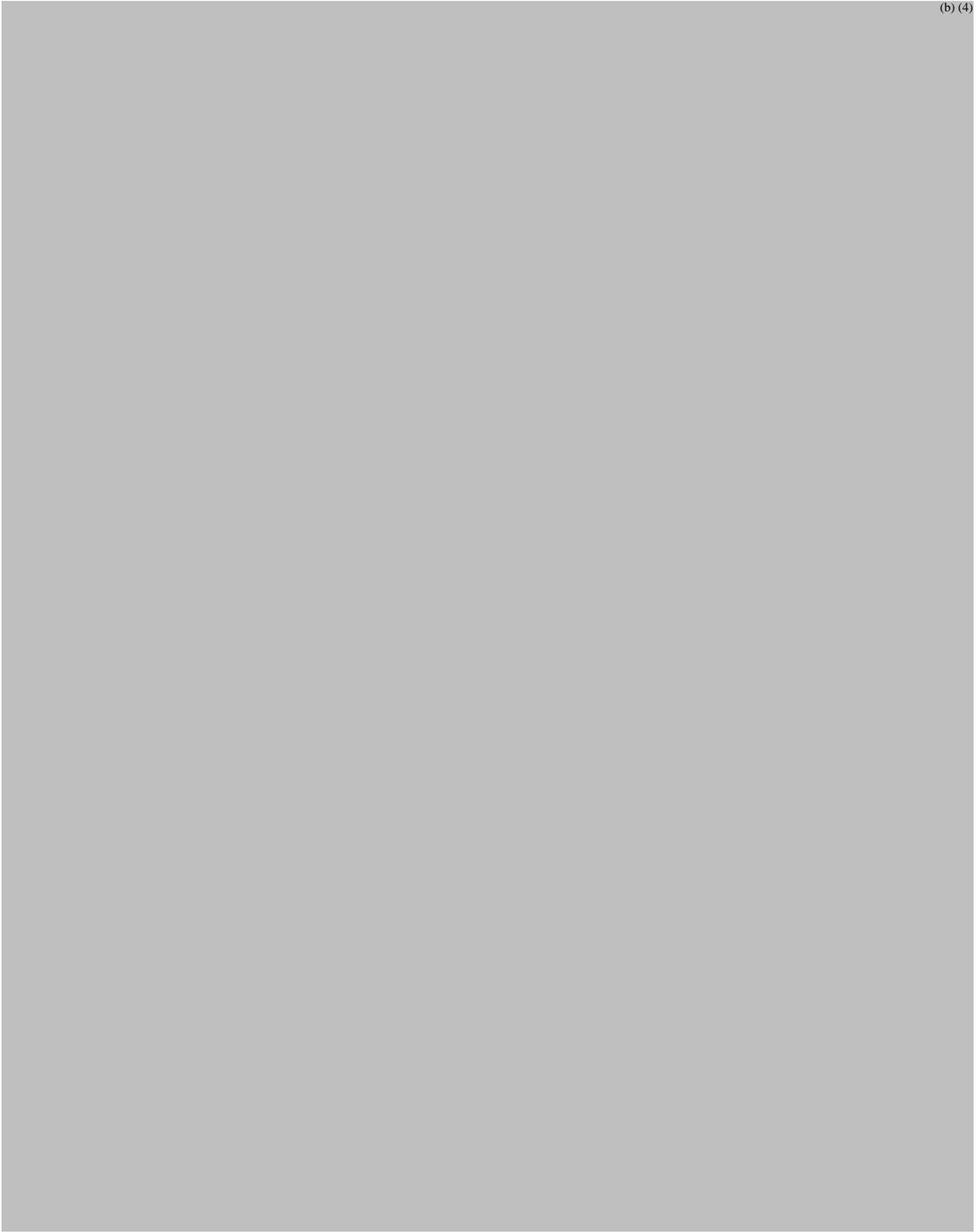
#### **2.2.1.6 Changes in the Conduct of the Study**

The Statistical Analysis Plan was finalized on May 27, 2013. The sponsor claimed that the following changes to the analysis sets were made in the SAP prior to database lock and unblinding:

- Replacing “subjects who received 1 dose of Eluxadoline” with “subjects in Randomized Set who received at least 1 dose of eluxadoline in the Treatment Phase” in all PK, PD, Safety Analysis Sets.
- The residuals from the mixed-effect model were investigated for normality using the Shapiro-Wilk W-test. Parameters were considered to be normally distributed if the W-test was not statistically significant at an  $\alpha$ -level of significance of 0.05. Parameters that did not meet this criterion were analyzed non-parametrically. Overall treatment effect was assessed using Friedman's test; pairwise treatment comparisons were assessed using the Wilcoxon sign-rank test on the within-subject differences.

### 2.2.1.7 Sponsor's Summary and Conclusions

The Sponsor summarized their PD analysis results as follows:



(b) (4)

The sponsor concluded that:



### 2.2.2 Reviewer's Assessment

This reviewer confirmed the sponsor's analyses results on Emax, Emin, and TA-AUE for PD population (See Table 22 in Appendix for the details) and focused on the primary endpoint of Drug Liking VAS, Pupillometry (MPC and PAOCavg), and percentage of dose insufflated (mg %) based on the completer population.

#### 2.2.2.1 Primary Endpoint – Drug Liking VAS

##### Descriptive Statistics

Table 4 shows the first quartiles of the primary endpoint are around 50 for eluxadoline doses which are much lower than those for oxycodone IR two doses (70 to 77). The mean difference between these treatments ranged between 25 to 36 points. The similar tables for High VAS, ARCI MBG, Good Effect VAS, Bad Effect VAS, Overall Drug Liking VAS, and Take Drug Again VAS for the oral study can be found in Table 21 in the Appendix.

The mean responses to both oxycodone placebo and eluxadoline placebo remained slightly below neutral (50) over time (Figure 2). Oxycodone IR 15 mg and 30 mg had similar profiles above placebos and reached the peak mean of drug liking at 0.5 hour and 1 hour, respectively. The peak mean response to oxycodone IR 30 mg was higher than that to oxycodone IR 15 mg. In contrast, the profiles for both doses of eluxadoline were below those of placebos, and in the “disliking” range (<50) until approximately 12 hours post-dose. Figure 3 is the heat map for Drug Liking VAS Emax by treatment for completer population. The density of the color green indicates the degree of the disliking and the density of the color red indicates the degree of the liking. This figure shows that most of subjects in eluxadoline doses were neutral and slightly above neutral except there were four subjects disliked and four subjects liked. The subjects in placebos were neutral and in oxycodone doses were highly liked. The heat maps for Drug Liking VAS Emax by treatment for PD population and time course response profiles for individual subjects to two doses (100 and 200 mg) of eluxadoline, two doses of oxycodone (15 and 30 mg), and placebo for completers population can be found in Figure 11 to Figure 17 in the Appendix.

Table 4: Summary Statistics for Emax of Drug Liking VAS (N=31)

Treatments	N	Mean	StdErr	Min	Q1	Med	Q3	Max
Elu 100 mg	31	53.26	3.96	0	50	51	51	100
Elu 200 mg	31	54.97	3.84	0	50	51	63	100

Treatments	N	Mean	StdErr	Min	Q1	Med	Q3	Max
Oxy 15 mg	31	80.42	3.90	3	70	84	100	100
Oxy 30 mg	31	88.55	2.67	50	77	96	100	100
Placebo Oxy 200 mg	31	49.10	1.63	0	50	51	51	52
Placebo Elu 200 mg	31	51.45	1.489	34	50	51	51	93

Figure 2: The Mean Time Course Profiles on Drug Liking VAS by Treatments (N=31)

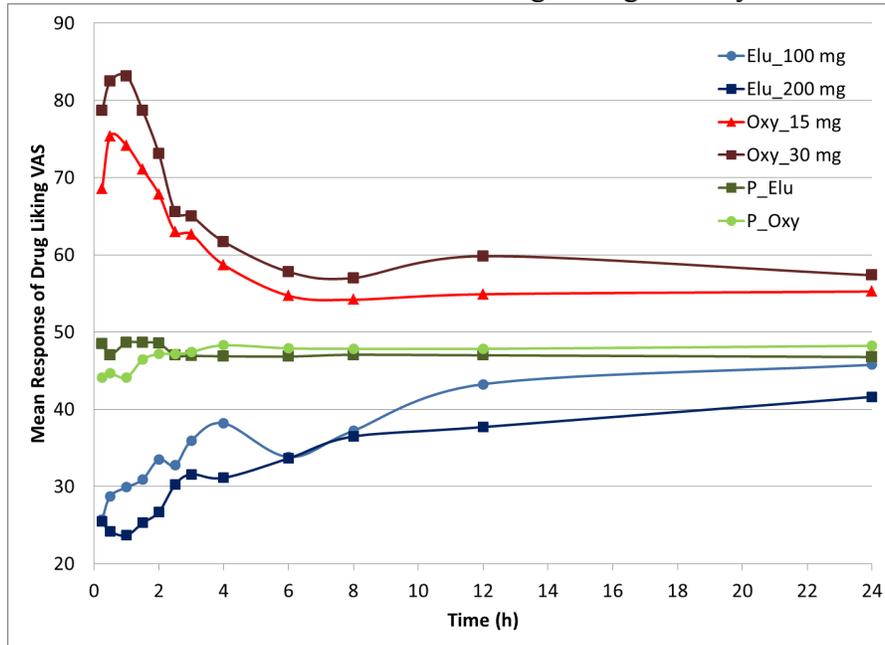
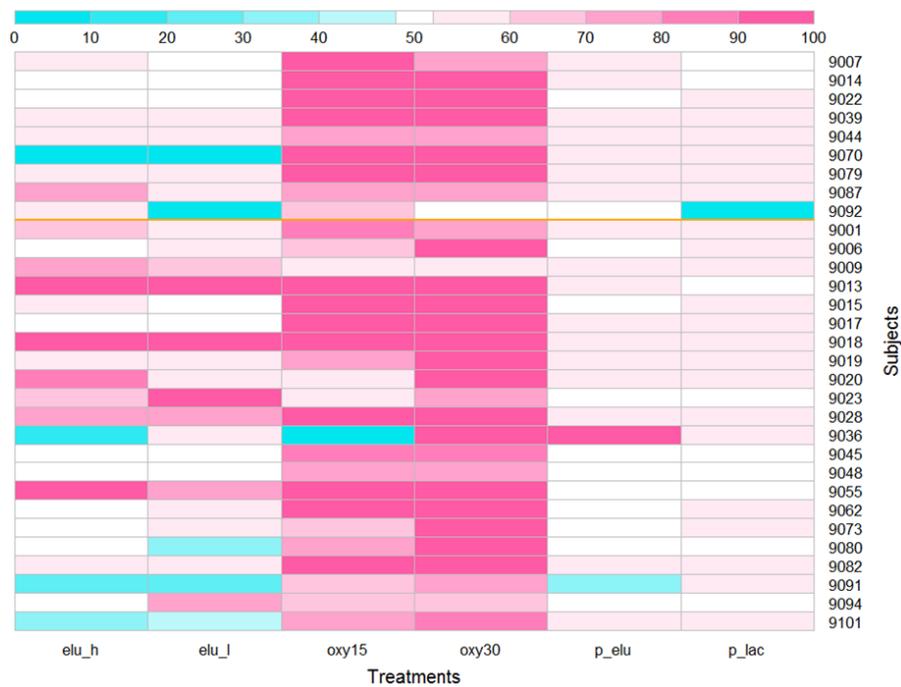


Figure 3: Heat Map for Drug Liking VAS Emax by Treatment (N=31)



## Inferential Statistics

Inferential analysis using ANCOVA model results for Drug Liking VAS are summarized in Table 5. The assumption of normal distribution of the data was examined using Shapiro-Wilk Normality test. Since the probability value was  $\leq 0.05$ , the pairwise treatment comparisons were assessed using the Wilcoxon signed-rank test on the within-subject differences (Table 7). The results are similar to the results from ANCOVA model. I confirmed the sponsor's analysis results based on the PD population, which can be found in Table 22 in the Appendix.

Pairwise comparisons using a mixed-effect model for a crossover study revealed significantly higher Drug Liking VAS Emax scores for oxycodone IR 15 and 30 mg compared to placebo lactose ( $P < 0.0001$  for both), confirming validity of the study. Drug Liking VAS Emax scores were significantly lower for eluxadoline (100 and 200 mg) compared to oxycodone IR (15 and 30 mg,  $P < 0.0001$  for all). There were no significant mean differences for Drug Liking VAS Emax between two placebo dose (lactose and eluxadoline placebo) with eluxadoline placebo had higher response than placebo (lactose). I performed the new test using the equivalence margin of 11 (Table 9). The results show that the difference in mean between the two doses of eluxadoline and eluxadoline placebo was significantly lower than the equivalence margin of 11. This suggests that the both doses of the eluxadoline were similar to placebo based on Drug Liking VAS.

Table 5: The Treatment Comparison in LS Means of Emax of Drug Liking (VAS) (N=31)

Treatment Comparison	LS Mean	LS Mean Diff.	Std Error	P-value	LL-95%CI	UL-95%CI
Oxy 15 mg -	77.92	28.58	3.97	<.0001	20.74	36.42
Oxy Placebo	49.34					
Oxy 30 mg -	85.92	36.57	3.99	<.0001	28.69	44.45
Oxy Placebo	49.34					
Elu 100 mg -	53.31	-24.61	3.97	<.0001	-32.46	-16.76
Oxy 15 mg	77.92					
Elu 200 mg -	53.32	-24.60	3.98	<.0001	-32.47	-16.73
Oxy 15 mg	77.92					
Elu 100 mg -	53.31	-32.60	3.99	<.0001	-40.48	-24.72
Oxy 30 mg	85.91					
Elu 200 mg -	53.32	-32.59	3.94	<.0001	-40.39	-24.80
Oxy 30 mg	85.91					
Elu 100 mg -	53.31	1.76	3.94	0.6562	-6.03	9.55
Elu Placebo	51.55					
Elu 200 mg -	53.32	1.77	3.96	0.6563	-6.07	9.61
Elu Placebo	51.55					
Elu 100 mg -	53.31	3.97	3.93	0.3149	-3.81	11.75
Oxy Placebo	49.34					
Elu 200 mg -	53.32	3.98	3.96	0.3164	-3.85	11.80
Oxy Placebo	49.34					
Elu Placebo -	51.55	2.21	3.97	0.5789	-5.65	10.07
Oxy Placebo	49.34					

Table 6: Analysis Results in Mean of Emax of Drug Liking (VAS) (N=31)

Test Drug	Placebo	N	LS mean Diff.	StdErr	P-value	95% CI	
						Lower	Upper
Elu 100 mg	Elu Placebo +11	31	-9.24	3.94	0.0204	-17.03	-1.45
Elu 200 mg	Elu Placebo +11	31	-9.23	3.96	0.0213	-17.07	-1.39
Elu 100 mg	Oxy Placebo +11	31	-7.02	3.96	0.0761	-14.85	0.75
Elu 200 mg	Oxy Placebo +11	31	-7.02	3.96	0.0782	-14.84	0.80

Figure 4: The Treatment Comparison in Means of Drug Liking VAS Emax (N=31)

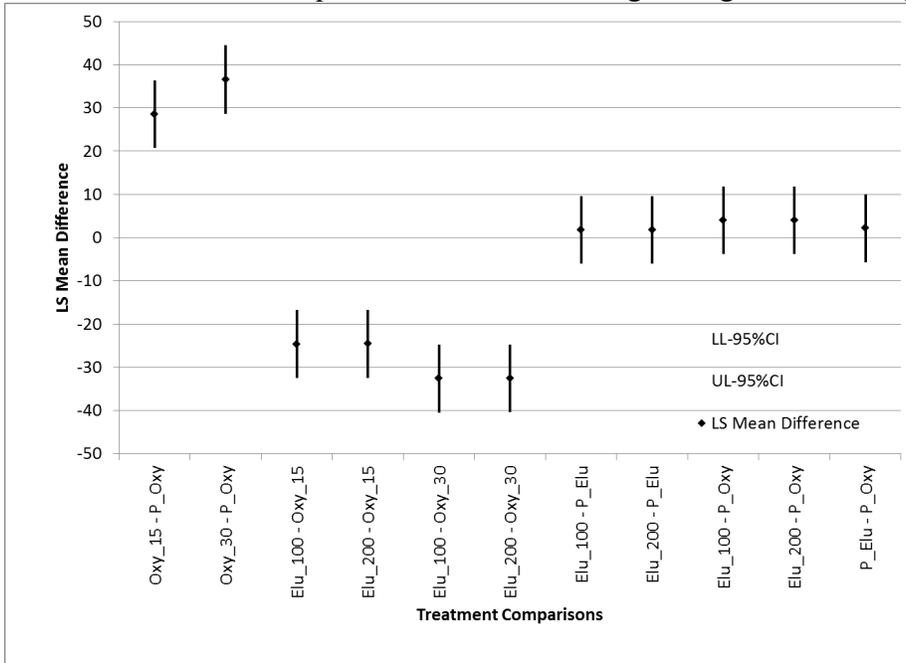


Table 7: The Treatment Comparison in Median of Emax of Drug Liking (VAS) Study CPS-1010 (N=31)

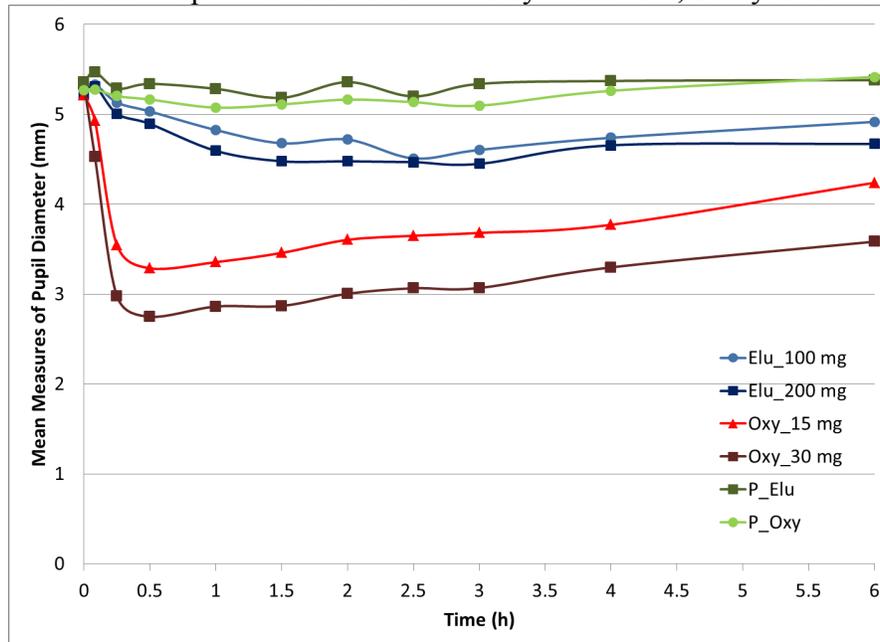
Overall Treatment Effect	Median Difference	IQR	P-value
Oxycodone HCl IR 15 mg – Placebo lactose	38	19, 49	<0.0001
Oxycodone HCl IR 30 mg – Placebo lactose	49	27, 49	<0.0001
Eluxadoline 100 mg – Oxycodone HCl IR 15 mg	-28	-48, -12	<0.0001
Eluxadoline 200 mg – Oxycodone HCl IR 15 mg	-26	-48, -9	<0.0001
Eluxadoline 100 mg – Oxycodone HCl IR 30 mg	-45	-49, -26	<0.0001
Eluxadoline 200 mg – Oxycodone HCl IR 30 mg	-45	-49, -26	<0.0001
Eluxadoline 100 mg – Placebo eluxadoline	0	-1, 1	0.73524
Eluxadoline 200 mg – Placebo eluxadoline	0	0, 12	0.24996
Eluxadoline 100 mg – Placebo lactose	0	-1, 20	0.21744
Eluxadoline 200 mg – Placebo Lactose	0	0, 0	0.90039
Placebo eluxadoline – Placebo lactose	0	-1, 2	0.41016

### 2.2.2.2 Pupillometry Endpoint

#### Descriptive Statistics

The pupil diameter was consistent with baseline scores across all time points for placebo lactose and placebo eluxadoline. Oxycodone IR 15 and 30 mg were associated with pronounced decreases in pupil diameter that peaked at approximately 0.5 hours post-dose and remained lower than placebo until 6 hours post-dose. Oxycodone IR 30 mg had a slightly greater decline in pupil diameter in comparison to the 15 mg dose. Both doses of eluxadoline were associated with a slight decline in pupil diameter that began approximately 1 hour post-dose, but pupil effects were much less than that seen with either dose of oxycodone IR (Figure 5).

Figure 5: The Mean Pupil Diameter Over Time by Treatment, Study CPS-1010 (N=31)



#### Inferential Statistics

A significant overall treatment effect was observed for MPC and PAOCavg. MPC and PAOCavg were significantly higher for oxycodone IR 15 and 30 mg than for placebo lactose and both doses of eluxadoline. Similarly, MPC and PAOCavg were significantly higher for eluxadoline 100 and 200 mg than for placebo eluxadoline and placebo lactose. No significant differences were observed between the 2 placebo doses (Table 8 and Table 9).

Table 8: The Treatment Comparison in LS Means of MPC (N=31)

Treatment Comparison	LS Mean Diff.	Std Error	P-value	LL_95%CI	UL_95%CI
Oxycodone HCl IR 15 mg – Placebo lactose	1.5583	0.1203	<.0001	1.3203	1.7962
Oxycodone HCl IR 30 mg – Placebo lactose	2.0805	0.1205	<.0001	1.8422	2.3188
Eluxadoline 100 mg – Oxycodone HCl IR 15 mg	-0.9907	0.1202	<.0001	-1.2283	-0.7530
Eluxadoline 200 mg – Oxycodone HCl IR 15 mg	-0.9599	0.1203	<.0001	-1.1978	-0.7220
Eluxadoline 100 mg – Oxycodone HCl IR 30 mg	-1.5129	0.1206	<.0001	-1.7515	-1.2743
Eluxadoline 200 mg – Oxycodone HCl IR 30 mg	-1.4821	0.1195	<.0001	-1.7184	-1.2458

Treatment Comparison	LS Mean Diff.	Std Error	P-value	LL-95%CI	UL_95%CI
Eluxadoline 100 mg – Placebo eluxadoline	0.5118	0.1191	<.0001	0.2764	0.7473
Eluxadoline 200 mg – Placebo eluxadoline	0.5426	0.1199	<.0001	0.3055	0.7797
Eluxadoline 100 mg – Placebo lactose	0.5676	0.1190	<.0001	0.3322	0.8030
Eluxadoline 200 mg – Placebo Lactose	0.5984	0.1199	<.0001	0.3614	0.8354
Placebo eluxadoline – Placebo lactose	0.05577	0.1202	0.6434	-0.1819	0.2934

Table 9: The Treatment Comparison in LS Means of PAOCavg (N=31)

Treatment Comparison	LS Mean Diff.	Std Error	P-value	LL-95%CI	UL_95%CI
Oxycodone HCl IR 15 mg – Placebo lactose	1.4580	0.09226	<.0001	1.2755	1.6405
Oxycodone HCl IR 30 mg – Placebo lactose	2.0950	0.09203	<.0001	1.9129	2.2771
Eluxadoline 100 mg – Oxycodone HCl IR 15 mg	-0.9475	0.09187	<.0001	-1.1293	-0.7658
Eluxadoline 200 mg – Oxycodone HCl IR 15 mg	-0.8599	0.09191	<.0001	-1.0418	-0.6780
Eluxadoline 100 mg – Oxycodone HCl IR 30 mg	-1.5846	0.09226	<.0001	-1.7671	-1.4020
Eluxadoline 200 mg – Oxycodone HCl IR 30 mg	-1.4969	0.09148	<.0001	-1.6779	-1.3159
Eluxadoline 100 mg – Placebo eluxadoline	0.4306	0.09095	<.0001	0.2506	0.6106
Eluxadoline 200 mg – Placebo eluxadoline	0.5183	0.09163	<.0001	0.3369	0.6996
Eluxadoline 100 mg – Placebo lactose	0.5104	0.09101	<.0001	0.3304	0.6905
Eluxadoline 200 mg – Placebo Lactose	0.5981	0.09174	<.0001	0.4166	0.7796
Placebo eluxadoline – Placebo lactose	0.07982	0.09184	0.3864	-0.1019	0.2615

### 2.2.2.3 Percentage of Dose Insufflated Endpoint

#### Descriptive Statistics

Mean percent dose insufflated was highest for oxycodone IR 15 and 30 mg and median percentage was 100 for both doses. Mean percent insufflated was only slightly lower for placebo lactose. In contrast, mean percent dose insufflated for both eluxadoline doses was lower than that for oxycodone IR, with approximately 50% insufflated and similar median scores. Placebo eluxadoline had only slightly higher mean and median percentages in comparison to eluxadoline active treatment (Table 10).

Table 10: Descriptive Statistics of Percentage of Dose Insufflated (N=31)

Treatments	N	Mean	StdErr	Min	Q1	Med	Q3	Max
Elu 100 mg	31	53.5484	6.56217	0	23	48	95	100
Elu 200 mg	31	49.3548	7.14317	0	8	42	100	100
Oxy 15 mg	31	91.1290	3.80315	11	100	100	100	100
Oxy 30 mg	31	96.0323	2.38024	40	100	100	100	100
Placebo Oxy 200 mg	31	85.2258	5.11853	7	79	100	100	100
Placebo Elu 200 mg	31	63.5484	5.85025	3	37	63	100	100

## Inferential Statistics

There were significant overall treatment effects observed for percentage of dose insufflated ( $P < 0.0001$ ). Percentage of dose insufflated was significantly greater for both oxycodone IR doses in comparison to eluxadoline (100 and 200 mg doses). Percentage of dose insufflated was also significantly greater for placebo lactose in comparison to both doses of eluxadoline active treatment and placebo eluxadoline. The percent of dose insufflated for placebo eluxadoline was also significantly greater than eluxadoline 200 mg (Table 11).

Table 11: The Treatment Comparison in LS Means of Percentage of Dose Insufflated (N=31)

Treatment Comparison	LS Mean Diff.	Std Error	P-value	LL-95%CI	UL_95%CI
Oxycodone HCl IR 15 mg – Placebo lactose	2.8553	5.7679	0.6214	-8.5481	14.2587
Oxycodone HCl IR 30 mg – Placebo lactose	8.5090	5.7995	0.1446	-2.9568	19.9749
Eluxadoline 100 mg – Oxycodone HCl IR 15 mg	-35.8556	5.7776	<.0001	-47.2782	-24.4329
Eluxadoline 200 mg – Oxycodone HCl IR 15 mg	-40.0721	5.7887	<.0001	-51.5166	-28.6276
Eluxadoline 100 mg – Oxycodone HCl IR 30 mg	-41.5093	5.7990	<.0001	-52.9744	-30.0443
Eluxadoline 200 mg – Oxycodone HCl IR 30 mg	-45.7259	5.7356	<.0001	-57.0654	-34.3863
Eluxadoline 100 mg – Placebo eluxadoline	-9.6432	5.7303	0.0946	-20.9723	1.6858
Eluxadoline 200 mg – Placebo eluxadoline	-13.8598	5.7673	0.0176	-25.2621	-2.4574
Eluxadoline 100 mg – Placebo lactose	-33.0003	5.7236	<.0001	-44.3161	-21.6844
Eluxadoline 200 mg – Placebo Lactose	-37.2168	5.7564	<.0001	-48.5976	-25.8361
Placebo eluxadoline – Placebo lactose	-23.3571	5.7819	<.0001	-34.7881	-11.9260

### 2.2.2.4 Conclusion

In this intranasal study, based on the primary endpoint, Emax of Drug Liking VAS, responses to crushed eluxadoline 100 mg and 200 mg were similar to those to placebo and much lower than two oxycodone IR doses. The study was validated by the comparison between each dose of the positive control and placebo.

Percentage of dose insufflated was significantly smaller for both eluxadoline doses in comparison to oxycodone IR and placebo lactose. Percentage of dose insufflated for 200 mg eluxadoline was significantly smaller than placebo eluxadoline.

Statistically significant decreases in pupil diameter were observed following eluxadoline in comparison to both placebos. Although, these decreases were much less than the decrease observed after either dose of oxycodone, the trend of dose response of eluxadoline was seen. The clinical and CSS reviewers will decide the clinical importance for this finding.

## 2.3 Human Abuse Potential Stud CPS-1006

### 2.3.1 Overview

The CPS-1006 was a randomized, double-blind, double-dummy, placebo- and active-controlled, 6-way crossover study to evaluate the abuse potential, pharmacodynamics (PD), PK, and safety

profile of orally administered eluxadoline compared to oxycodone HCl IR in recreational opioid users.

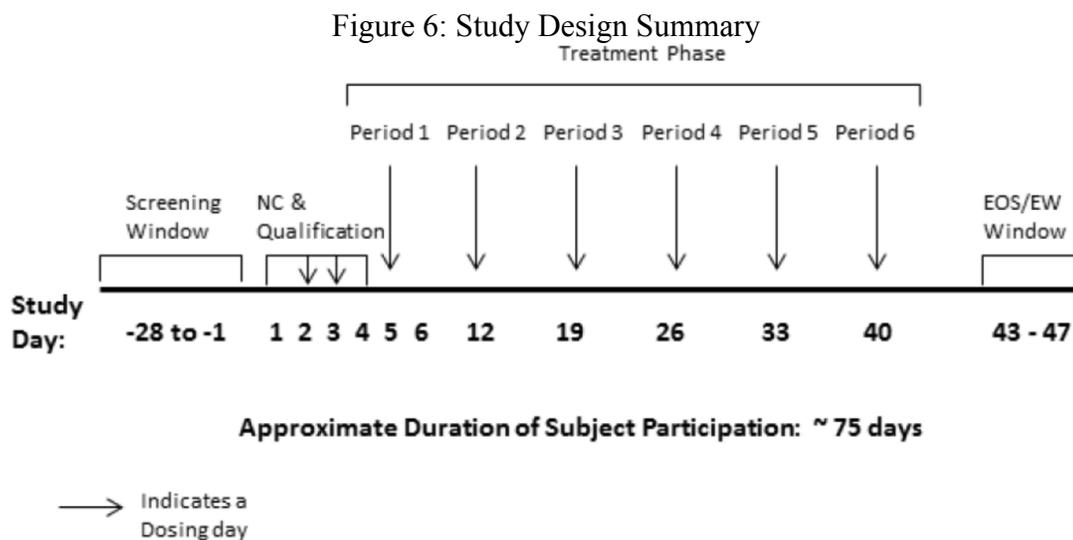
### 2.3.1.1 Objectives of the Study

The primary objective was to evaluate the abuse potential of orally administered eluxadoline tablets (100, 300, and 1000 mg) compared to placebo and oral oxycodone IR tablets in healthy recreational opioid users with a history of abuse.

The secondary objectives were to evaluate the safety and tolerability of orally administered eluxadoline tablets (100, 300, and 1000 mg) and to assess the pharmacokinetics of eluxadoline in healthy recreational opioid users with a history of abuse.

### 2.3.1.2 Study Design

The study consisted of 3 phases: Pre-Treatment (Screening, Naloxone Challenge [NC], and Qualification), Treatment, and Follow-up. The Pre-Treatment Phase includes a standard medical screening visit followed by a NC/Qualification. Subjects will be admitted to the clinic for the NC/Qualification. Subjects who successfully complete the NC and Qualification will enter the Treatment Phase and will be re-randomized to 1 of 6 treatment sequences. The Follow-up Phase will include a single End-of-Study/Early Withdrawal (EOS/EW) Visit. The approximate total duration for any subject will be approximately 75 days and approximate inpatient stay will be 17 days (Figure 6).



[Source: Figure 1 of study report CPS-1006-study-report.pdf, page 1411]

In the Qualification period, subjects will be given 40 mg oxycodone (2 × oxycodone 20 mg tablet, encapsulated) or oxycodone placebo (2 × lactose tablet, encapsulated) as a single oral dose on 2 consecutive days in the morning under fasting conditions. In order to be eligible to participate in the Treatment Phase of the study, subjects have to meet the following criteria during Qualification:

- Distinguish oxycodone from placebo on Drug Liking Visual Analog Scale (VAS),  $\geq 15$  point peak increase for Drug Liking relative to placebo within the first 2 hours following drug administration;
- Display an acceptable placebo response, defined as a VAS response between 45 to 55 inclusive for Drug Liking;
- Tolerate study treatments (ie. no episodes of vomiting within the first 2 hours post-dose);
- Demonstrate general behavior suggestive that the subject could successfully complete the study, as judged by the study center staff.

The washout period between the last dose of study drug in the Qualification period and the first dose of study drug in the Treatment Phase will be a minimum of 48 hours.

The Treatment Phase included six 3-day (2-night) inpatient visits (Visits 3 to 8). The washout period from the last drug administration at the NC/Qualification visit and the first study drug administration in the Treatment Phase was at least 72 hours. Subjects received each of the intranasal treatments randomization sequence outlined in Table 2 in blinded fashion (one per Treatment visit):

The Treatment Phase will consist of 6 single-dose treatment periods, where each dosing separated by a washout period of at least 168 hours (7 days). Subjects received the first treatment period to 1 of 6 treatment sequences using a 6×6 William square design outlined in Table 12 in blinded fashion:

- Treatment A: Eluxadoline 100 mg (1 × 100 mg eluxadoline tablet; 9 × eluxadoline placebo tablet; 3 × oxycodone placebo tablet, encapsulated)
- Treatment B: Eluxadoline 300 mg (3 × 100 mg eluxadoline tablet; 7 × eluxadoline placebo tablet; 3 × oxycodone placebo tablet, encapsulated)
- Treatment C: Eluxadoline 1000 mg (10 × 100 mg eluxadoline tablet; 3 × oxycodone placebo tablet, encapsulated)
- Treatment D: Oxycodone HCl IR 30 mg (10 × eluxadoline placebo tablet; 1 × 10 mg oxycodone tablet; 2 × 20 mg oxycodone tablet, encapsulated; 1 × oxycodone placebo tablet, encapsulated)
- Treatment E: Oxycodone HCl IR 60 mg (10 × eluxadoline placebo tablet; 3 × 20 mg oxycodone tablet, encapsulated)
- Treatment F: Placebo (10 × eluxadoline placebo tablet; 3 × oxycodone placebo tablet, encapsulated)

Table 12: Treatment Randomization Sequence

Treatment Sequence Group (n= 6 per group)	Treatment Period					
	1	2	3	4	5	6
1	A	B	F	C	E	D
2	B	C	A	D	F	E
3	C	D	B	E	A	F
4	D	E	C	F	B	A
5	E	F	D	A	C	B
6	F	A	E	B	D	C

The Follow-up Phase included a single End-of-Study/ Early Withdrawal (EOS/EW) Visit (Visit 9). The EOS/EW visit was planned to occur between 3 and 7 days after the last study drug administration or at the time of early discontinuation.

The eligible subjects were male or female recreational opioid users, 18 to 55 years of age, who were not physically dependent on opioids, but had experience using opioids for non-therapeutic

purposes (i.e., for psychoactive effects) on at least 10 occasions within the last year and at least once in the 8 weeks prior to Screening.

Based on the unpublished internal placebo and oral oxycodone data from the investigational site, the sponsor estimated the sample size with assumption of a 15-point difference on the drug liking scale between oxycodone 60 mg and placebo, a common standard deviation of 16.6 and a 2-sided  $\alpha$  level of 0.05. The sponsor claimed that 28 subject would yield approximately 90% power (employing a paired t-test) to detect a significant difference in Drug Liking VAS (bipolar scale) between oxycodone HCl oral administration and placebo (study validity). A sufficient number of subjects will be screened and entered into the NC/Qualification so that approximately 36 qualified subjects will be enrolled in the Treatment Phase in order to ensure that at least 28 subjects complete all 6 periods of the study.

### 2.3.1.3 Abuse Potential Measures

Pharmacodynamic (PD), pharmacokinetic (PK), and safety assessments were conducted up to 24 hours post-dose. All subjects were discharged from each visit after completion of the final (i.e., 24 hours) post-dose procedures. Each study drug administration was separated by a minimum of 72 hours.

**The primary endpoint** was the peak score (Emax) for Drug Liking VAS. All other PD endpoints (Peak scores, Emax and/or TEmax (time of maximum effect), Emin, and time-averaged area under the effect curve [TA-AUE]) were secondary endpoints.

Subjective and objective measures and corresponding endpoints are listed below:

Balance of effects:

- Drug Liking VAS (Emax, TEmax, Emin, Temin, and TA\_AUE)
- Overall Drug Liking VAS (12 hours and 24 hours)
- Take Drug Again VAS (Emax; end-of-day and next day scores)
- Subjective Drug Value (SDV) (12 hours, and 224 hours)

Positive effects:

- High VAS (Emax, TEmax, and TA\_AUE)
- Good Effects VAS (Emax, TEmax, and TA\_AUE)
- ARCI MBG scale (Emax, TEmax, and TA\_AUE)

Negative effects:

- Bad Effects VAS (Emax, TEmax, and TA\_AUE)
- ARCI LSD scale (Emax, TEmax, and TA\_AUE)

Other drug effects:

- Any Effects VAS (Emax, TEmax, and TA\_AUE)
- Alertness/Drowsiness VAS (Emax, TEmax, and TA\_AUE)
- ARCI Pentobarbital Chlorpromazine Alcohol Group (PCAG) scale (Emax, TEmax, and TA-AUE)
- Drug Similarity VAS (score at 12 hours)

Objective measures:

- Pupillometry (maximum pupil constriction [MPC], time-averaged pupillometry area over the curve [PAOCavg])

Of note, pupil diameters (mm) were collected at pre-dose and at 5 min, 0.25, 0.5, 1, 1.5, 2 2.5, 3, 4, 6, and 8 hours. The MPC was the maximum pupil constriction (minimum pupil diameter vs. pre-dose) at each period; PAOCavg was the time-averaged pupillometry area over the curve.

#### 2.3.1.4 Number of Subject

The primary analysis was based on the PD Analysis Set which was defined as all enrolled subjects who received at least 1 dose of eluxadoline in the treatment phase and had sufficient PD samples to allow accurate calculation of PD parameters. Missing data for Plasma concentration, PD score or response to questionnaire were considered as non-informative missing. No imputation was performed for any missing observed value. Any subject who discontinued participation in the study for any reason after Day 1 of Treatment period 1 was not replaced.

A total of 126 subjects were screened for enrollment. Of these subjects, 88 subjects passed Screening and were eligible for the Qualification Phase and 58 were dosed during the Qualification Phase. Of the 43 subjects passed qualification criteria, 40 subjects were randomized and 33 (83%) subjects completed all 6 treatment periods (Table 13).

Table 13: Subject Disposition (Randomized Set)

	Number of Subjects (%) <sup>a</sup>
Number of subjects randomized	40
Number of completers	33 (82.5)
Eluxadoline 100 mg	35 (87.5)
Eluxadoline 300 mg	36 (90.0)
Eluxadoline 1000 mg	36 (90.0)
Oxycodone HCl IR 30 mg	37 (92.5)
Oxycodone HCl IR 60 mg	37 (92.5)
Placebo	37 (92.5)
Number of subjects who withdrew early	7 (17.5)
Reason for withdrawal	
Adverse event or serious adverse event	2 (5.0)
Study terminated by sponsor	2 (5.0) <sup>b</sup>
Non-compliance	3 (7.5)

A: Percentage is calculated based on the number of subjects in the Randomized Set as the denominator.

B: Study protocol version 6.0 specified that the sponsor may stop the study after 28 subjects complete.

[Source: Table 5 of study report CPS-1006-study-report.pdf, page 56]

#### 2.3.1.5 Statistical Methodologies used in the Sponsor's Analyses

Pharmacodynamic data at each time point were summarized by descriptive statistics and presented graphically (where appropriate) for the Pharmacodynamic Population for the Treatment Phase; the primary measures, pertinent to qualification, were also summarized for the Qualification Phase. Derived parameters were summarized using descriptive statistics and boxplots. PD endpoints for the treatment phase (E<sub>max</sub>, E<sub>min</sub>, and TA-AUE) were analyzed using a mixed-effect model for a crossover study. The model included treatment, period, sequence, and first-order carryover effect as fixed effects, baseline (pre-dose) measurement as covariate where applicable, and subject nested within treatment sequence as random effect. A washout of at least 3 days was used in order to minimize the potential for carryover effects. If the carryover effect was found to be non-significant at the 25% level, then the term was dropped from the analysis model. Baseline and carryover were included as applicable. Least square means, standard errors (SE) and 95% two-sided confidence intervals for treatments and treatment differences were derived from the mixed-effects model. P values were provided for the effects and the contrasts. The contrasts were presented only if there was an overall treatment effect.

#### Hypothesis testing:

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

The following 9 contrasts will be evaluated for all primary and secondary endpoints, except Drug Similarity VAS.

Assay Sensitivity Contrasts:

- Oxycodone IR 30 mg vs. Placebo
- Oxycodone IR 60 mg vs. Placebo

Abuse Potential Contrasts:

- Eluxadoline 100 mg vs. Oxycodone IR 30 mg
- Eluxadoline 300 mg vs. Oxycodone IR 30 mg
- Eluxadoline 1000 mg vs. Oxycodone IR 30 mg
- Eluxadoline 100 mg vs. Oxycodone IR 60 mg
- Eluxadoline 300 mg vs. Oxycodone IR 60 mg
- Eluxadoline 1000 mg vs. Oxycodone IR 60 mg

Abuse Liability Contrasts:

- Eluxadoline 100 mg vs. Placebo
- Eluxadoline 300 mg vs. Placebo
- Eluxadoline 1000 mg vs. Placebo

The primary endpoint, Emax for Drug Liking VAS, was compared between the positive control (oxycodone) and placebo to confirm the sensitivity of the study.

The abuse potential of eluxadoline was assessed through evaluation and integrative interpretation of the pattern of results across the various types of measures: measures of positive response (i.e., measures most predictive of the drug's abuse potential and reinforcing properties), measures of negative response (i.e., measures that potentially mitigate abuse potential), and measures of other effects. The various planned comparisons helped to evaluate the importance of the steepness of the dose-response curves and the similarity of responses to eluxadoline, as compared to the responses to oxycodone.

#### 2.3.1.6 Changes in the Conduct of the Study

The Statistical Analysis Plan was finalized on January 10, 2014. The sponsor claimed that the following changes to the analysis sets were made in the SAP prior to database lock and unblinding:

Due to the unapproved concomitant medications were found during the treatment period 1, the sponsor conducted a sensitivity analysis for the endpoints Drug Liking VAS Emax and Emin. An incomplete block design using model fitting was run on the PD population with treatment period 1 removed to assess any potential impact.

The sponsor's sensitivity analysis results suggest that overall results were not likely affected by the protocol deviation. A broad visual inspection of individual response data was conducted, and the by-period plots do not suggest that Drug Liking VAS Emax patterns were different across the period.

#### 2.3.1.7 Sponsor's Summary and Conclusions

The Sponsor summarized their PD analysis results as follows:



(b) (4)

The sponsor concluded that:



(b) (4)

### 2.3.2 Reviewer's Assessment

This reviewer confirmed the sponsor's analyses results on Emax, Emin, and TA-AUE for PD population (See Table 27 in Appendix for the details) and focused on the primary endpoint of Drug Liking VAS, Pupillometry (MPC and PAOCavg) based on the completer population.

#### 2.3.2.1 Primary Endpoint – Drug Liking VAS

##### **Descriptive Statistics**

Table 14 shows the first quartiles of the primary endpoint are around 50 for eluxadoline three doses which are much lower than oxycodone IR two doses (88 to 100). Placebo scores remained close to the neutral mark (50), showing very little change across the sampling period with a mean Emax of 54.3. The mean difference and the median difference between these treatments are about 30 and 40, respectively. The similar tables for High VAS, ARCI MBG, Good Effect VAS, Bad Effect VAS, Overall Drug Liking VAS, and Take Drug Again VAS for the oral study can be found in Table 24 and Table 25 in the Appendix.

An additional sensitivity analysis was conducted for the endpoints Drug Liking VAS Emax to evaluate the impact of unapproved concomitant medication discovery during the first period of the treatment phase. The primary analysis was run on the completer population with treatment period 1 removed. The results from this model were similar with those run on the completer population with all period included (Table 14).

For Drug Liking VAS, the mean responses to placebo remained slightly around neutral (50) over time (Figure 7). Oxycodone 30 mg and 60 mg had similar profiles above placebo and reached the peak mean of drug liking between 1.5 and 2 hour. The peak mean response to Oxycodone 60 mg was higher than that to Oxycodone IR 30 mg. In contrast, the profiles for three doses of eluxadoline were similar to those of placebo and slightly above 50. Figure 8 is the heat map for Drug Liking VAS Emax by treatment for completer population. The density of the color green indicates the degree of the disliking and the density of the color red indicates the degree of the liking. This figure shows that the subjects in placebos were neutral and in oxycodone doses were highly liked. The most of subjects in eluxadoline doses were neutral and a few disliked. The heat maps for the time course response profiles for individual subjects to three doses (100, 300, and 1000 mg) of eluxadoline, two doses of oxycodone (30 and 60 mg), and placebo for completers population can be found in Figure 18 to Figure 23 in the Appendix.

Table 14: Summary Statistics for Emax of Drug Liking VAS (N=33)

TRTP	N	Mean	StdErr	Min	Q1	Med	Q3	Max
Elu 100 mg	33	57.1212	2.44669	50	50	51	53	100
Elu 300 mg	33	59.3939	2.40302	50	51	52	63	100
Elu 1000 mg	33	60.5152	2.63000	50	51	51	65	100
Oxy 30 mg	33	85.9394	2.53571	51	80	88	99	100
Oxy 60 mg	33	90.4242	2.08304	55	83	100	100	100
Placebo	33	54.6970	1.74267	50	51	51	53	100
<b>Completers with treatment period 1 removed</b>								
Elu 100 mg	29	54.7	1.97	50	51	51	52	94
Elu 300 mg	29	60.3	2.82	50	51	51	65	100
Elu 1000 mg	29	58.8	2.69	50	51	51	59	100
Oxy 30 mg	30	86.8	2.57	51	84	88	99	100
Oxy 60 mg	31	91.2	2.04	55	84	100	100	100
Placebo	30	54.5	1.87	50	51	51	51	100

Figure 7: The Mean Time Course Profiles on Drug Liking VAS by Treatment (N=33)

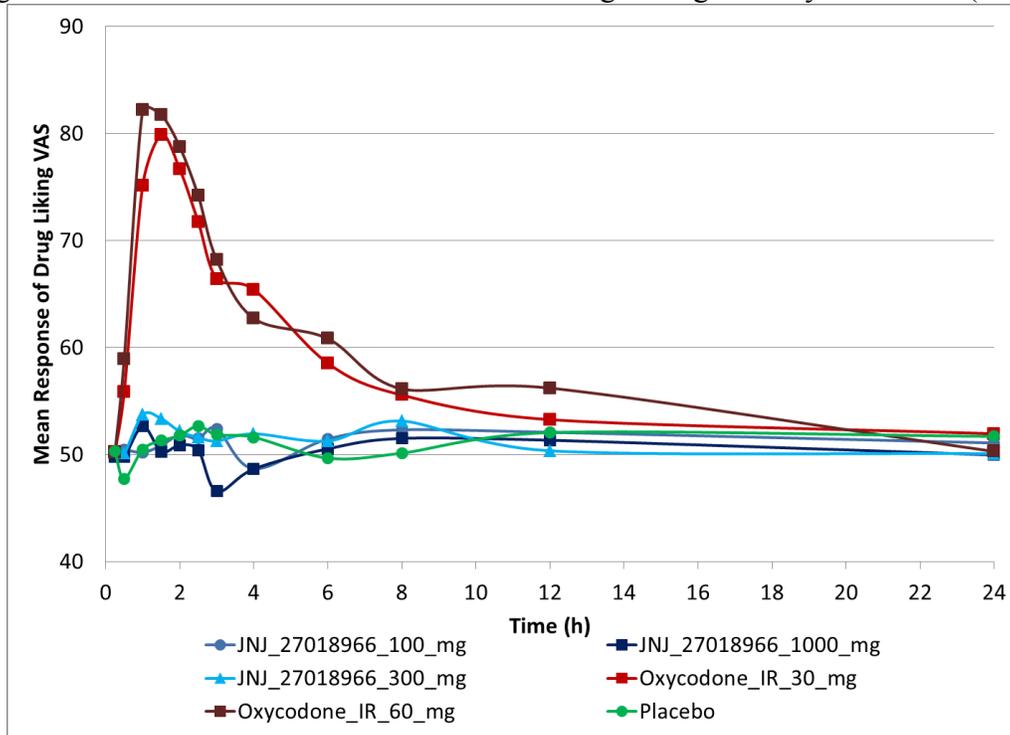
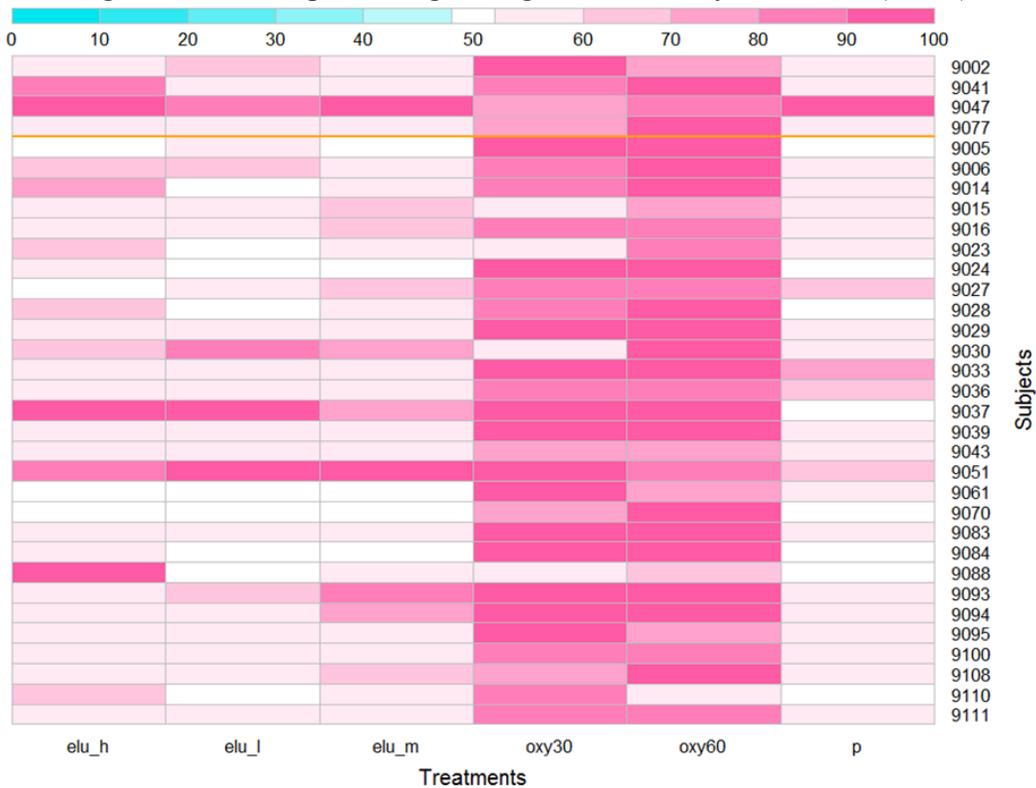


Figure 8: Heat Map for Drug Liking VAS Emax by Treatment (N=33)



### Inferential Statistics

Inferential analysis using ANCOVA model results for Drug Liking VAS are summarized in Table 15. The assumption of normal distribution of the data was examined using Shapiro-Wilk Normality test. Since the probability value was  $\leq 0.05$ , the pairwise treatment comparisons were assessed using the Wilcoxon signed-rank test on the within-subject differences (Table 17). The results are not similar to the results from ANCOVA model. I confirmed the sponsor's analysis results based on the PD population, which can be found in Table 26 in the Appendix.

Pairwise comparisons using a mixed-effect model for a crossover study revealed significantly higher Drug Liking VAS Emax scores for oxycodone IR 30 mg and 60 mg compared to placebo lactose ( $P < 0.0001$  for both), confirming validity of the study. Drug Liking VAS Emax scores were significantly lower for eluxadoline (100 mg, 300 mg, and 1000 mg) compared to oxycodone IR (30 mg and 60 mg,  $P < 0.0001$  for all). There was no statistical significant difference for Drug Liking VAS Emax between eluxadoline doses (100, 300, and 1000 mg) and placebo. The results of the primary analysis based on the completers population with treatment period 1 removed were similar with those run on the completers population with all period included (See Table 26 in Appendix for the details). Figure 9 graphically shows these results. The sponsor's analysis results also confirmed these results (See Table 22 in Appendix for the details).

I performed the new test using the equivalence margin of 11 (Table 16). The results show that the difference in mean between the eluxadoline 100 mg and placebo was significantly lower than

the equivalence margin of 11. This suggests that the only eluxadoline 100 mg dose was similar to placebo based on the Emax of the Drug Liking VAS. This result was supported by the pairwise treatment comparisons, assessed using the Wilcoxon signed-rank test on the within-subject differences (Table 17). These test results shows that eluxadoline 300 and 1000 mg were significantly different from the placebo.

Table 15: The Treatment Comparison in Means of Emax of Drug Liking (VAS) (N=33)

Treatment Comparison	LS Mean	LS Mean Diff.	Std Error	Pr-value	LL-95%CI	UL-95%CI
Oxy 30 mg -	85.49	30.97	2.92	<.0001	25.21	36.74
Placebo	54.52					
Oxy 60 mg -	89.07	34.55	2.91	<.0001	28.80	40.30
Placebo	54.52					
Elu 100 mg -	56.80	-28.69	2.92	<.0001	-34.45	-22.93
Oxy 30 mg	85.49					
Elu 300 mg -	59.07	-26.43	2.93	<.0001	-32.22	-20.63
Oxy 30 mg	85.49					
Elu 1000 mg -	60.01	-25.48	2.94	<.0001	-31.28	-19.68
Oxy 30 mg	85.49					
Elu 100 mg -	56.80	-32.27	2.93	<.0001	-38.06	-26.47
Oxy 60 mg	89.07					
Elu 300 mg -	59.07	-30.00	2.93	<.0001	-35.80	-24.20
Oxy 60 mg	89.07					
Elu 1000 mg -	60.01	-29.06	2.93	<.0001	-34.84	-23.27
Oxy 60 mg	89.07					
Elu 100 mg -	56.80	2.28	2.93	0.4382	-3.52	8.08
Placebo	54.52					
Elu 300 mg -	59.07	4.55	2.92	0.1219	-1.23	10.33
Placebo	54.52					
Elu 1000 mg -	60.01	5.49	2.94	0.0623	-0.2857	11.27
Placebo	54.52					

Table 16: Statistical Test Results for The Treatment Comparison in Means of Emax of Drug Liking (VAS) (N=33)

Test Drug	Placebo	N	LS mean Diff.	StdErr	P-value	95% CI	
						Lower	Upper
Elu 100 mg	Placebo +11	33	-8.72	2.94	0.0035	-14.52	-2.92
Elu 300 mg	Placebo +11	33	-6.45	2.92	0.089	-12.23	-0.67
Elu 1000 mg	Placebo +11	33	-5.51	2.92	0.0617	-11.29	0.27

Figure 9: The Treatment Comparison in Means of Emax of Drug Liking (VAS) (N=33)

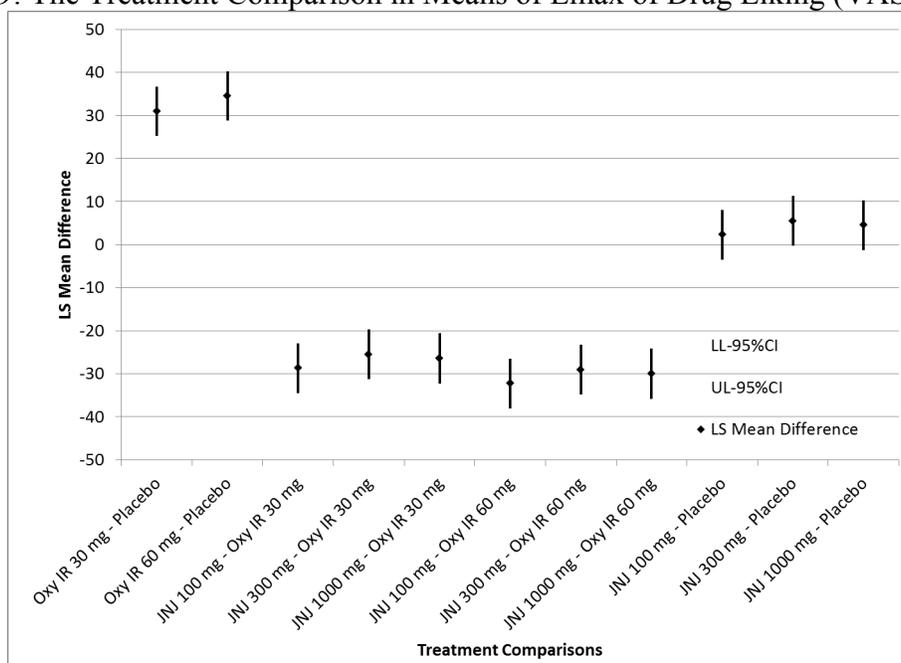


Table 17: The Treatment Comparison in Median of Emax of Drug Liking (VAS) (N=33)

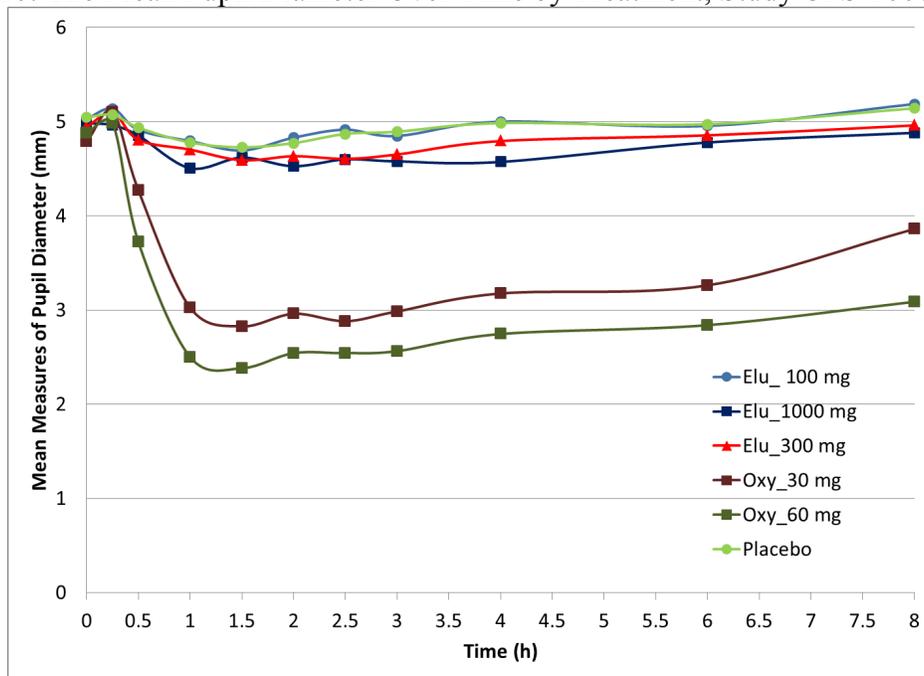
Overall Treatment Effect	Median Difference	IQR	P-value
Oxycodone HCl IR 30 mg – Placebo	34	19, 49	0.00000
Oxycodone HCl IR 60 mg – Placebo	41	27, 49	0.00000
Eluxadoline 100 mg – Oxycodone HCl IR 30 mg	-35	-48, -12	0.00000
Eluxadoline 300 mg – Oxycodone HCl IR 30 mg	-31	-48, -9	0.00000
Eluxadoline 1000 mg – Oxycodone HCl IR 30 mg	-33	-49, -26	0.00000
Eluxadoline 100 mg – Oxycodone HCl IR 60 mg	-37	-49, -26	0.00000
Eluxadoline 300 mg – Oxycodone HCl IR 60 mg	-31	-1, 1	0.00000
Eluxadoline 1000 mg – Oxycodone HCl IR 60 mg	-34	0, 12	0.00000
Eluxadoline 100 mg – Placebo	0	-1, 20	0.63110
Eluxadoline 300 mg – Placebo	0	0, 0	0.02433
Eluxadoline 1000 mg – Placebo	0	-1, 2	0.04719

### 2.3.2.2 Pupillometry Endpoint

#### Descriptive Statistics

Pupil diameter was consistent for all doses of eluxadoline (100 mg, 300 mg, and 1000 mg) and for placebo, with little change from baseline across all time points. Oxycodone IR 30 mg and 60 mg were associated with pronounced decreases in pupil diameter that reached a nadir at approximately 1.5 hours post-dose, consistent with the oral route of administration, and remained lower than placebo for the duration of the sampling period (8 hours post-dose). Oxycodone IR 60 mg had a slightly greater decline in pupil diameter in comparison to the 30 mg dose (Figure 10).

Figure 10: The Mean Pupil Diameter Over Time by Treatment, Study CPS-1006 (N=33)



### Inferential Statistics

A significant baseline effect was also observed for PAOCavg ( $P < 0.0001$ ). MPC and PAOCavg were significantly higher for oxycodone IR 30 mg and 60 mg in comparison to all doses of eluxadoline (100 mg, 300 mg, and 1000 mg) and placebo ( $P < 0.0001$  for all). Eluxadoline 1000 mg had a significantly higher MPC and PAOCavg value in comparison to placebo. Oxycodone 30 mg and 60 mg doses had significantly higher PAOCavg than placebo, with a least squares mean difference (Table 18 and Table 19).

Table 18: The Treatment Comparison in LS Means of MPC (N=33)

Treatment Comparison	LS Mean Diff.	Std Error	P-value	LL-95%CI	UL_95%CI
Oxycodone HCl IR 30 mg – Placebo	1.5812	0.1088	<.0001	1.3662	1.7961
Oxycodone HCl IR 60 mg – Placebo	1.9525	0.1077	<.0001	1.7397	2.1653
Eluxadoline 100 mg – Oxycodone HCl IR 30 mg	-1.5990	0.1085	<.0001	-1.8134	-1.3847
Eluxadoline 300 mg – Oxycodone HCl IR 30 mg	-1.4468	0.1085	<.0001	-1.6614	-1.2323
Eluxadoline 1000 mg – Oxycodone HCl IR 30 mg	-1.3410	0.1090	<.0001	-1.5564	-1.1256
Eluxadoline 100 mg – Oxycodone HCl IR 60 mg	-1.9704	0.1083	<.0001	-2.1844	-1.7563
Eluxadoline 300 mg – Oxycodone HCl IR 60 mg	-1.8182	0.1082	<.0001	-2.0321	-1.6042
Eluxadoline 1000 mg – Oxycodone HCl IR 60 mg	-1.7123	0.1080	<.0001	-1.9258	-1.4989
Eluxadoline 100 mg – Placebo	-0.01785	0.1083	0.8693	-0.2319	0.1962
Eluxadoline 300 mg – Placebo	0.1343	0.1081	0.2160	-0.07935	0.3480
Eluxadoline 1000 mg – Placebo	0.2402	0.1079	0.0276	0.02684	0.4535

Table 19: The Treatment Comparison in LS Means of PAOCavg (N=33)

<b>Treatment Comparison</b>	<b>LS Mean Diff.</b>	<b>Std Error</b>	<b>P-value</b>	<b>LL-95%CI</b>	<b>UL_95%CI</b>
Oxycodone HCl IR 30 mg – Placebo	1.5034	0.06985	<.0001	1.3653	1.6415
Oxycodone HCl IR 60 mg – Placebo	1.9811	0.06886	<.0001	1.8450	2.1173
Eluxadoline 100 mg – Oxycodone HCl IR 30 mg	-1.4909	0.06956	<.0001	-1.6284	-1.3534
Eluxadoline 300 mg – Oxycodone HCl IR 30 mg	-1.3767	0.06942	<.0001	-1.5139	-1.2394
Eluxadoline 1000 mg – Oxycodone HCl IR 30 mg	-1.2606	0.07042	<.0001	-1.3998	-1.1214
Eluxadoline 100 mg – Oxycodone HCl IR 60 mg	-1.9687	0.06922	<.0001	-2.1055	-1.8318
Eluxadoline 300 mg – Oxycodone HCl IR 60 mg	-1.8544	0.06911	<.0001	-1.9910	-1.7178
Eluxadoline 1000 mg – Oxycodone HCl IR 60 mg	-1.7383	0.06975	<.0001	-1.8762	-1.6004
Eluxadoline 100 mg – Placebo	0.01247	0.06915	0.8572	-0.1242	0.1492
Eluxadoline 300 mg – Placebo	0.1267	0.06912	0.0688	-0.00989	0.2634
Eluxadoline 1000 mg – Placebo	0.2428	0.06966	0.0007	0.1051	0.3806

### 2.3.2.3 Conclusion

In this oral study based on the primary endpoint, responses to crushed eluxadoline 100 mg were similar to those to placebo and much lower than those to two doses of oxycodone IR. Responses to the eluxadoline 300 mg and 1000 mg doses were significantly higher than those to placebo based on the Wilcoxon signed-rank test on the within-subject differences. The study was validated by the comparison between each dose of the positive control and placebo.

The statistically significant decreases in pupil diameter were observed for eluxadoline 1000 mg in comparison to placebo in Study CPS-1006. Although the decreases in pupil diameter also were observed for eluxadoline 300 mg, the change in pupil diameter was not statistically significant compared to placebo.

### 3 APPENDIX

Table 20: Patients' Demographic and Baseline Characteristics, Study CPS-1010

Characteristic	Randomized Analysis Set N = 36	Safety Analysis Set N = 35	PD Analysis Set N = 35	PK Analysis Set N = 33
<b>Age (years)</b>				
Mean (SD)	35.6 (8.84)	35.4 (8.82)	35.4 (8.82)	35.2 (8.43)
Range	23.0 - 54.0	23.0 - 54.0	23.0 - 54.0	23.0 - 54.0
<b>Sex, n (%)</b>				
Female	10 (27.8)	10 (28.6)	10 (28.6)	9 (27.3)
Male	26 (72.2)	25 (71.4)	25 (71.4)	24 (72.7)
<b>Racial Designation, n (%)</b>				
White	30 (83.3)	29 (82.9)	29 (82.9)	27 (81.8)
Black or African American	5 (13.9)	5 (14.3)	5 (14.3)	5 (15.2)
Asian	1 (2.8)	1 (2.9)	1 (2.9)	1 (3.0)
<b>BMI (kg/m<sup>2</sup>)</b>				
Mean (SD)	25.46 (2.98)	25.42 (3.01)	25.42 (3.01)	25.59 (2.91)
Range	19.4 - 31.8	19.4 - 31.8	19.4 - 31.8	19.8 - 31.8

[Source: Table 7 in CPS-1010-study-report.pdf, page 62]

Table 21: Summary Statistics for Other Abuse Potential Measures, Study CPS-1010 (N=31)

Measures	Treatments	N	Mean	StdErr	Min	Q1	Med	Q3	Max
High VAS	Elu 100 mg	31	42.8710	5.99995	0	1	50	70	100
	Elu 200 mg	31	48.4194	6.14078	0	22	50	78	100
	Oxy IR 15 mg	31	70.5806	5.22603	2	61	78	90	100
	Oxy IR 30 mg	31	87.4516	2.90785	40	84	93	100	100
	Oxy-P	31	9.9355	3.58969	0	0	0	1	64
	JNJ-P	31	12.6129	3.95830	0	0	0	16	68
ARCI MBG	Elu 100 mg	31	2.74194	0.64085	0	1	1	3	15
	Elu 200 mg	31	2.77419	0.61646	0	1	2	3	14
	Oxy IR 15 mg	31	8.29032	0.87029	0	4	8	12	16
	Oxy IR 30 mg	31	8.51613	0.80438	0	5	8	12	15
	Oxy-P	31	1.29032	0.16193	0	1	1	2	3
	JNJ-P	31	1.54839	0.26976	0	1	1	2	6
Good Effects VAS	Elu 100 mg	31	28.0323	5.69125	0	0	16	51	100
	Elu 200 mg	31	27.1935	6.14527	0	0	12	50	100
	Oxy IR 15 mg	31	70.2903	5.75227	0	60	82	93	100
	Oxy IR 30 mg	31	86.7419	3.24914	39	82	93	100	100
	Oxy-P	31	4.0645	2.45516	0	0	0	0	58
	ELU-P	31	9.0645	3.55870	0	0	0	1	72

Measures	Treatments	N	Mean	StdErr	Min	Q1	Med	Q3	Max
Bad Effects VAS	ELU 100 mg	31	61.6129	6.94938	0	24	73	100	100
	ELU 200 mg	31	74.1290	5.84214	0	59	85	100	100
	Oxy IR 15 mg	31	23.3548	5.08626	0	0	12	44	100
	Oxy IR 30 mg	31	36.3548	6.28662	0	1	32	60	100
	Oxy-P	31	2.2258	1.59752	0	0	0	0	49
	ELU-P	31	17.0645	4.61762	0	0	0	42	72
Overall Drug Liking VAS	ELU 100 mg	31	21.9355	4.64207	0	0.0	9.0	39.5	81
	ELU 200 mg	31	16.8710	4.63999	0	0.0	0.0	25.5	100
	Oxy IR 15 mg	31	77.0161	4.46597	0	70.5	79.0	100.0	100
	Oxy IR 30 mg	31	80.4032	4.18943	0	63.5	88.5	100.0	100
	Oxy-P	31	42.8226	3.11608	0	50.0	50.0	50.0	51
	ELU-P	31	38.7097	3.68065	0	25.0	50.0	50.0	86
Take Drug Again VAS	ELU 100 mg	31	14.7419	4.95604	0.0	0.0	0.0	19.0	100.0
	ELU 200 mg	31	9.4194	4.17443	0.0	0.0	0.0	2.5	100.0
	Oxy IR 15 mg	31	79.2581	5.31233	0.0	71.0	93.5	100.0	100.0
	Oxy IR 30 mg	31	81.6452	4.20421	14.5	67.5	95.5	100.0	100.0
	Oxy-P	31	5.9677	2.59538	0.0	0.0	0.0	0.0	50.5
	ELU-P	31	7.0000	3.53645	0.0	0.0	0.0	0.0	87.5

Figure 11: Heat Map for Drug Liking VAS Emox by Treatment (PD Population), Study CPS-1010



Figure 12: Time Course Response Profiles for Individual Subjects to the eluxadoline 100 mg for Drug Liking VAS (Completers Population), Study CPS-1010

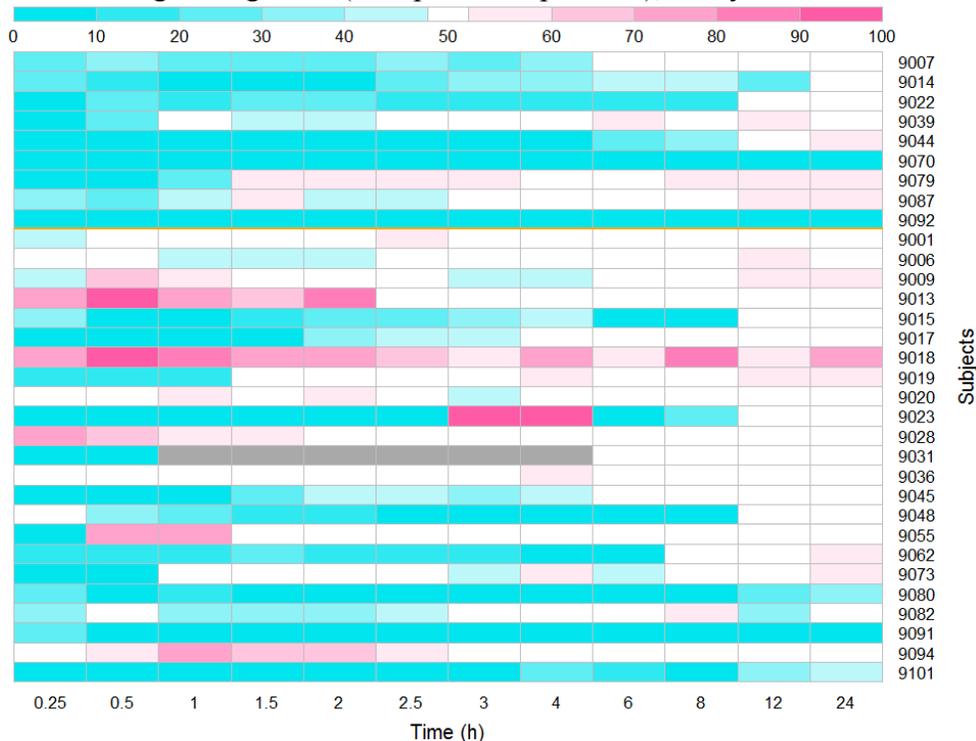


Figure 13: Time Course Response Profiles for Individual Subjects to the eluxadoline 200 mg for Drug Liking VAS (Completers Population), Study CPS-1010

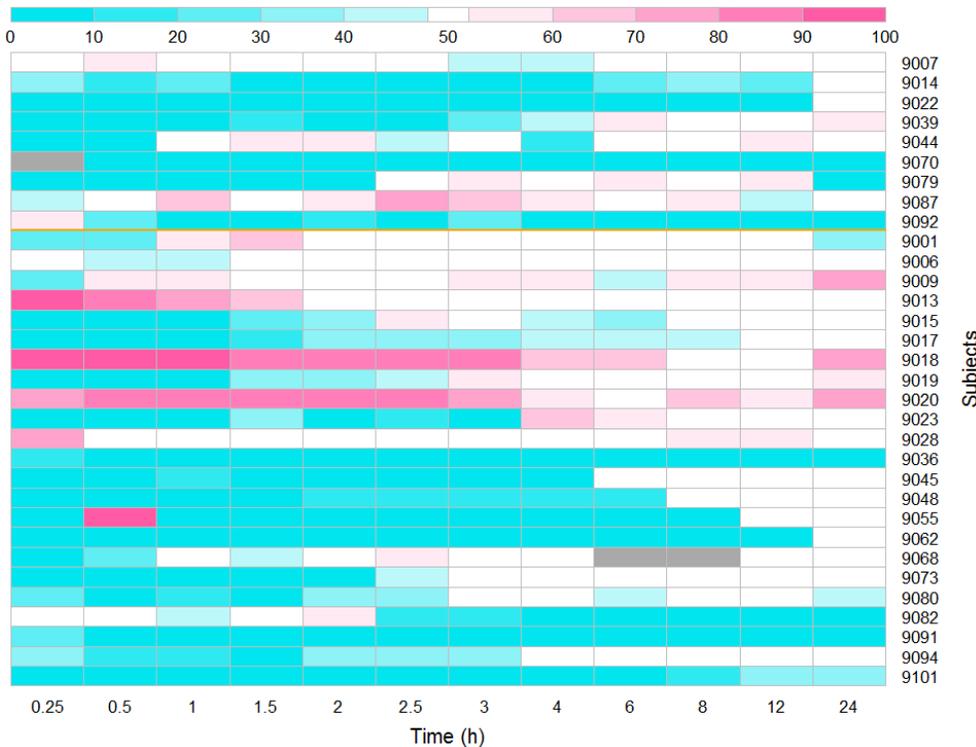


Figure 14: Time Course Response Profiles for Individual Subjects to the oxycodone 15 mg for Drug Liking VAS (Completers Population), Study CPS-1010

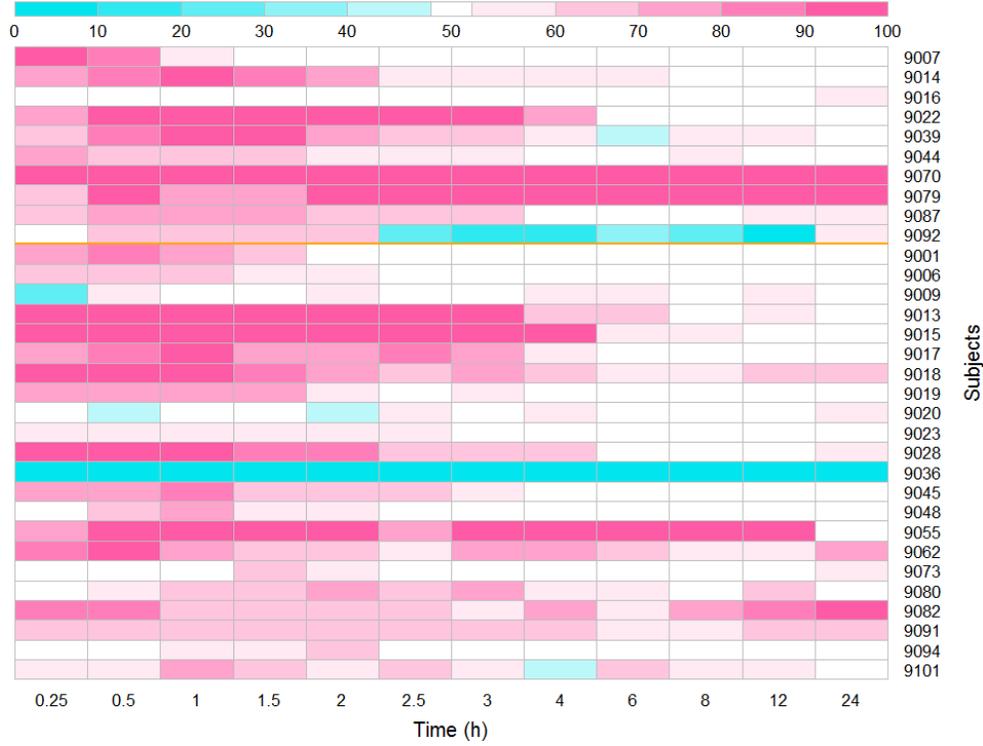


Figure 15: Time Course Response Profiles for Individual Subjects to the oxycodone 30 mg for Drug Liking VAS (Completers Population), Study CPS-1010

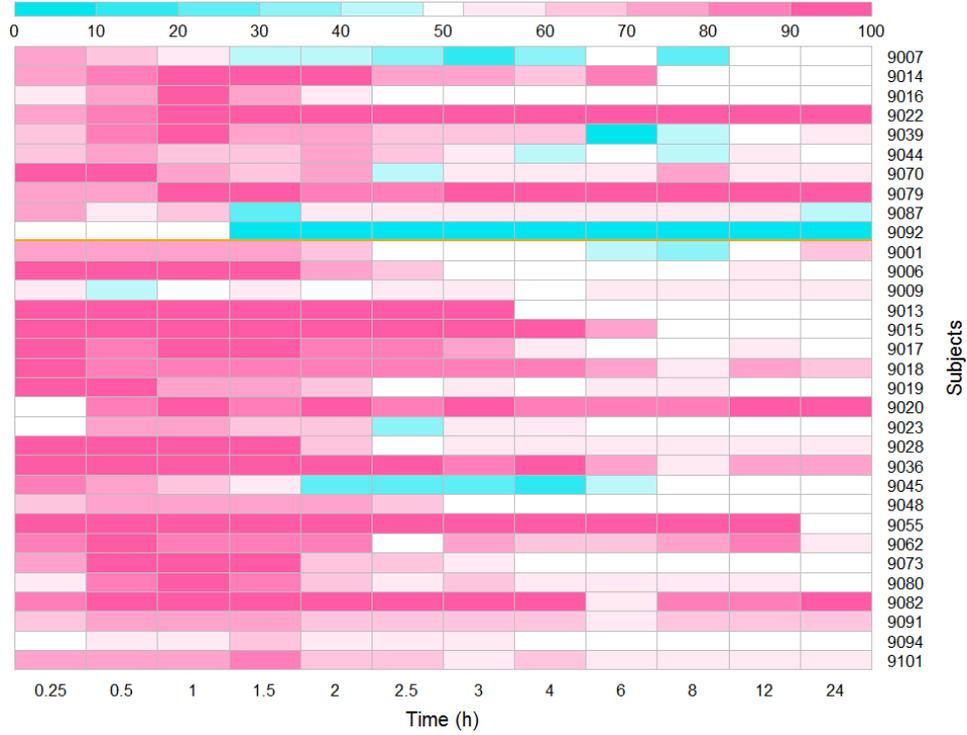


Figure 16: Time Course Response Profiles for Individual Subjects to the Placebo that Matches Weight of the high dose of eluxadoline (200 mg) for Drug Liking VAS (Completers Population), Study CPS-1010

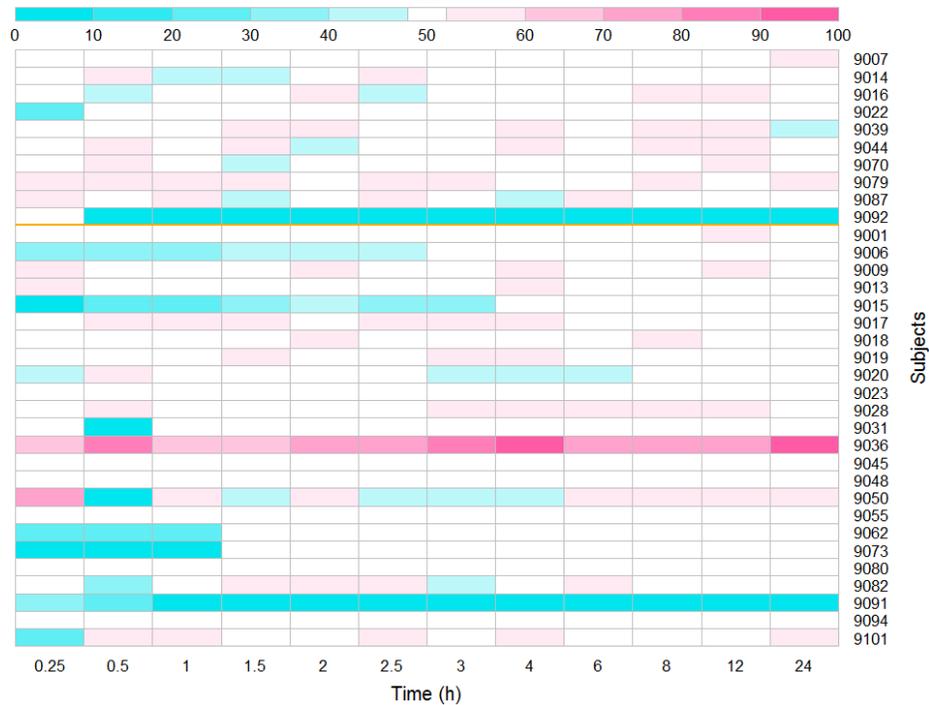


Figure 17: Time Course Response Profiles for Individual Subjects to the Placebo that Matches Weight of the high dose of oxycodone (30 mg) for Drug Liking VAS (Completers Population), Study CPS-1010

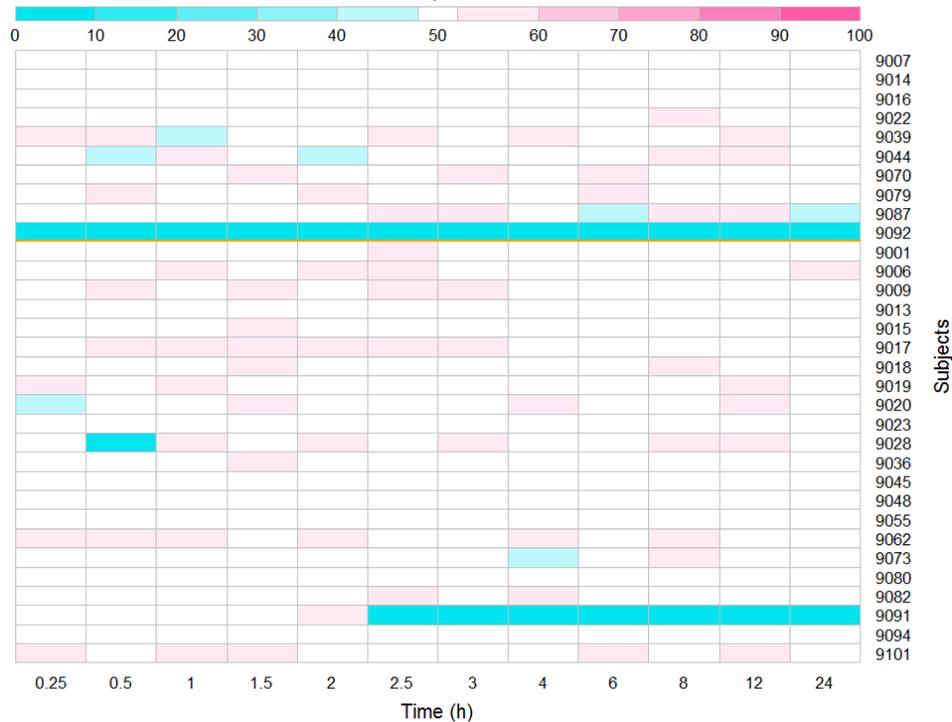


Table 22: The Sponsor's Analysis Results for Drug Liking VAS Emax, Emin, and TA-AUE for Study CPS-1010 (PD Analysis Set)

	E <sub>max</sub>			LS Mean Difference (SE)	E <sub>min</sub>		TA_AUE		
	Median Difference	IQR	P Value		95% CI	P Value	Median Difference	IQR	P Value
(b) (4)									

Table 23: Patients' Demographic and Baseline Characteristics, Study CPS-1006

	Randomized Set (N=40)	Safety Analysis Set (N=40)	PD Analysis Set (N=39)	PK Analysis Set (N=37)
Age (years)				
Mean (SD)	39.8 (9.16)	39.8 (9.16)	40.1 (9.08)	39.4 (8.79)
Min, Max	27, 55	27, 55	27, 55	27, 55
Sex, n (%)				
Female	8 (20.0)	8 (20.0)	8 (20.5)	6 (16.2)
Male	32 (80.0)	32 (80.0)	31 (79.5)	31 (83.8)
Racial Designation, n (%)				
White	29 (72.5)	29 (72.5)	29 (74.4)	27 (73.0)
Black or African American	7 (17.5)	7 (17.5)	6 (15.4)	6 (16.2)
Asian	3 (7.5)	3 (7.5)	3 (7.7)	3 (8.1)
American Indian or Alaska Native	1 (2.5)	1 (2.5)	1 (2.6)	1 (2.7)
BMI (kg/m <sup>2</sup> )				
Mean (SD)	26.47 (3.169)	26.47 (3.169)	26.45 (3.208)	26.45 (3.255)
Min, Max	19.8, 32.9	19.8, 32.9	19.8, 32.9	19.8, 32.9

[Source: Table 7 in CPS-1006-study-report.pdf, page 60]

Table 24: Summary Statistics for Other Abuse Potential Measure, Study CPS-1006

Abuse Potential Measures	Treatments	N	Mean	StdErr	Min	Q1	Med	Q3	Max
High VAS	ELU 100 mg	33	22.5758	5.68724	0	0	0	53	100
	ELU 300 mg	33	37.9697	5.50507	0	4	50	62	100
	ELU 1000 mg	33	35.9091	5.78421	0	4	29	64	100
	Oxy IR 30 mg	33	80.6970	4.24163	0	76	85	100	100
	Oxy IR 60 mg	33	89.0303	2.58620	51	82	99	100	100
	Placebo	33	18.2727	4.86431	0	0	0	50	83
ARCI MBG	ELU 100 mg	33	4.12121	0.81622	0	1	2	5	16
	ELU 300 mg	33	4.60606	0.83930	0	1	3	6	16
	ELU 1000 mg	33	4.69697	0.81590	0	1	3	7	16
	Oxy IR 30 mg	33	8.06061	0.84156	0	5	8	12	16
	Oxy IR 60 mg	33	8.78788	0.85364	1	4	9	13	16
	Placebo	33	3.51515	0.71658	0	1	2	4	16
Good Effects VAS	ELU 100 mg	33	20.3030	5.47074	0	0	0	51	100
	ELU 300 mg	33	36.9091	5.57004	0	5	37	58	100
	ELU 1000 mg	33	34.0000	5.86173	0	0	40	67	100
	Oxy IR 30 mg	33	82.9394	4.37038	0	77	91	100	100
	Oxy IR 60 mg	33	89.5152	2.38410	55	84	96	100	100
	Placebo	33	19.2121	5.17126	0	0	0	50	86
Bad Effects VAS	ELU 100 mg	33	12.2727	5.12408	0	0	0	1	100
	ELU 300 mg	33	27.7273	4.95706	0	0	17	51	83
	ELU 1000 mg	33	21.6970	4.99744	0	0	11	32	100
	Oxy IR 30 mg	33	20.0606	4.83280	0	0	3	45	94
	Oxy IR 60 mg	33	35.4545	6.42852	0	2	21	69	100
	Placebo	33	9.8182	3.89042	0	0	0	3	78
Overall Drug Liking VAS	ELU 100 mg	33	51.2727	3.26701	0	50.0	50.0	51.5	100.0
	ELU 300 mg	33	46.5303	4.34568	0	40.5	50.0	58.0	100.0
	ELU 1000 mg	33	50.9242	3.86001	0	49.5	50.5	60.0	100.0
	Oxy IR 30 mg	33	79.1667	2.89320	45	68.0	83.5	92.5	100.0
	Oxy IR 60 mg	33	78.1515	3.35907	31	68.5	78.0	95.0	100.0
	Placebo	33	50.8485	2.41910	21	50.0	50.0	51.0	98.5
Take Drug Again VAS	ELU 100 mg	33	17.2727	5.73937	0.0	0.0	0.0	11.0	100.0
	ELU 300 mg	33	25.5909	5.59087	0.0	0.0	5.5	58.5	100.0
	ELU 1000 mg	33	29.4394	5.95865	0.0	0.0	10.5	62.0	100.0
	Oxy IR 30 mg	33	78.2273	4.97523	0.0	75.5	87.0	100.0	100.0
	Oxy IR 60 mg	33	75.9394	4.68176	7.5	61.5	88.5	97.5	100.0
	Placebo	33	14.8485	5.05099	0.0	0.0	0.0	5.0	99.5

Table 25: Summary Statistics for Other Abuse Potential Measure, Study CPS-1006 with Period 1 data Removed, Study CPS-1006

Abuse Potential Measures	Treatments	N	Mean	StdErr	Min	Q1	Med	Q3	Max
High VAS	ELU 100 mg	29	18.7586	5.19038	0	0	0	51	75
	ELU 1000 mg	29	38.2069	6.29751	0	4	32	69	100
	ELU 300 mg	29	39.8276	5.85815	0	4	50	59	100
	Oxy IR 30 mg	30	80.7333	4.51280	0	79	85	100	100
	Oxy IR 60 mg	31	90.0968	2.60700	51	84	99	100	100
	Placebo	30	15.7000	4.78387	0	0	0	25	83
ARCI MBG	ELU 100 mg	29	3.68966	0.81262	0	1	2	4	16
	Elu 1000 mg	29	4.72414	0.90415	0	1	3	7	16
	Elu 300 mg	29	3.72414	0.79080	0	1	3	4	16
	Oxy IR 30 mg	30	7.93333	0.89306	0	5	8	12	16
	Oxy IR 60 mg	31	8.45161	0.91562	0	3	8	13	16
	Placebo	30	3.56667	0.77857	0	1	2	4	16
Good Effects VAS	Elu 100 mg	29	14.6897	4.58099	0	0	0	11	82
	Elu 1000 mg	29	33.5172	6.23031	0	0	30	67	100
	Elu 300 mg	29	37.7931	6.01934	0	5	50	56	100
	Oxy IR 30 mg	30	83.2667	4.65448	0	77	91	100	100
	Oxy IR 60 mg	31	89.7419	2.43274	55	84	96	100	100
	Placebo	30	14.8667	4.98958	0	0	0	6	86
Bad Effects VAS	Elu 100 mg	29	15.9655	5.86895	0	0	0	4	100
	Elu 1000 mg	29	26.2069	5.99412	0	0	13	58	100
	Elu 300 mg	29	29.1724	5.12289	0	0	18	51	74
	Oxy IR 30 mg	30	25.3333	5.73361	0	0	4	51	94
	Oxy IR 60 mg	31	42.0323	6.85651	0	2	32	83	100
	Placebo	30	6.4667	3.27257	0	0	0	0	74
Overall Drug Liking VAS	Elu 100 mg	29	47.3448	3.15234	0.0	50.0	50.00	50.5	86.5
	Elu 1000 mg	29	48.9483	4.32247	0.0	36.0	50.50	59.5	100.0
	Elu 300 mg	29	46.3276	4.55280	0.0	40.5	50.00	54.0	100.0
	Oxy IR 30 mg	30	78.6667	3.02436	45.0	62.5	83.25	90.0	100.0
	Oxy IR 60 mg	31	75.7419	3.87838	24.5	66.5	75.50	95.0	100.0
	Placebo	30	52.7000	2.27879	25.5	50.0	50.00	51.0	98.5
Take Drug Again VAS	Elu 100 mg	29	11.3621	5.15898	0.0	0.0	0.00	0.0	100.0
	Elu 1000 mg	29	28.5345	6.26920	0.0	0.0	10.50	58.5	100.0
	Elu 300 mg	29	23.7241	5.99710	0.0	0.0	2.50	47.0	100.0
	Oxy IR 30 mg	30	78.1000	5.07736	0.0	75.5	85.25	100.0	100.0
	Oxy IR 60 mg	31	74.6613	4.89845	7.5	60.0	85.00	97.5	100.0
	Placebo	30	14.7333	5.38291	0.0	0.0	0.00	5.0	99.5

Table 26: Statistical Test Results for The Treatment Comparison in Means of Emax of Drug Liking (VAS) (with Period 1 Data Removed), Study CPS-1006

<b>Treatment Comparison</b>	<b>LS Mean</b>	<b>LS Mean Diffence</b>	<b>Std Error</b>	<b>Pr-value</b>	<b>LL-95%CI</b>	<b>UL- 95%CI</b>
Oxy 30 mg - Placebo	85.69 54.71	30.98	3.39	<.0001	24.28	37.69
Oxy 60 mg - Placebo	89.56 54.71	34.85	3.34	<.0001	28.24	41.45
Elu 100 mg - Oxy 30 mg	56.53 85.69	-29.17	3.35	<.0001	-35.81	-22.52
Elu 300 mg - Oxy 30 mg	59.21 85.69	-25.05	3.40	<.0001	-31.78	-18.31
1000 mg - Oxy 30 mg	60.65 85.69	-26.49	3.41	<.0001	-33.24	-19.73
Elu 100 mg - Oxy 60 mg	56.53 89.56	-33.03	3.37	<.0001	-39.69	-26.37
Elu 300 mg - Oxy 60 mg	59.21 89.56	-28.91	3.35	<.0001	-35.56	-22.27
Elu 1000 mg - Oxy 60 mg	60.65 89.56	-30.35	3.34	<.0001	-36.96	-23.74
Elu 100 mg - Placebo	56.52 54.71	1.82	3.47	0.6010	-5.04	8.68
Elu 300 mg - Placebo	59.21 54.71	4.50	3.43	0.1918	-2.29	11.28
Elu 1000 mg - Placebo	60.65 54.71	5.94	3.40	0.0837	-0.81	12.67

Figure 18: Time Course Response Profiles for Individual Subjects to the eluxadoline 100 mg for Drug Liking VAS (Completers Population), Study CPS-1006

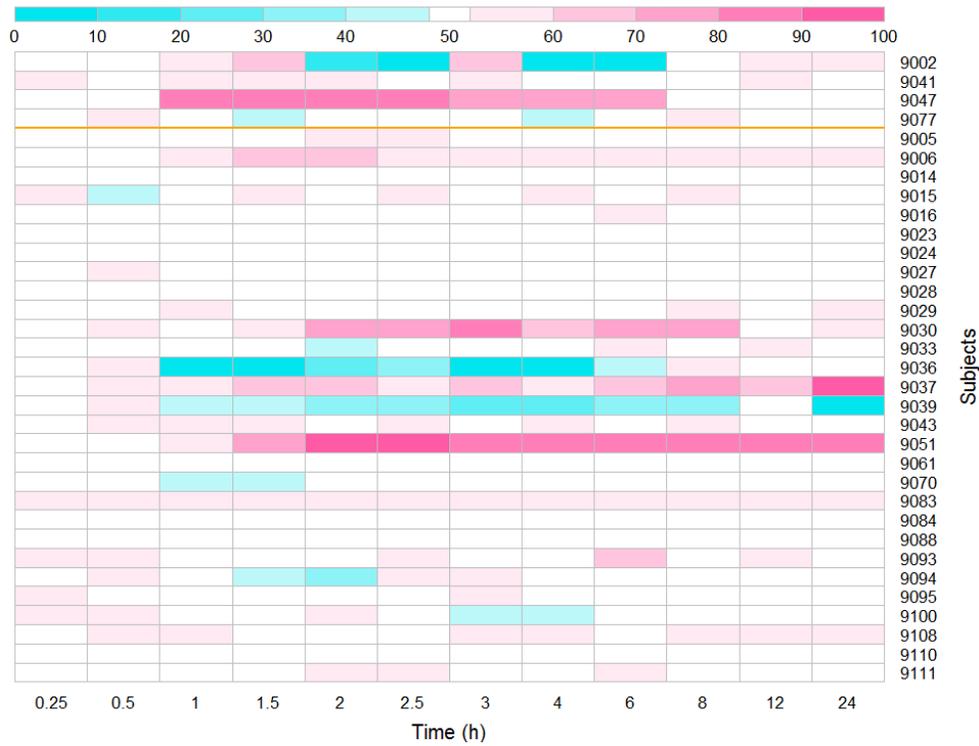


Figure 19: Time Course Response Profiles for Individual Subjects to the eluxadoline 300 mg for Drug Liking VAS (Completers Population), Study CPS-1006

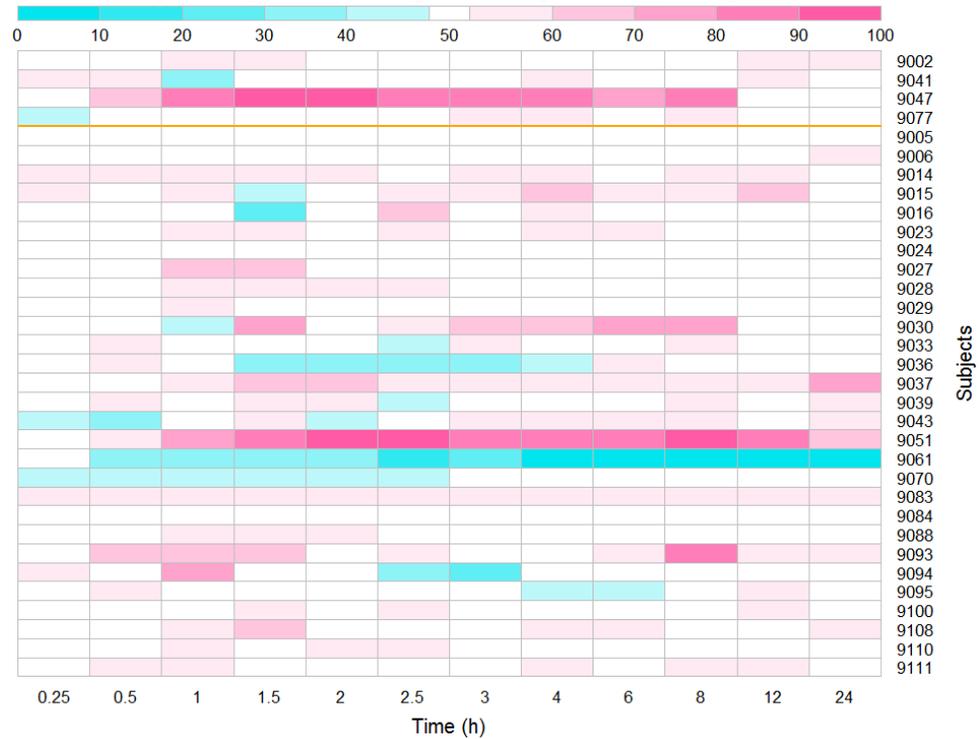


Figure 20: Time Course Response Profiles for Individual Subjects to the eluxadoline 1000 mg for Drug Liking VAS (Completers Population), Study CPS-1006

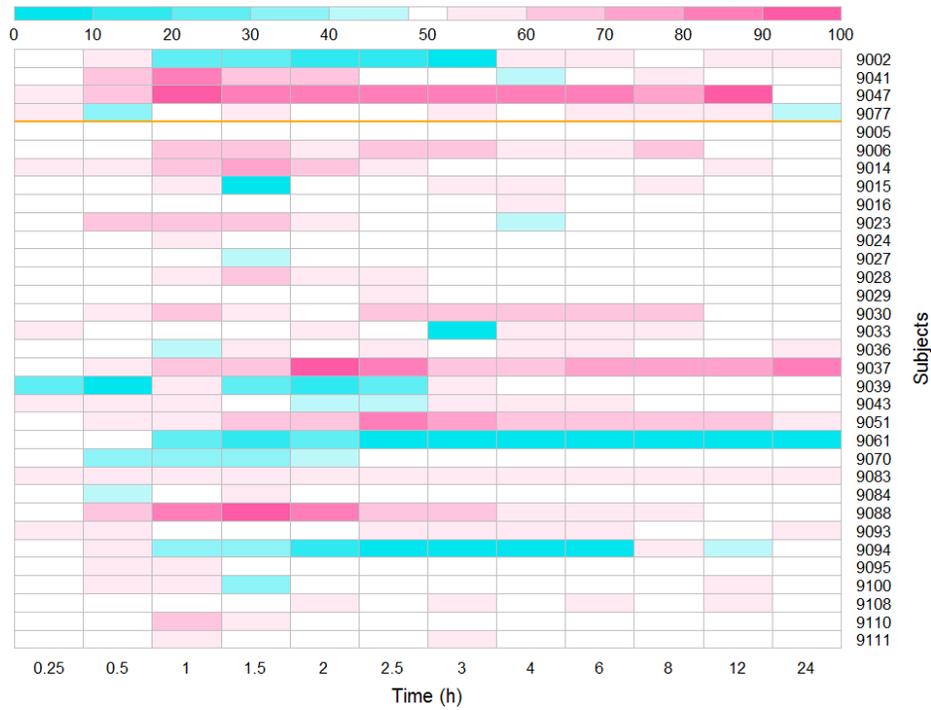


Figure 21: Time Course Response Profiles for Individual Subjects to the oxycodone 30 mg for Drug Liking VAS (Completers Population), Study CPS-1006

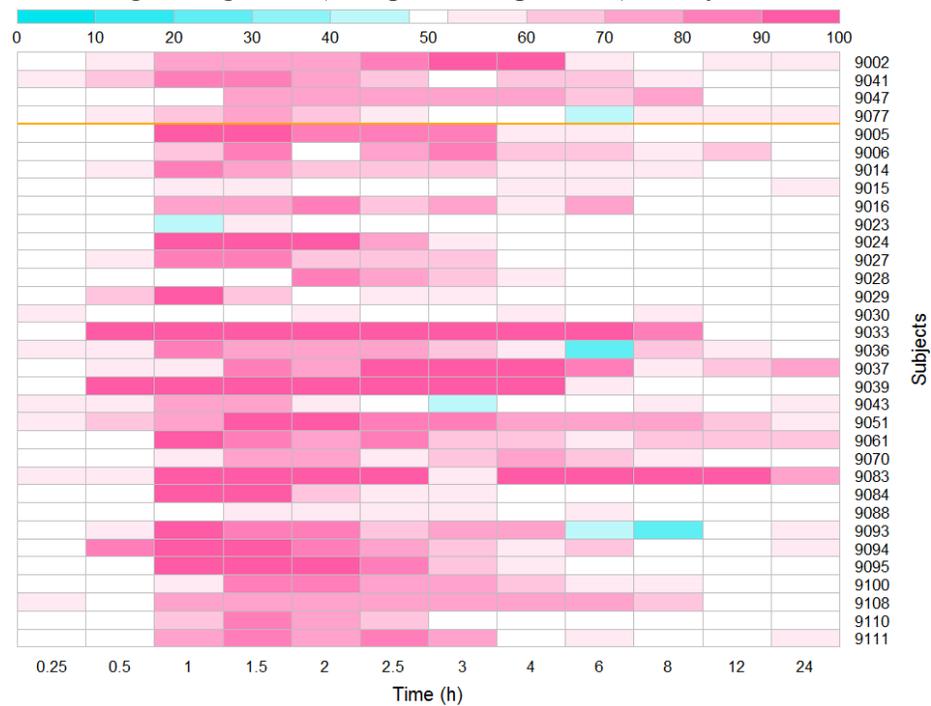


Figure 22: Time Course Response Profiles for Individual Subjects to the oxycodone 60 mg for Drug Liking VAS (Completers Population), Study CPS-1006

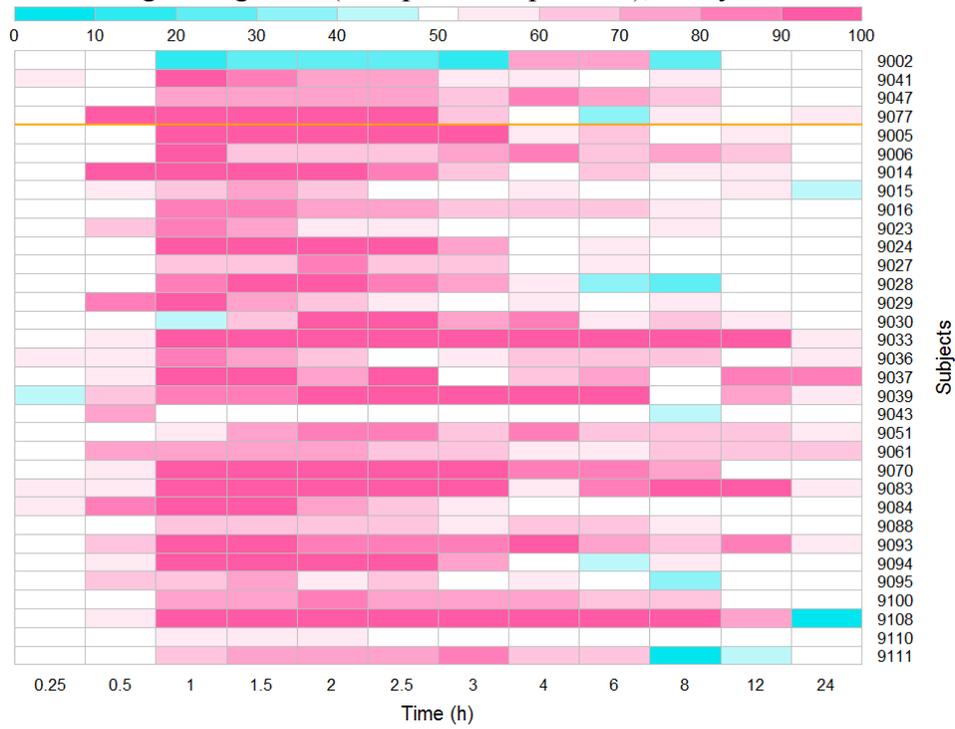


Figure 23: Time Course Response Profiles for Individual Subjects to the Placebo for Drug Liking VAS (Completers Population), Study CPS-1006

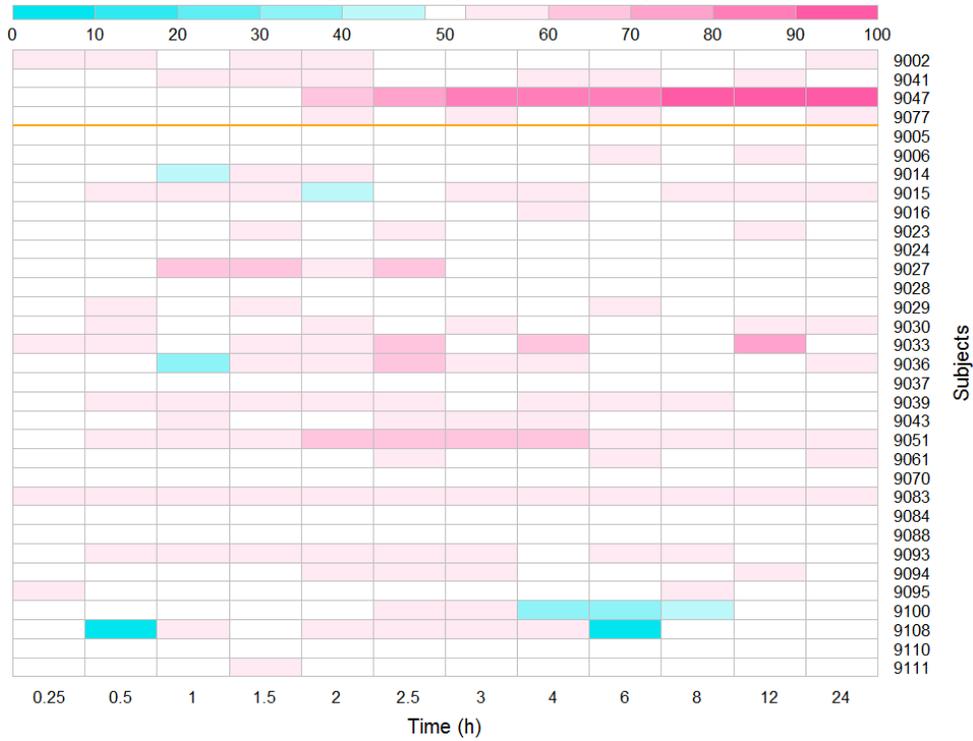


Table 27: The Sponsor's Analysis Results for Drug Liking VAS Emax, Emin, and TA-AUE for Study CPS-1006 (PD Analysis Set)

E <sub>max</sub>			E <sub>min</sub>			TA_AUE		
Median Difference	IQR	P Value	Median Difference	IQR	P Value	Median Difference	IQR	P Value
(b) (4)								

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FENG ZHOU  
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02/27/2015



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

### Statistical Review and Evaluation

#### CARCINOGENICITY STUDIES

**IND/NDA Number:** IND 079-214

**Drug Name:** JNJ-27018966-AAA

**Applicant:** Sponsor: Furiex Pharmaceuticals, Inc. 3900 Paramount Parkway  
Morrisville, North Carolina 27560

**Test Facility:** [REDACTED] (b) (4)

**Documents Reviewed:** Electronic data submitted on April 15, 2014, Also include the sponsor's reports submitted.

**Review Priority:** Standard

**Biometrics Division:** Division of Biometrics -6

**Statistical Reviewer:** Min Min, Ph.D.

**Concurring Reviewer:** Karl Lin, Ph.D.

**Medical Division:** Division of Gastroenterology and Inborn Errors Products

**Reviewing Pharmacologist:** Tamal K Chakraborti Ph.D.

**Project Manager:** Anissa Davis

**Keywords:** Carcinogenicity, Dose response

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## 1. Background

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to further assess the carcinogenic potential of JNJ-27018966-AAA, when administered daily via oral gavage to male and female rats for up to 98 or 99 weeks and to male and female mice for up to 104 weeks, respectively. Results of this review have been discussed with the reviewing pharmacologist Dr. Chakraborti who suggested doing analysis for rat and mouse studies.

## 2. Rat Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and one control group. Three treatment groups of 65 male and 65 female experimentally naïve CD® [CrI:CD®(SD)] rats were administered JNJ-27018966-AAA at respective dose levels of 150, 500, or 1500 mg/kg/day. One additional group of 65 animals per sex served as the control (0 mg/kg/day) and received the vehicle, 0.5% hydroxypropyl methylcellulose [high viscosity (HPMC)] in Purified Water, USP. The vehicle or JNJ-27018966-AAA formulations were administered to all groups via oral gavage, once daily for up to 693 consecutive days, at a dose volume of 10 mL/kg. At study termination or following euthanasia *in extremis* for individual main study animals and individual main study animals found dead, necropsy examinations were performed and tissues were microscopically examined.

Male and female naïve CD® [CrI:CD®(SD)] rats were assigned to groups, and doses were administered as indicated in the following table. Rats were dosed via oral gavage.

<b>Group Assignments</b>			
Group Number	Dose Level (mg/kg/day)	Number of Animals	
		Male	Female
<b>Main Study Groups</b>			
1	0 <sup>a</sup>	65	65
2	150	65	65
3	500	65	65
4	1500	65	65
<b>Toxicokinetic Groups</b>			
5	0 <sup>a</sup>	12	12
6	150	18	18
7	500	18	18
8	1500	18	18
<b>Sentinel Animals<sup>b</sup></b>			
98	-	35	35
<sup>a</sup> Administered the vehicle formulation only. <sup>b</sup> Sentinel animals were not administered the vehicle or JNJ-27018966-AAA formulations.			

## 2.1. Sponsor's analyses

### 2.1.1. Survival analysis

Intercurrent mortality data were analyzed using the Kaplan-Meier product-limit method. An overall test comparing all groups was conducted using a log-rank test. If this overall test was significant ( $p < 0.05$ ) and there were more than two groups, then a follow up analysis was conducted where each treatment group was compared to the control group using a log-rank test.

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:** The Kaplan-Meier product-limit survival curves from the sponsor's report are presented in Figure 1 and Figure 2 for males and females, respectively. No test article-related cause of death/moribundity occurred in either sex. The most common causes of death/moribundity in males across all groups were pituitary tumors or could not be determined. In females, the most common causes of death/moribundity across all groups were pituitary tumors and mammary tumors. The survival rates to scheduled sacrifice were 48, 55, 49 and 51% in males and 43, 42, 42 and 37% in females given 0 vehicle control, 150, 500, or 1500 mg/kg/day, respectively.

Figure 1: Kaplan-Meier plot of Survival in Male Rats

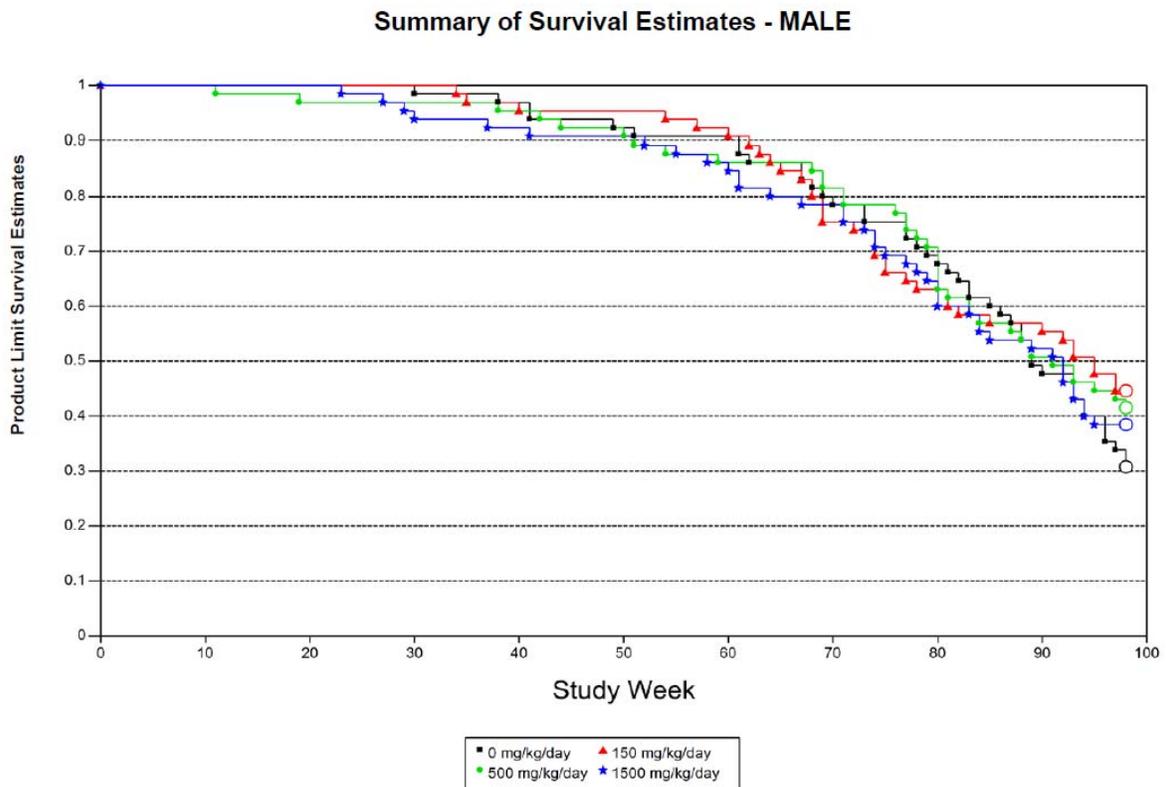
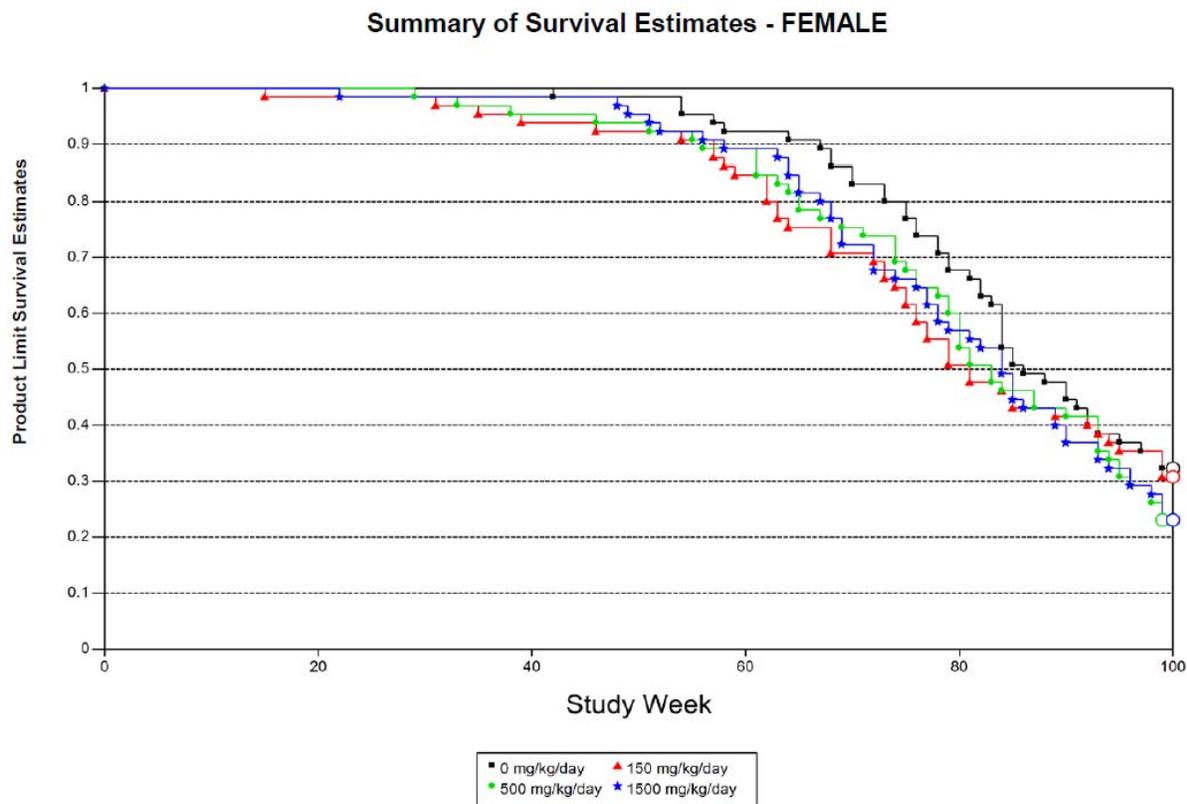


Figure 2: Kaplan-Meier plot of Survival in Female Rats



**2.1.2. Tumor data analysis**

Tumor incidence data were analyzed using both survival adjusted and unadjusted tests. The unadjusted tests were based on the incidence and number of sites examined for each tumor type. Certain tumor types were combined, as determined by the pathologist, prior to data analysis. The Cochran-Armitage trend test was calculated and Fisher’s exact test was used to compare each treatment group with the control group. The survival adjusted test was conducted according to the prevalence/mortality methods described by Peto *et al.* Evaluation criteria (levels of significance) were applied differently for rare tumors (background rate of 1% or less) and common tumors (background rate greater than 1%). The evaluation criteria (from the FDA) are presented in the following table.

<b>Evaluation Criteria for Common and Rare Tumors</b>	
<b>Test for Positive Trends</b>	<b>Control-High Pair-wise Comparisons</b>
Common and rare tumors were tested at respective significance levels of 0.005 and 0.025	Common and rare tumors were tested at respective significance levels of 0.01 and 0.05

**Sponsor's findings:** No test article-related increases in tumor incidence occurred in either sex. The most common tumor types were pituitary tumors in both males and females and mammary tumors in females. Tumors noted were typical of those seen in rats of this strain and age and were considered incidental to test article administration.

In conclusion, daily oral administration of JNJ-27018966-AAA for up to 725 and 679 days to male and female Crl:CD1®(ICR) rats, respectively, at dose levels of 150, 500, and 1500 mg/kg/day did not produce evidence of an oncogenic effect. There was no statistically significant increase in the incidence of any tumor type in any tissue for either sex.

## 2.2. Reviewer's analyses

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

### 2.2.1. Survival analysis

The survival distributions of animals in all four treatment groups (three treated groups and one vehicle control group) were estimated by the Kaplan-Meier product limit method. The dose response relationship and homogeneity of survival distributions were tested using the Cox test (Cox, 1972). The inter-current mortality data are given in Tables 1A and 1B in the appendix for four treatment groups in males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for four treatment groups in males and females, respectively. Results for the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for males and females, respectively.

**Reviewer's findings:** The test results showed no statistically significant dose-response mortality in both females and males when compared with vehicle control. The tests showed statistically significant pair-wise differences between medium dose group and the vehicle control group in survivals in females. There were few differences between reviewer's and sponsor's survival rates and the differences may be caused by the different dates of starting the terminal killing.

### 2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships and pair-wise comparisons between the vehicle control group with each of the treated groups were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). 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. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for males and females, respectively.

According to pharmacologist request, we have done analysis on the following tumor combinations in rat study:

- Hepatocellular adenoma and carcinoma in liver (male rat).
- Bronchiolar alveolar adenoma and adenocarcinoma in lung (male rat).
- Adenocarcinoma and fibroadenoma in mammary gland.

- Islet cell adenoma and carcinoma in pancreas (male rat).
- Pars distalis carcinoma and pars intermedia adenoma in pituitary gland (male rat).
- Pars distalis carcinoma and adenoma in pituitary gland.
- Adenocarcinoma and adenoma in prostate gland (male rat).
- Squamous cell carcinoma and papilloma in skin (male rat).
- Sebaceous cell adenoma and carcinoma in skin (female rat).
- Fibrosarcoma and histiocytic sarcoma in skin subcutis (female rat).
- Leiomyosarcoma and leiomyoma in small intestine jejunum (female rat).
- C cell adenoma and carcinoma in thyroid gland.
- Follicular cell adenoma and carcinoma in thyroid gland.
- Endometrial stromal polyp and sarcoma in uterus with cervix (female rat).

**Multiple testing adjustment:** Adjustment for the multiple dose response relationship testing was done using the criteria developed by Lin and Rahman (1998). The criteria recommend the use of a significance level  $\alpha=0.025$  for rare tumors and  $\alpha=0.005$  for common tumors for a submission with two species, and a significance level  $\alpha=0.05$  for rare tumors and  $\alpha=0.01$  for common tumors for a submission with only one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the spontaneous tumor rate is less than 1%. The adjustment for multiple pair-wise comparisons was done using the criteria developed by Haseman (1983) that recommends the use of significance level  $\alpha=0.05$  for rare tumors and  $\alpha=0.01$  for common tumors, in order to keep the false-positive rate at the nominal level of approximately 10%.

It should be noted that the recommended test levels by Lin and Rahman for the adjustment of multiple testing were originally based on the result of a simulation and an empirical study using the Peto method for dose response relationship analysis. However, some later simulation results by Rahman and Lin (2008) indicate that the criteria apply equally well to the analysis using the poly-3 test.

**Reviewer’s findings:** Following tumor types showed p-values less than or equal to 0.05 either tests for dose response relationship and/or pair-wise comparisons between the vehicle control and each of individual treated groups for males and females, respectively.

**Tumor Types with P-Values  $\leq 0.05$  for Dose Response Relationship or Pair-wise Comparisons (Vehicle control, low, medium and high dose groups)**

		1500 m								
		0 mg	150 mg	500 mg	g					
		Cont	Low	Med	High	P_Value	P_Value	P_Value	P_Value	
Organ Name	Tumor Name	N=65	N=65	N=65	N=65	Dos Resp	C vs. L	C vs. M	C vs. H	
Female										
	pituitary gland	ADENOMA, PARS DISTAL	52	55	55	50	0.645	0.092	0.049	0.460
		#EXAMINED ANIMALS	(65)	(65)	(65)	(65)	.	.	.	.
		PERCENTAGE	80%	85%	85%	77%	.	.	.	.
		ADJUSTED N	[62]	[59]	[58]	[58]	.	.	.	.

Based on the criteria of adjustment for multiple testing of trends proposed by Lin and Rahman, the incidence

of none of the above or any other tested tumor types in either sex was considered to have a statistically significant positive dose response relationship. Also based on the criteria by Haseman, none of the pair-wise comparisons of treated groups with the vehicle control was considered to be statistically significant in either sex for increased tumor incidence in the treated group.

### 3. Mouse Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and one control group. Three treatment groups of 65 male and 65 female experimentally naïve Crl:CD1®(ICR) mice were administered JNJ-27018966-AAA at respective dose levels of 150, 500, and 1500 mg/kg/day. One additional group of 65 animals per sex served as the control (0 mg/kg/day) and received the vehicle formulation, 0.5% hydroxypropyl methylcellulose [high viscosity (HPMC)] in Purified Water, USP. The vehicle or JNJ-27018966-AAA formulations were administered to all groups via oral gavage, once daily for up to 725 consecutive days, at a dose volume of 10 mL/kg. In this review these dose groups would be referred to as the low, medium, and high dose group, respectively.

Male and female experimentally naïve Crl:CD1®(ICR) mice were assigned to groups, and doses were administered as indicated in the following table. Mice were dosed via oral gavage.

<b>Group Assignments</b>			
<b>Group Number</b>	<b>Dose Level (mg/kg/day)</b>	<b>Number of Animals</b>	
		<b>Male</b>	<b>Female</b>
<b>Main Study Groups</b>			
1	0 <sup>a</sup>	65	65
2	150	65	65
3	500	65	65
4	1500	65	65
<b>Toxicokinetic Groups</b>			
5	0 <sup>a</sup>	20	20
6	150	56	56
7	500	56	56
8	1500	56	56
<b>Sentinel Animals<sup>b</sup></b>			
89	-	35	35
<sup>a</sup> Administered the vehicle formulation only. <sup>b</sup> Sentinel animals were not administered the vehicle or test article.			

### 3.1. Sponsor's analyses

#### 3.1.1. Survival analysis

Survival data from the mouse study were analyzed by the sponsor using the same statistical methodologies that were used to analyze the survival data from the rat study. All statistical analysis was performed for males and females separately.

**Sponsor's findings:** Kaplan-Meier product limit survival curves are presented in Figure 3 (males) and Figure 4 (females). There were no test article-related differences in mortality in either males or females. All causes of death/morbidity were either commonly seen in mice of this strain and age or were considered incidental and unrelated to treatment due to the lack of a dose response and/or the lack of similar findings in both sexes. The most common causes of death/morbidity in males across all groups were lymphoid tumors, skin inflammation/necrosis, and urogenital inflammation/obstruction/calculi while in females the most common causes of death/morbidity across all groups were lymphoid tumors, death/morbidity of a nature undetermined, or chronic progressive nephropathy/uremia. The incidence of skin inflammation/necrosis was greater in males at 150 and 1500 mg/kg/day than in control males; however, this is a common background finding in mice. Due to the lack of a clear dose response and the lack of a similar trend in females, this cause of death/morbidity was not considered to be test article related. The survival rates to scheduled sacrifice were 55, 52, 48 and 48% in males and 40, 45, 49 and 49% in females given 0 vehicle control, 150, 500, or 1500 mg/kg/day, respectively.

Figure 3: Kaplan-Meier plot of Survival in Male Mice

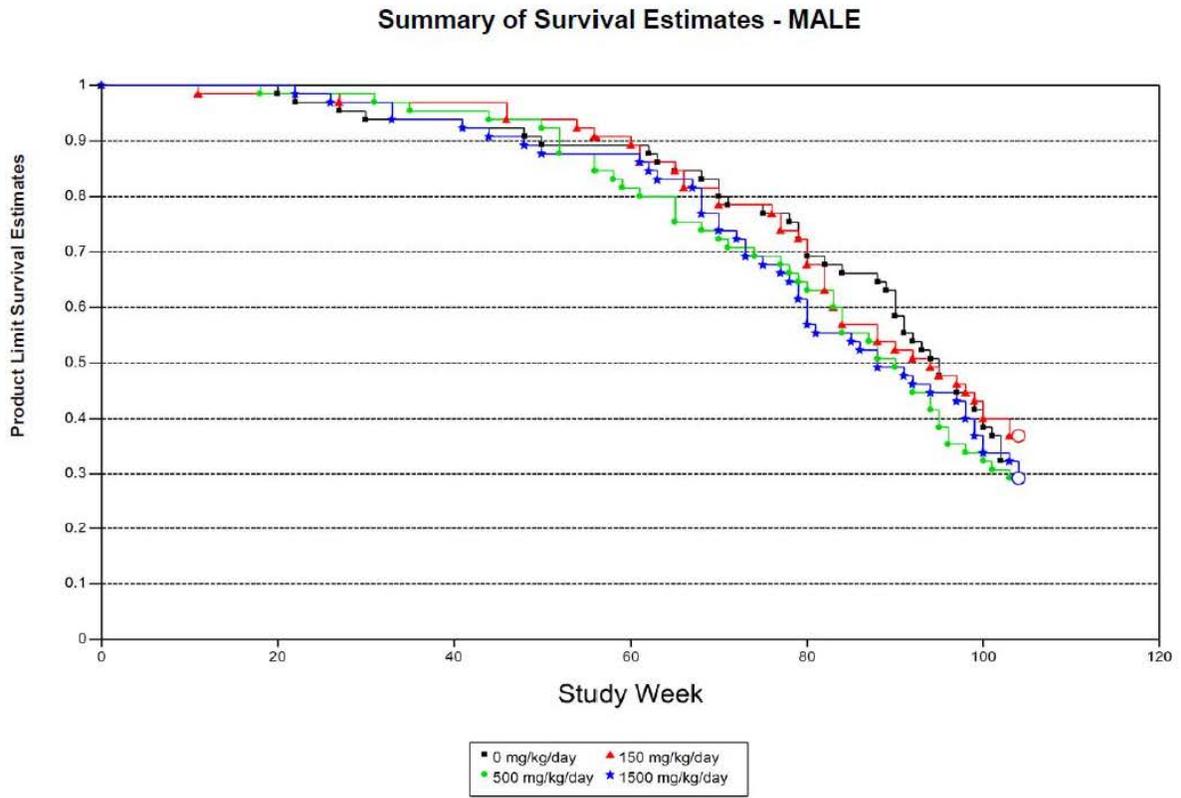
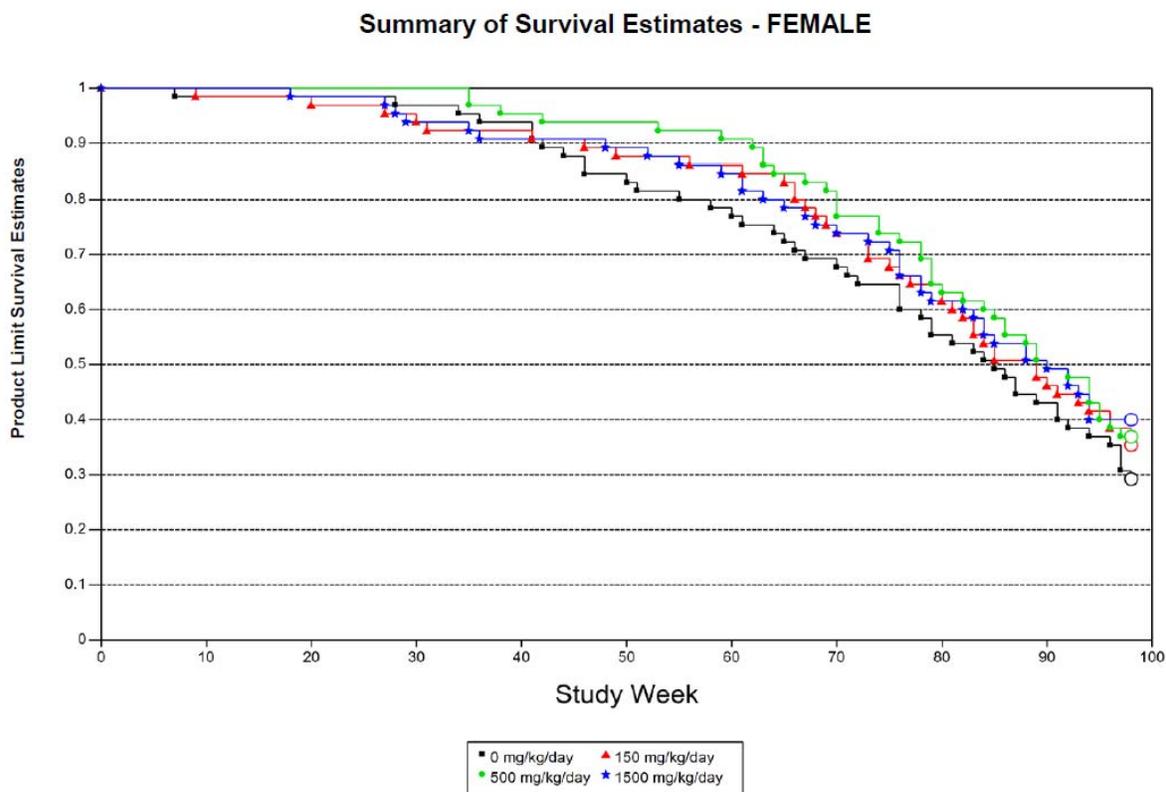


Figure 4: Kaplan-Meier plot of Survival in Female Mice



### 3.1.2. Tumor data analysis

Tumor data from mouse study were also analyzed by the sponsor using the same statistical methodologies that were used to analyze the tumor data from the rat study.

**Sponsor's findings:** No test article-related increases in tumor incidence occurred in either sex, and there were no statistically significant neoplastic findings. The most common tumor types in males were bronchiolar-alveolar adenomas in the lung, lymphomas, and hepatocellular adenomas in the liver of males while in females the most common tumor types were lymphomas, bronchiolar-alveolar adenomas in the lung, endometrial stromal polyps in the uterus, and histiocytic sarcomas. Tumors noted were typical of those seen in mice of this strain and age and were considered incidental to test article administration.

### 3.2. Reviewer's analyses

This reviewer independently performed survival and tumor data analyses for the mouse study. For the mouse data analyses this reviewer used similar methodologies that she used to analyze the data from the rat study. Data used in this reviewer's analyses were provided by the sponsor electronically. According to pharmacologist request, we have done analysis on the following tumor combinations in mouse study:

- Hemangioma and Hemangiosarcoma in bone marrow femur (male mouse).
- Tubular cell adenoma and carcinoma in kidneys (male mouse).
- Bronchiolar alveolar adenoma and carcinoma in lung.
- Hepatocellular adenoma and carcinoma in liver.
- Hemangioma and hemangiosarcoma in lymph node mesenteric.
- Hemangioma and hemangiosarcoma in multicentric neoplasm.
- Hemangioma and hemangiosarcoma in ovaries (female mouse).
- Islet cell adenoma and carcinoma in pancreas (male mouse).
- Hemangioma and hemangiosarcoma in spleen (male mouse).
- Hemangioma and hemangiosarcoma in urinary bladder (female mouse).
- Leiomyoma and leiomyosarcoma in uterus with cervix (female mouse).
- Endometrial stromal polyp and sarcoma in uterus with cervix (female mouse).

**3.2.1. Survival analysis**

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

**Reviewer’s findings:** The test results showed no statistically significant dose-response mortality and statistically significant difference in mortality in both females and males when compared with the vehicle control group. There were some differences between reviewer’s and sponsor’s survival rates and the differences may be caused by the different dates of starting the terminal killing.

**3.2.2. Tumor data analysis**

The tumor rates and the p-values of the tumor types tested for dose response relationship and pair-wise comparisons of control and treated groups are given in Table 6A and 6B in the appendix for males and females, respectively. As suggested by the reviewing pharmacologist Dr. Chakraborti.

**Reviewer’s findings:** Following tumor types showed p-values less than or equal to 0.05 either tests for dose response relationship or pair-wise comparisons between vehicle control and each of individual treated groups.

**Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pair-wise Comparisons (Vehicle control, low, medium and high dose groups)**

		1500 mg							
		0 mg	150 mg	500 mg	g	P_Value		P_Value	
		Cont	Low	Med	High	Dos Resp	C vs. L	C vs. M	C vs. H
Organ Name	Tumor Name	N=65	N=65	N=65	N=65				
<b>Male</b>									
adrenal glands									
	ADENOMA, SUBCAPSULAR	0	5	2	2	0.474	0.028	0.224	0.230
	#EXAMINED ANIMALS	(65)	(65)	(65)	(65)	.	.	.	.
	PERCENTAGE	0%	7.7%	3.1%	3.1%	.	.	.	.
	ADJUSTED N	[44]	[44]	[40]	[41]	.	.	.	.

	liver	ADENOMA, HEPATOCELLU	6	15	10	7	0.693	0.034	0.150	0.427
		#EXAMINED ANIMALS	(65)	(65)	(65)	(65)	.	.	.	.
		PERCENTAGE	9.2%	23%	15%	11%	.	.	.	.
		ADJUSTED N	[45]	[48]	[41]	[41]	.	.	.	.
	Female									
	parathyroid gla	LYMPHOMA	0	0	1	3	0.022	.	0.535	0.144
		#EXAMINED ANIMALS	(65)	(65)	(65)	(65)	.	.	.	.
		PERCENTAGE	0%	0%	1.54%	4.6%	.	.	.	.
		ADJUSTED N	[40]	[43]	[46]	[45]	.	.	.	.
	salivary gland,									
		LYMPHOMA	2	2	3	7	0.026	0.727	0.567	0.123
		#EXAMINED ANIMALS	(65)	(65)	(65)	(65)	.	.	.	.
		PERCENTAGE	3.1%	3.1%	4.6%	11%	.	.	.	.
		ADJUSTED N	[40]	[44]	[46]	[47]	.	.	.	.
	small intestine									
		LYMPHOMA	7	3	4	11	0.038	0.962	0.932	0.299
		#EXAMINED ANIMALS	(65)	(65)	(65)	(65)	.	.	.	.
		PERCENTAGE	11%	4.6%	6.2%	17%	.	.	.	.
		ADJUSTED N	[43]	[45]	[48]	[46]	.	.	.	.
	uterus with cervix									
		HEMANGIOMA	1	0	0	3	0.049	.	.	0.336
		#EXAMINED ANIMALS	(65)	(65)	(65)	(65)	.	.	.	.
		PERCENTAGE	1.54%	0%	0%	4.6%	.	.	.	.
		ADJUSTED N	[40]	[43]	[46]	[43]	.	.	.	.

Based on the criteria of adjustment for multiple testing of trends by Lin and Rahman, the dose response relationship in the incidence of lymphoma of parathyroid gland for vehicle control with three treated groups in female mice was considered to be statistically significant since the p-values were less than 0.025. Also based on the criteria of Haseman, the increased tumor incidence of subcapsular cell adenoma in adrenal glands in low dose group in male mice was considered to be statistically significant when compared to the vehicle control because the p-value is less than 0.05.

#### 4. Evaluation of validity of the designs of the rat study

As having been noted, the tumor data analyses from rat study including the vehicle control group and three treated groups showed no statistically significant dose-response relationship in any tested single tumor type. Before drawing any conclusion regarding the carcinogenic or non-carcinogenic potential of the drug in rats and mice, it is important to look into the following two issues, as have been pointed out in the paper by Haseman (1984).

- (i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumors?
- (ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There is no consensus among experts regarding the number of animals and length of time at risk, although most

carcinogenicity studies are designed to run for two years with fifty animals per treatment group. The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman (1985) has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP). It was found that, on the average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Division of Biometrics-6, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals or 20 to 30 animals still alive in the high dose group, between weeks 80-90, would be considered as a sufficient number and adequate exposure. In addition Chu, Cueto and Ward (1981), suggested that "to be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the maximum tolerated dose (MTD). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy. A high dose is considered as close to MTD if any of the criteria is met.

(i) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."

(ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

(iii) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

We will now investigate the validity of the JNJ-27018966-AAA rat study, in the light of the above guidelines.

#### 4.1. Rat Study

The following is the summary of survival data of rats in the high dose groups:

##### Percentage of survival in the high dose group at the end of Weeks 52, 78, and 91

	Percentage of survival		
	End of 52 weeks	End of 78 weeks	End of 91 weeks
Male	89%	66%	36%
Female	92%	59%	37%

Based on the survival criterion Haseman proposed, it could be concluded that there were enough rats that were exposed to the high dose for a sufficient amount of time in both males and females.

The following table shows the percent difference in mean body weight gain from the concurrent combined control, defined as

$$(\text{Final BW} - \text{Baseline BW})_{\text{Treated}} - (\text{Final BW} - \text{Baseline BW})_{\text{Control}}$$

$$\text{Percent difference} = \frac{\text{-----}}{(\text{Final BW} - \text{Baseline BW})_{\text{Control}}} \times 100$$

**Percent Difference in Mean body Weight Gain  
From combined controls**

Male			Female		
150mg	500mg	1500mg	150mg	500mg	1500mg
5.52	6.76	-3.91	-10.3	7.58	6.36

Therefore, relative to the vehicle control group, there had been up to 3.91% loss and 6.36% increase in body weight gain in the treated groups in both males and females, respectively.

The mortality rates at the end of the experiment were as follows:

**Mortality Rates at the End of the Experiment**

	<b>Cont.</b>	<b>Low</b>	<b>Medium</b>	<b>High</b>
Male	66%	55%	57%	62%
Female	65%	65%	74%	72%

The mortality rate of in the high dose group in males is 4% lower than the vehicle control group and 7% higher in females. Thus, from the body weight gain and mortality data it can be concluded that for males and females the used high dose level might be close the MTD. For a final determination of the adequacy of the doses used in rats, other clinical signs and histopathological toxic effects must be considered.

## 5. Summary

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to further assess the carcinogenic potential of JNJ-27018966-AAA, when administered daily via oral gavage to male and female rats for up to 98 or 99 weeks and to male and female mice for up to 104 weeks, respectively.

**Rat Study:** Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and one control group. Three treatment groups of 65 male and 65 female experimentally naïve CD® [CrI:CD®(SD)] rats were administered JNJ-27018966-AAA at respective dose levels of 150, 500, or 1500 mg/kg/day. One additional group of 65 animals per sex served as the control (0 mg/kg/day) and received the vehicle, 0.5% hydroxypropyl methylcellulose [high viscosity (HPMC)] in Purified Water, USP

The test results showed no statistically significant dose-response mortality in both females and males when compared with vehicle control. The tests showed statistically significant pair-wise differences between medium dose group and the vehicle control group in survivals in females. There were few differences between reviewer's and sponsor's survival rates and the differences may be caused by the different dates of starting the terminal killing.

Based on the criteria of adjustment for multiple testing of trends proposed by Lin and Rahman, the incidence of none of the above or any other tested tumor types in either sex was considered to have a statistically significant positive dose response relationship. Also based on the criteria by Haseman, none of the pair-wise comparisons of treated groups with the vehicle control was considered to be statistically significant in either sex for increased tumor incidence in the treated group.

From the body weight gain and mortality data it can be concluded that for males and females the used high dose level might be close the MTD. For a final determination of the adequacy of the doses used in rats, other clinical signs and histopathological toxic effects must be considered.

**Mouse Study:** Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and one control group. Three treatment groups of 65 male and 65 female experimentally naïve Crl:CD1®(ICR) mice were administered JNJ-27018966-AAA at respective dose levels of 150, 500, and 1500 mg/kg/day. One additional group of 65 animals per sex served as the control (0 mg/kg/day) and received the vehicle formulation, 0.5% hydroxypropyl methylcellulose [high viscosity (HPMC)] in Purified Water, USP.

The test results showed no statistically significant dose-response mortality and statistically significant difference in mortality in both females and males when compared with the vehicle control group. There were some differences between reviewer's and sponsor's survival rates and the differences may be caused by the different dates of starting the terminal killing.

Based on the criteria of adjustment for multiple testing of trends by Lin and Rahman, the dose response relationship in the incidence of lymphoma of parathyroid gland for vehicle control with three treated groups in female mice was considered to be statistically significant since the p-values were less than 0.025. Also based on the criteria of Haseman, the increased tumor incidence of subcapsular cell adenoma in adrenal glands in low dose group in male mice was considered to be statistically significant when compared to the vehicle control because the p-value is less than 0.05.

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## 6. Appendix

**Table 1A: Intercurrent Mortality Rate  
Male Rats**

Week	CONTROL		150mg		500mg		1500mg	
	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT
0-52	6	9.2%	3	4.6%	7	10.8%	7	10.8%
53-78	13	29.2%	21	36.9%	11	27.7%	15	33.9%
79-92	15	52.3%	6	46.2%	15	50.8%	13	53.9%
93-97	9	66.2%	6	55.4%	4	56.9%	5	61.5%
Term. Sac.	22	100.0%	29	100.0%	28	100.0%	25	100.0%

**Table 1B: Intercurrent Mortality Rate  
Female Rats**

Week	CONTROL		150mg		500mg		1500mg	
	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT
0-52	1	1.5%	5	7.7%	5	7.7%	5	7.7%
53-78	18	29.3%	24	44.6%	19	36.9%	22	41.5%
79-92	20	60.0%	10	60.0%	14	58.5%	14	63.1%
93-98	3	64.6%	3	64.6%	10	73.9%	6	72.3%
Term. Sac.	23	100.0%	23	100.0%	17	100.0%	18	100.0%

**Table 2A: Intercurrent Mortality Comparison  
Male Rats**

Test	P-Value (across four groups)	P-Value (vehicle_contr ol vs low)	P-Value (vehicle_con trol vs medium)	P-Value (vehicle_contro l vs high)
Dose Response	0.8551	0.4959	0.5708	0.9034
Homogeneity	0.7040	0.2611	0.3856	0.7004

**Table 2B: Intercurrent Mortality Comparison  
Female Rats**

Test	P-Value (across four groups)	P-Value (vehicle_contr ol1 vs low)	P-Value (vehicle_con trol1 vs medium)	P-Value (vehicle_contro l1 vs high)
Dose Response	0.3842	0.5084	0.0052	0.2861
Homogeneity	0.5697	0.4166	0.2141	0.2031

**Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Male Rats (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 mg				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	1500 mg High N=65				
LIVER	ADENOMA+CARCINOMA	(65)	(65)	(65)	(65)	.	.	.	.
		2	0	0	1	0.579	1.000	1.000	0.871
		[45]	[46]	[45]	[43]	.	.	.	.
LUNG	ADENOMA+AENOCARCINOMA	(65)	(65)	(65)	(65)	.	.	.	.
		1	0	0	2	0.147	1.000	1.000	0.483
		[46]	[46]	[45]	[44]	.	.	.	.
MAMMARY_GLAND	ADENOCARCINOMA+FIBROADENOMA	(65)	(65)	(65)	(65)	.	.	.	.
		1	0	2	2	0.161	1.000	0.508	0.492
		[45]	[46]	[46]	[44]	.	.	.	.
PANCREAS	ISLET_CELL_ADENOMA+CARCINOMA	(65)	(65)	(65)	(65)	.	.	.	.
		13	3	8	6	0.771	0.999	0.924	0.969
		[48]	[46]	[47]	[44]	.	.	.	.
PITUITARY_GLAND	PARS_D+I_ADENOMA+CARCINOMA	(65)	(65)	(65)	(65)	.	.	.	.
		2	0	0	0	1.000	1.000	1.000	1.000
		[45]	[46]	[45]	[43]	.	.	.	.
PITUITARY_GLAND	PARS_D_ADENOMA+CARCINOMA	(65)	(65)	(65)	(65)	.	.	.	.
		43	40	33	40	0.491	0.914	0.986	0.772
		[54]	[57]	[53]	[53]	.	.	.	.
PROSTATE_GLAND	ADENOMA+ADENOCARCINOMA	(65)	(65)	(65)	(65)	.	.	.	.
		1	1	1	0	0.822	0.753	0.753	1.000
		[46]	[46]	[46]	[43]	.	.	.	.
SKIN	SQUAMOUS_CELL_ADENOMA+CARCINOM	(65)	(65)	(65)	(65)	.	.	.	.
		3	2	1	1	0.837	0.826	0.942	0.939
		[45]	[46]	[45]	[44]	.	.	.	.
THYROID_GLAND	C_CELL_ADENOMA+CARCINOMA	(65)	(65)	(65)	(65)	.	.	.	.
		7	5	12	7	0.365	0.833	0.152	0.579
		[46]	[47]	[46]	[44]	.	.	.	.
THYROID_GLAND	F_CELL_ADENOMA+CARCINOMA	(65)	(65)	(65)	(65)	.	.	.	.
		1	0	1	1	0.376	1.000	0.753	0.741
		[45]	[46]	[45]	[43]	.	.	.	.
adipose tissue,	HIBERNOMA	(65)	(65)	(65)	(65)	.	.	.	.
		0	1	0	0	0.749	0.506	.	.
		[45]	[46]	[45]	[43]	.	.	.	.
adrenal glands	ADENOMA, CORTICAL	(65)	(65)	(65)	(65)	.	.	.	.
		2	1	0	1	0.672	0.879	1.000	0.866
		[46]	[46]	[45]	[43]	.	.	.	.

**Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 mg				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
	LEUKEMIA, GRANULOCYTIC	1 [46]	0 [46]	1 [46]	1 [44]	0.380 .	1.000 .	0.753 .	0.742 .
	LEUKEMIA, LARGE GRANULAR LYMP	1 [45]	0 [46]	0 [45]	0 [43]	1.000 .	1.000 .	1.000 .	1.000 .
	LYMPHOMA	1 [46]	0 [46]	0 [45]	0 [43]	1.000 .	1.000 .	1.000 .	1.000 .
	PHEOCHROMOCYTOMA	7 [46]	5 [46]	5 [46]	5 [45]	0.643 .	0.823 .	0.823 .	0.812 .
	PHEOCHROMOCYTOMA, COMPLEX	1 [45]	1 [46]	0 [45]	0 [43]	0.938 .	0.758 .	1.000 .	1.000 .
bone		(65)	(65)	(65)	(65)	.	.	.	.
	OSTEOSARCOMA	0 [45]	0 [46]	1 [45]	0 [43]	0.492 .	.	0.500 .	.
bone marrow, fe		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1 [46]	0 [46]	1 [46]	1 [44]	0.380 .	1.000 .	0.753 .	0.742 .
	LEUKEMIA, LARGE GRANULAR LYMP	0	1	0	0	0.749	0.506	.	.
bone marrow, fe	LEUKEMIA, LARGE GRANULAR LYMP	[45]	[46]	[45]	[43]	.	.	.	.
bone marrow, st		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1 [46]	0 [46]	1 [46]	1 [44]	0.380 .	1.000 .	0.753 .	0.742 .
	LEUKEMIA, LARGE GRANULAR LYMP	0 [45]	1 [46]	0 [45]	0 [43]	0.749 .	0.506 .	.	.
bone marrow, ti		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0 [45]	0 [46]	0 [45]	1 [44]	0.244 .	.	.	0.494 .
bone, femur		(65)	(65)	(65)	(65)	.	.	.	.
	OSTEOSARCOMA	1 [45]	0 [46]	0 [45]	0 [43]	1.000 .	1.000 .	1.000 .	1.000 .
brain		(65)	(65)	(65)	(65)	.	.	.	.
	ASTROCYTOMA	0 [45]	1 [47]	0 [45]	2 [43]	0.100 .	0.511 .	.	0.236 .
	CARCINOMA, PARS DISTALIS	1 [45]	0 [46]	0 [45]	0 [43]	1.000 .	1.000 .	1.000 .	1.000 .
	GRANULAR CELL TUMOR	1 [46]	1 [46]	0 [45]	0 [43]	0.936 .	0.753 .	1.000 .	1.000 .
	LEUKEMIA, GRANULOCYTIC	1	0	1	0	0.743	1.000	0.753	1.000

**Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 mg				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
	MIXED GLIOMA	[46] 0	[46] 1	[46] 0	[43] 0	. 0.749	. 0.506	. .	. .
		[45]	[46]	[45]	[43]	.	.	.	.
cavity, abdomin		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOCARCINOMA (PRIMARY SITE)	0	1	1	0	0.617	0.506	0.506	.
		[45]	[46]	[46]	[43]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	1	0.428	1.000	1.000	0.742
		[46]	[46]	[45]	[44]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	2	1	1	0.401	0.253	0.506	0.489
		[45]	[46]	[46]	[43]	.	.	.	.
cavity, oral		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, SQUAMOUS CELL	0	0	0	1	0.244	.	.	0.494
		[45]	[46]	[45]	[44]	.	.	.	.
	FIBROSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[46]	[46]	[45]	[43]	.	.	.	.
cavity, thoraci		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	1	0.428	1.000	1.000	0.742
		[46]	[46]	[45]	[44]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	1	0.179	.	0.506	0.489
		[45]	[46]	[46]	[43]	.	.	.	.
epididymides		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[46]	[46]	[45]	[43]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	2	0	0	0.808	0.253	.	.
		[45]	[46]	[45]	[43]	.	.	.	.
eyes		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	1	0.428	1.000	1.000	0.742
		[46]	[46]	[45]	[44]	.	.	.	.
galt		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	1	0.428	1.000	1.000	0.742
		[46]	[46]	[45]	[44]	.	.	.	.
	LYMPHOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[46]	[46]	[45]	[43]	.	.	.	.
harderian gland		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOCARCINOMA	1	0	0	0	1.000	1.000	1.000	1.000

**Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 mg				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H	
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	1500 mg High N=65					
heart	SCHWANNOMA	[45]	[46]	[45]	[43]	.	.	.	.	
		0	1	0	0	0.750	0.511	.	.	
		[45]	[47]	[45]	[43]	.	.	.	.	
	LEUKEMIA, GRANULOCYTIC	(65)	(65)	(65)	(65)	.	.	.	.	
		1	0	1	1	0.380	1.000	0.753	0.742	
		[46]	[46]	[46]	[44]	.	.	.	.	
		OSTEOSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
			[45]	[46]	[45]	[43]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.494	.	0.506	.	
		[45]	[46]	[46]	[43]	.	.	.	.	
SCHWANNOMA	1	1	0	0	0.938	0.758	1.000	1.000		
	[45]	[46]	[45]	[43]	.	.	.	.		
joint, tibiofem	LEUKEMIA, GRANULOCYTIC	(65)	(65)	(65)	(65)	.	.	.	.	
		1	0	0	1	0.428	1.000	1.000	0.742	
	[46]	[46]	[45]	[44]	.	.	.	.		
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.494	.	0.506	.	
		[45]	[46]	[46]	[43]	.	.	.	.	
kidneys	ADENOCARCINOMA	(65)	(65)	(65)	(65)	.	.	.	.	
		1	0	0	0	1.000	1.000	1.000	1.000	
	[46]	[46]	[45]	[43]	.	.	.	.		
	ADENOCARCINOMA (PRIMARY SITE)	0	1	0	0	0.749	0.506	.	.	
		[45]	[46]	[45]	[43]	.	.	.	.	
	LEUKEMIA, GRANULOCYTIC	1	0	1	1	0.380	1.000	0.753	0.742	
		[46]	[46]	[46]	[44]	.	.	.	.	
	LEUKEMIA, LARGE GRANULAR LYMP	1	0	0	0	1.000	1.000	1.000	1.000	
		[45]	[46]	[45]	[43]	.	.	.	.	
	LIPOSARCOMA	0	1	0	1	0.307	0.506	.	0.494	
		[45]	[46]	[45]	[44]	.	.	.	.	
	LYMPHOMA	1	0	0	0	1.000	1.000	1.000	1.000	
		[46]	[46]	[45]	[43]	.	.	.	.	
OSTEOSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000		
	[45]	[46]	[45]	[43]	.	.	.	.		
SARCOMA, HISTIOCYTIC	0	1	1	1	0.284	0.506	0.506	0.489		
	[45]	[46]	[46]	[43]	.	.	.	.		
lacrimal glands	LEUKEMIA, GRANULOCYTIC	(65)	(65)	(65)	(65)	.	.	.	.	
		1	0	0	1	0.428	1.000	1.000	0.742	
		[46]	[46]	[45]	[44]	.	.	.	.	

**Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Male Rats (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 mg				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
large intestine		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[46]	[46]	[45]	[43]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.494	.	0.506	.
		[45]	[46]	[45]	[43]	.	.	.	.
		0	1	0	0	0.749	0.506	.	.
		[45]	[46]	[46]	[43]	.	.	.	.
larynx		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	1	0.428	1.000	1.000	0.742
		[46]	[46]	[45]	[44]	.	.	.	.
liver		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOCARCINOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[46]	[46]	[45]	[43]	.	.	.	.
	ADENOMA, HEPATOCELLULAR	2	0	0	0	1.000	1.000	1.000	1.000
		[45]	[46]	[45]	[43]	.	.	.	.
	CARCINOMA, HEPATOCELLULAR	0	0	0	1	0.240	.	.	0.489
		[45]	[46]	[45]	[43]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	1	1	0.380	1.000	0.753	0.742
liver	LEUKEMIA, GRANULOCYTIC	[46]	[46]	[46]	[44]	.	.	.	.
	LEUKEMIA, LARGE GRANULAR LYMP	1	1	0	0	0.938	0.758	1.000	1.000
		[45]	[46]	[45]	[43]	.	.	.	.
	LYMPHOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[46]	[46]	[45]	[43]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	2	1	0	0.726	0.253	0.506	.
		[45]	[46]	[46]	[43]	.	.	.	.
lung		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOCARCINOMA	1	0	0	1	0.428	1.000	1.000	0.742
		[46]	[46]	[45]	[44]	.	.	.	.
	ADENOCARCINOMA (PRIMARY SITE)	0	1	0	0	0.749	0.506	.	.
		[45]	[46]	[45]	[43]	.	.	.	.
	ADENOMA, BRONCHIOLAR ALVEOLAR	0	0	0	1	0.244	.	.	0.494
		[45]	[46]	[45]	[44]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	1	1	0.380	1.000	0.753	0.742
		[46]	[46]	[46]	[44]	.	.	.	.
	LEUKEMIA, LARGE GRANULAR LYMP	1	0	0	0	1.000	1.000	1.000	1.000
	[45]	[46]	[45]	[43]	.	.	.	.	
	LYMPHOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[46]	[46]	[45]	[43]	.	.	.	.
	OSTEOSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[45]	[46]	[45]	[43]	.	.	.	.

**Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Male Rats (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 mg				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
	PHEOCHROMOCYTOMA, COMPLEX	1 [45]	0 [46]	0 [45]	0 [43]	1.000 .	1.000 .	1.000 .	1.000 .
	SARCOMA, HISTIOCYTIC	0 [45]	0 [46]	1 [46]	2 [43]	0.056 .	. .	0.506 .	0.236 .
lymph node, hep		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0 [45]	0 [46]	0 [45]	1 [44]	0.244 .	. .	. .	0.494 .
lymph node, ili		(65)	(65)	(65)	(65)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0 [45]	2 [46]	0 [45]	0 [43]	0.808 .	0.253 .	. .	. .
lymph node, ing		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0 [45]	0 [46]	0 [45]	1 [44]	0.244 .	. .	. .	0.494 .
lymph node, man		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, SEBACEOUS CELL	1 [46]	0 [46]	0 [45]	0 [43]	1.000 .	1.000 .	1.000 .	1.000 .
	LEUKEMIA, GRANULOCYTIC	1 [46]	0 [46]	1 [46]	1 [44]	0.380 .	1.000 .	0.753 .	0.742 .
lymph node, med		(65)	(65)	(65)	(65)	.	.	.	.
	LYMPHOMA	1 [46]	0 [46]	0 [45]	0 [43]	1.000 .	1.000 .	1.000 .	1.000 .
	SARCOMA, HISTIOCYTIC	0 [45]	1 [46]	0 [45]	1 [43]	0.302 .	0.506 .	. .	0.489 .
lymph node, mes		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOCARCINOMA (PRIMARY SITE)	0 [45]	1 [46]	0 [45]	0 [43]	0.749 .	0.506 .	. .	. .
	HEMANGIOSARCOMA	1 [45]	0 [46]	3 [46]	1 [43]	0.388 .	1.000 .	0.317 .	0.741 .
	LEUKEMIA, GRANULOCYTIC	1 [46]	0 [46]	1 [46]	1 [44]	0.380 .	1.000 .	0.753 .	0.742 .
	LYMPHOMA	1 [46]	0 [46]	0 [45]	0 [43]	1.000 .	1.000 .	1.000 .	1.000 .
mammary gland		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOCARCINOMA	0	0	1	1	0.182	.	0.506	0.494

**Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 mg				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
mammary gland	ADENOCARCINOMA	[45]	[46]	[46]	[44]	.	.	.	.
	FIBROADENOMA	1	0	2	1	0.360	1.000	0.508	0.747
		[45]	[46]	[46]	[44]	.	.	.	.
multicentric ne		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	1	1	0.380	1.000	0.753	0.742
		[46]	[46]	[46]	[44]	.	.	.	.
	LEUKEMIA, LARGE GRANULAR LYMP	1	1	0	0	0.938	0.758	1.000	1.000
		[45]	[46]	[45]	[43]	.	.	.	.
	LYMPHOMA	1	0	0	0	1.000	1.000	1.000	1.000
	[46]	[46]	[45]	[43]	.	.	.	.	
	SARCOMA, HISTIOCYTIC	0	2	1	2	0.184	0.253	0.506	0.236
		[45]	[46]	[46]	[43]	.	.	.	.
nerve, cranial		(65)	(65)	(65)	(65)	.	.	.	.
	SCHWANNOMA	0	1	0	0	0.750	0.511	.	.
		[45]	[47]	[45]	[43]	.	.	.	.
nose, level a		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	1	0.428	1.000	1.000	0.742
		[46]	[46]	[45]	[44]	.	.	.	.
nose, level b		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	1	0.428	1.000	1.000	0.742
		[46]	[46]	[45]	[44]	.	.	.	.
nose, level c		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOCARCINOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[45]	[46]	[45]	[43]	.	.	.	.
	ADENOMA	0	0	1	0	0.492	.	0.500	.
		[45]	[46]	[45]	[43]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	1	0.428	1.000	1.000	0.742
	[46]	[46]	[45]	[44]	.	.	.	.	
	LEUKEMIA, LARGE GRANULAR LYMP	0	1	0	0	0.749	0.506	.	.
		[45]	[46]	[45]	[43]	.	.	.	.
nose, level d		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, SQUAMOUS CELL	1	0	0	0	1.000	1.000	1.000	1.000
		[45]	[46]	[45]	[43]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	1	0.428	1.000	1.000	0.742
		[46]	[46]	[45]	[44]	.	.	.	.
	LEUKEMIA, LARGE GRANULAR LYMP	0	1	0	0	0.749	0.506	.	.
		[45]	[46]	[45]	[43]	.	.	.	.

**Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Male Rats (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 mg				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
oral cavity		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, SQUAMOUS CELL	0	0	1	0	0.492	.	0.500	.
		[45]	[46]	[45]	[43]	.	.	.	.
pancreas		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOCARCINOMA (PRIMARY SITE)	0	1	0	0	0.749	0.506	.	.
		[45]	[46]	[45]	[43]	.	.	.	.
	ADENOMA, ISLET CELL	12	2	4	4	0.894	1.000	0.992	0.990
		[48]	[46]	[46]	[44]	.	.	.	.
	CARCINOMA, ISLET CELL	1	1	4	2	0.289	0.758	0.187	0.483
		[45]	[46]	[46]	[43]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	1	1	0.380	1.000	0.753	0.742
		[46]	[46]	[46]	[44]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	1	1	0.284	0.506	0.506	0.489
		[45]	[46]	[46]	[43]	.	.	.	.
parathyroid gla		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA	2	0	1	1	0.544	1.000	0.875	0.866
		[46]	[46]	[45]	[43]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
parathyroid gla	LEUKEMIA, GRANULOCYTIC	[46]	[46]	[45]	[43]	.	.	.	.
pituitary gland		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA, PARS DISTALIS	42	40	33	40	0.438	0.870	0.976	0.695
		[54]	[57]	[53]	[53]	.	.	.	.
	ADENOMA, PARS INTERMEDIA	1	0	0	0	1.000	1.000	1.000	1.000
		[45]	[46]	[45]	[43]	.	.	.	.
	CARCINOMA, PARS DISTALIS	1	0	0	0	1.000	1.000	1.000	1.000
	[45]	[46]	[45]	[43]	.	.	.	.	
	LEUKEMIA, GRANULOCYTIC	1	0	1	1	0.380	1.000	0.753	0.742
		[46]	[46]	[46]	[44]	.	.	.	.
preputial gland		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	1	0.428	1.000	1.000	0.742
		[46]	[46]	[45]	[44]	.	.	.	.
prostate gland		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOCARCINOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[46]	[46]	[45]	[43]	.	.	.	.
	ADENOCARCINOMA (PRIMARY SITE)	0	1	0	0	0.749	0.506	.	.
	[45]	[46]	[45]	[43]	.	.	.	.	
	ADENOMA	0	1	1	0	0.617	0.506	0.506	.

**Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Male Rats (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 mg				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
		[45]	[46]	[46]	[43]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[46]	[46]	[45]	[43]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	1	0.302	0.506	.	0.489
		[45]	[46]	[45]	[43]	.	.	.	.
salivary gland,		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
					1	0.428	1.000	1.000	0.742
		[46]	[46]	[45]	[43]	.	.	.	.
					[44]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.494	.	0.506	.
		[45]	[46]	[46]	[43]	.	.	.	.
	SARCOMA, UNDIFFERENTIATED	0	1	0	0	0.749	0.506	.	.
		[45]	[46]	[45]	[43]	.	.	.	.
seminal vesicle		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[46]	[46]	[45]	[43]	.	.	.	.
	LYMPHOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[46]	[46]	[45]	[43]	.	.	.	.
skeletal muscle		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOCARCINOMA (PRIMARY SITE)	0	1	0	0	0.749	0.506	.	.
		[45]	[46]	[45]	[43]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[46]	[46]	[45]	[43]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	0	1	0.240	.	.	0.489
			1	0	1	0.302	0.506	.	0.489
		[45]	[46]	[45]	[43]	.	.	.	.
skin		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, BASAL CELL	1	0	0	1	0.424	1.000	1.000	0.741
		[45]	[46]	[45]	[43]	.	.	.	.
	CARCINOMA, SEBACEOUS CELL	1	2	0	0	0.934	0.500	1.000	1.000
		[46]	[46]	[45]	[43]	.	.	.	.
	CARCINOMA, SQUAMOUS CELL	1	0	1	0	0.743	1.000	0.753	1.000
		[45]	[46]	[45]	[43]	.	.	.	.
	HAIR FOLLICLE TUMOR	1	0	0	0	1.000	1.000	1.000	1.000
		[45]	[46]	[45]	[43]	.	.	.	.
	KERATOACANTHOMA	3	4	2	3	0.538	0.512	0.820	0.640
		[46]	[47]	[46]	[44]	.	.	.	.

**Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 mg				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
skin	LEUKEMIA, GRANULOCYTIC	0 [45]	0 [46]	0 [45]	1 [44]	0.244 .	. .	. .	0.494 .
	PAPILLOMA, SQUAMOUS CELL	2 [45]	2 [46]	0 [45]	1 [44]	0.754 .	0.700 .	1.000 .	0.875 .
	SARCOMA, HISTIOCYTIC	0 [45]	1 [46]	0 [45]	0 [43]	0.749 .	0.506 .	. .	. .
		(65)	(65)	(65)	(65)	.	.	.	.
skin, subcutis	FIBROMA	0 [45]	2 [46]	3 [46]	2 [44]	0.244 .	0.253 .	0.125 .	0.242 .
	FIBROSARCOMA	1 [46]	0 [46]	0 [45]	1 [43]	0.422 .	1.000 .	1.000 .	0.736 .
	FIBROUS HISTIOCYTOMA	0 [45]	0 [46]	0 [45]	2 [44]	0.059 .	. .	. .	0.242 .
	LIPOMA	0 [45]	0 [46]	1 [45]	0 [43]	0.492 .	. .	0.500 .	. .
	LIPOSARCOMA	0 [45]	1 [46]	0 [45]	0 [43]	0.749 .	0.506 .	. .	. .
	OSTEOSARCOMA	0 [45]	1 [47]	0 [45]	0 [43]	0.750 .	0.511 .	. .	. .
	SARCOMA, HISTIOCYTIC	0 [45]	2 [46]	1 [46]	2 [43]	0.184 .	0.253 .	0.506 .	0.236 .
	SCHWANNOMA	0 [45]	0 [46]	0 [45]	2 [45]	0.061 .	. .	. .	0.247 .
		(65)	(65)	(65)	(65)	.	.	.	.
	spinal cord, ce	ASTROCYTOMA	1 [45]	0 [46]	0 [45]	0 [43]	1.000 .	1.000 .	1.000 .
	LEUKEMIA, GRANULOCYTIC	0 [45]	0 [46]	1 [46]	0 [43]	0.494 .	. .	0.506 .	. .
spinal cord, lu	ASTROCYTOMA	0 [45]	0 [46]	2 [47]	0 [43]	0.486 .	. .	0.258 .	. .
	LEUKEMIA, GRANULOCYTIC	0 [45]	0 [46]	1 [46]	0 [43]	0.494 .	. .	0.506 .	. .
		(65)	(65)	(65)	(65)	.	.	.	.
spinal cord, th	ASTROCYTOMA	0 [45]	0 [46]	1 [46]	0 [43]	0.494 .	. .	0.506 .	. .
	LEUKEMIA, GRANULOCYTIC	0 [45]	0 [46]	1 [46]	0 [43]	0.494 .	. .	0.506 .	. .
		(65)	(65)	(65)	(65)	.	.	.	.

**Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 mg				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
spleen		(65)	(65)	(65)	(65)	.	.	.	.
	HEMANGIOSARCOMA	0	0	0	1	0.240	.	.	0.489
		[45]	[46]	[45]	[43]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	1	1	0.380	1.000	0.753	0.742
		[46]	[46]	[46]	[44]	.	.	.	.
	LEUKEMIA, LARGE GRANULAR LYMP	1	1	0	0	0.938	0.758	1.000	1.000
		[45]	[46]	[45]	[43]	.	.	.	.
	LYMPHOMA	1	0	0	0	1.000	1.000	1.000	1.000
stomach, glandu		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOCARCINOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[46]	[46]	[45]	[43]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[46]	[46]	[45]	[43]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	0	0.749	0.506	.	.
		[45]	[46]	[45]	[43]	.	.	.	.
		(65)	(65)	(65)	(65)	.	.	.	.
testes	ADENOMA, INTERSTITIAL CELL	0	4	1	0	0.880	0.061	0.500	.
		[45]	[46]	[45]	[43]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[46]	[46]	[45]	[43]	.	.	.	.
thymus		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	1	1	0.380	1.000	0.753	0.742
		[46]	[46]	[46]	[44]	.	.	.	.
	THYMOMA	1	0	0	0	1.000	1.000	1.000	1.000
thyroid gland		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA, C-CELL	6	5	11	7	0.295	0.751	0.141	0.465
		[46]	[47]	[46]	[44]	.	.	.	.
	ADENOMA, FOLLICULAR CELL	1	0	0	1	0.424	1.000	1.000	0.741
		[45]	[46]	[45]	[43]	.	.	.	.
	CARCINOMA, C-CELL	1	0	1	0	0.743	1.000	0.753	1.000
		[45]	[46]	[45]	[43]	.	.	.	.
	CARCINOMA, FOLLICULAR CELL	0	0	1	0	0.492	.	0.500	.

**Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 mg				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	1500 mg High N=65				
		[45]	[46]	[45]	[43]	.	.	.	.
	GANGLIONEUROMA	0	1	0	0	0.749	0.506	.	.
		[45]	[46]	[45]	[43]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[46]	[46]	[45]	[43]	.	.	.	.
tongue		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[46]	[46]	[45]	[43]	.	.	.	.
trachea		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	1	0.428	1.000	1.000	0.742
		[46]	[46]	[45]	[44]	.	.	.	.
ureters		(65)	(65)	(65)	(65)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.494	.	0.506	.
		[45]	[46]	[46]	[43]	.	.	.	.
urinary bladder		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOCARCINOMA (PRIMARY SITE)	0	1	0	0	0.749	0.506	.	.
		[45]	[46]	[45]	[43]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	1	0.428	1.000	1.000	0.742
		[46]	[46]	[45]	[44]	.	.	.	.
	PAPILLOMA, TRANSITIONAL CELL	0	1	0	0	0.749	0.506	.	.
		[45]	[46]	[45]	[43]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	1	0.179	.	0.506	0.489
		[45]	[46]	[46]	[43]	.	.	.	.
zymbal's gland		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, SEBACEOUS CELL	1	1	0	1	0.522	0.753	1.000	0.742
		[46]	[46]	[45]	[44]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[46]	[46]	[45]	[43]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

**Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Rats (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 mg				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	1500 mg High N=65				
MAMMARY_GLAND		(65)	(65)	(65)	(65)	.	.	.	.
	FIBROADENOMA+ADENOCARCINOMA	36 [57]	36 [51]	35 [52]	36 [53]	0.415	0.270	0.401	0.321
PITUITARY_GLAND		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA+CARCINOMA	56 [63]	56 [59]	57 [59]	51 [59]	0.877	0.190	0.098	0.754
SKIN		(65)	(65)	(65)	(65)	.	.	.	.
	SEBACEOUS_CELL_ADENOMA+CARCINO	0 [45]	0 [40]	1 [41]	1 [41]	0.180	.	0.477	0.476
SKIN_SUBCUTIS		(65)	(65)	(65)	(65)	.	.	.	.
	FIBROSARCOMA+HISTIOCYTIC_SARCO	2 [46]	0 [40]	1 [41]	3 [41]	0.121	1.000	0.857	0.444
SMALL_INTESTINE		(65)	(65)	(65)	(65)	.	.	.	.
	LEIOMYOMA+LEIOMYSARCOMA	0 [45]	0 [40]	1 [41]	1 [41]	0.180	.	0.477	0.476
THYROID_GLAND		(65)	(65)	(65)	(65)	.	.	.	.
	C_CELL_ADENOMA+CARCINOMA	10 [48]	5 [40]	6 [42]	9 [42]	0.297	0.915	0.862	0.594
	F_CELL_ADENOMA+CARCINOMA	1 [45]	1 [40]	2 [41]	1 [41]	0.483	0.722	0.465	0.729
UTERUS_CERVIX		(65)	(65)	(65)	(65)	.	.	.	.
	E_STROMAL_POLYP+SARCOMA	6 [45]	6 [40]	6 [43]	1 [41]	0.980	0.535	0.588	0.991
adrenal_glands		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA, CORTICAL	2 [45]	1 [40]	0 [41]	1 [41]	0.678	0.856	1.000	0.856
	OSTEOSARCOMA	0 [45]	0 [40]	0 [41]	1 [41]	0.246	.	.	0.476
	PHEOCHROMOCYTOMA	1 [45]	4 [40]	3 [42]	4 [41]	0.188	0.145	0.282	0.159
brain		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, PARS DISTALIS	4 [46]	1 [40]	2 [41]	1 [41]	0.830	0.960	0.870	0.963
	GRANULAR CELL TUMOR	0 [45]	1 [40]	0 [41]	0 [41]	0.731	0.470	.	.

**Table 3B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Rats (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 mg				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
	MENINGIOMA	0 [45]	1 [40]	0 [41]	0 [41]	0.731 .	0.476 .	. .	. .
cavity, abdomin		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, ISLET CELL	0 [45]	0 [40]	0 [41]	1 [41]	0.246 .	. .	. .	0.476 .
	LIPOSARCOMA	0 [45]	0 [40]	1 [41]	0 [41]	0.491 .	. .	0.477 .	. .
	SARCOMA, HISTIOCYTIC	0 [45]	0 [40]	0 [41]	1 [41]	0.246 .	. .	. .	0.476 .
clitoral glands		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, SQUAMOUS CELL	0 [45]	1 [40]	0 [41]	0 [41]	0.731 .	0.470 .	. .	. .
heart		(65)	(65)	(65)	(65)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0 [45]	0 [40]	0 [41]	1 [41]	0.246 .	. .	. .	0.476 .
kidneys		(65)	(65)	(65)	(65)	.	.	.	.
	LIPOMA	0 [45]	0 [40]	1 [41]	0 [41]	0.491 .	. .	0.477 .	. .
liver		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA, HEPATOCELLULAR	0 [45]	1 [40]	0 [41]	1 [41]	0.299 .	0.470 .	. .	0.476 .
	SARCOMA, HISTIOCYTIC	0 [45]	0 [40]	0 [41]	1 [41]	0.246 .	. .	. .	0.476 .
lung		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOCARCINOMA	1 [45]	0 [40]	0 [41]	0 [41]	1.000 .	1.000 .	1.000 .	1.000 .
	CARCINOMA, SEBACEOUS CELL	0 [45]	0 [40]	0 [41]	1 [41]	0.246 .	. .	. .	0.476 .
	LIPOSARCOMA	0 [45]	0 [40]	1 [41]	0 [41]	0.491 .	. .	0.477 .	. .
	OSTEOSARCOMA	0 [45]	0 [40]	0 [41]	1 [41]	0.246 .	. .	. .	0.482 .
	PHEOCHROMOCYTOMA	0 [45]	0 [40]	0 [41]	1 [41]	0.246 .	. .	. .	0.476 .
	SARCOMA, HISTIOCYTIC	0 [45]	0 [40]	0 [41]	1 [41]	0.246 .	. .	. .	0.476 .

**Table 3B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Rats (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H	
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65					
lymph node, ing	LYMPHOMA	(65)	(65)	(65)	(65)	.	.	.	.	
		0	1	0	0	0.731	0.470	.	.	
		[45]	[40]	[41]	[41]	.	.	.	.	
		SARCOMA, HISTIOCYTIC	0	0	0	1	0.246	.	.	0.476
		[45]	[40]	[41]	[41]	.	.	.	.	
lymph node, med	SARCOMA, HISTIOCYTIC	(65)	(65)	(65)	(65)	.	.	.	.	
		1	0	0	0	1.000	1.000	1.000	1.000	
		[45]	[40]	[41]	[41]	.	.	.	.	
lymph node, mes	HEMANGIOSARCOMA	(65)	(65)	(65)	(65)	.	.	.	.	
		1	0	0	1	0.432	1.000	1.000	0.729	
		[45]	[40]	[41]	[41]	.	.	.	.	
		OSTEOSARCOMA	0	0	0	1	0.246	.	.	0.482
		[45]	[40]	[41]	[41]	.	.	.	.	
mammary gland	ADENOCARCINOMA	(65)	(65)	(65)	(65)	.	.	.	.	
		19	21	24	19	0.583	0.268	0.166	0.521	
			[52]	[48]	[50]	[50]	.	.	.	.
	ADENOMA	1	1	0	1	0.516	0.723	1.000	0.723	
			[46]	[40]	[41]	[41]	.	.	.	.
	CARCINOSARCOMA	0	1	0	0	0.731	0.470	.	.	
		[45]	[40]	[41]	[41]	.	.	.	.	
FIBROADENOMA	27	23	24	26	0.318	0.568	0.532	0.446		
		[53]	[45]	[46]	[47]	.	.	.	.	
multicentric ne	LYMPHOMA	(65)	(65)	(65)	(65)	.	.	.	.	
		0	1	0	1	0.299	0.470	.	0.476	
		[45]	[40]	[41]	[41]	.	.	.	.	
		SARCOMA, HISTIOCYTIC	1	0	0	2	0.150	1.000	1.000	0.455
		[45]	[40]	[41]	[41]	.	.	.	.	
nose, level c	ADENOCARCINOMA	(65)	(65)	(65)	(65)	.	.	.	.	
		1	0	0	0	1.000	1.000	1.000	1.000	
		[45]	[40]	[41]	[41]	.	.	.	.	
nose, level d	OSTEOSARCOMA	(65)	(65)	(65)	(65)	.	.	.	.	
		0	0	0	1	0.246	.	.	0.482	
		[45]	[40]	[41]	[41]	.	.	.	.	
pancreas	ADENOMA, ACINAR CELL	(65)	(65)	(65)	(65)	.	.	.	.	
		0	0	0	1	0.246	.	.	0.476	

**Table 3B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Rats (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 mg				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
		[45]	[40]	[41]	[41]	.	.	.	.
	ADENOMA, ISLET CELL	4	1	2	2	0.629	0.960	0.876	0.876
		[45]	[40]	[41]	[41]	.	.	.	.
	CARCINOMA, ISLET CELL	0	0	0	1	0.246	.	.	0.476
		[45]	[40]	[41]	[41]	.	.	.	.
parathyroid gla		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA	0	1	0	1	0.299	0.470	.	0.476
		[45]	[40]	[41]	[41]	.	.	.	.
pituitary gland		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA, PARS DISTALIS	52	55	55	50	0.645	0.092	0.049	0.460
		[62]	[59]	[58]	[58]	.	.	.	.
	CARCINOMA, PARS DISTALIS	4	1	2	1	0.830	0.960	0.870	0.963
		[46]	[40]	[41]	[41]	.	.	.	.
skeletal muscle		(65)	(65)	(65)	(65)	.	.	.	.
	OSTEOSARCOMA	0	1	0	0	0.731	0.470	.	.
		[45]	[40]	[41]	[41]	.	.	.	.
skin		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA, BASAL CELL	0	0	0	1	0.246	.	.	0.482
		[45]	[40]	[41]	[41]	.	.	.	.
	ADENOMA, SEBACEOUS CELL	0	0	1	0	0.491	.	0.477	.
		[45]	[40]	[41]	[41]	.	.	.	.
	CARCINOMA, SEBACEOUS CELL	0	0	0	1	0.246	.	.	0.476
		[45]	[40]	[41]	[41]	.	.	.	.
	LYMPHOMA	0	1	0	0	0.731	0.470	.	.
		[45]	[40]	[41]	[41]	.	.	.	.
skin, subcutis		(65)	(65)	(65)	(65)	.	.	.	.
	FIBROSARCOMA	1	0	1	1	0.381	1.000	0.729	0.723
		[45]	[40]	[41]	[41]	.	.	.	.
	LIPOMA	1	1	0	0	0.929	0.722	1.000	1.000
		[45]	[40]	[41]	[41]	.	.	.	.
	OSTEOSARCOMA	0	0	0	2	0.059	.	.	0.230
		[45]	[40]	[41]	[41]	.	.	.	.
	SARCOMA, HISTIOCYTIC	1	0	0	2	0.150	1.000	1.000	0.455
		[45]	[40]	[41]	[41]	.	.	.	.
small intestine		(65)	(65)	(65)	(65)	.	.	.	.
	LEIOMYOMA	0	0	0	1	0.246	.	.	0.476
		[45]	[40]	[41]	[41]	.	.	.	.

**Table 3B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Rats (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
thymus	LEIOMYOSARCOMA	0 [45]	0 [40]	1 [41]	0 [41]	0.491 .	.	0.477 .	.
	LYMPHOMA	(65) [45]	(65) [40]	(65) [41]	(65) [41]	. .	.	. .	. 0.476
	THYMOMA	0 [45]	0 [40]	0 [41]	1 [41]	0.246 .	.	. .	0.482 .
thyroid gland	ADENOMA, C-CELL	(65) [47]	(65) [40]	(65) [42]	(65) [42]	. .	. .	. .	. 0.518
	ADENOMA, FOLLICULAR CELL	9 [45]	5 [40]	6 [41]	9 [41]	0.247 .	0.881 .	0.814 .	1.000 .
	CARCINOMA, C-CELL	1 [45]	0 [40]	0 [41]	0 [41]	1.000 .	1.000 .	1.000 .	1.000 .
	CARCINOMA, FOLLICULAR CELL	1 [46]	0 [40]	0 [41]	0 [41]	1.000 .	1.000 .	1.000 .	1.000 .
	CARCINOMA, FOLLICULAR CELL	0 [45]	1 [40]	2 [41]	1 [41]	0.310 .	0.470 .	0.224 .	0.476 .
urinary bladder	GRANULAR CELL TUMOR	(65) [45]	(65) [40]	(65) [41]	(65) [41]	. .	. .	. .	. .
		0 [45]	1 [40]	0 [41]	0 [41]	0.731 .	0.470 .	. .	. .
uterus with cer	ADENOCARCINOMA	(65) [45]	(65) [40]	(65) [41]	(65) [41]	. .	. .	. .	. 0.482
	FIBROSARCOMA	0 [45]	0 [40]	0 [41]	1 [41]	0.246 .	.	. .	0.482 .
	GRANULAR CELL TUMOR	1 [45]	0 [40]	2 [41]	1 [41]	0.358 .	1.000 .	0.465 .	0.729 .
	POLYP, ENDOMETRIAL STROMAL	5 [45]	6 [40]	6 [43]	1 [41]	0.968 .	0.416 .	0.467 .	0.981 .
	SARCOMA, ENDOMETRIAL STROMAL	1 [45]	0 [40]	0 [41]	0 [41]	1.000 .	1.000 .	1.000 .	1.000 .
	SCHWANNOMA	1 [45]	0 [40]	0 [41]	0 [41]	1.000 .	1.000 .	1.000 .	1.000 .
vagina	GRANULAR CELL TUMOR	(65) [45]	(65) [40]	(65) [41]	(65) [41]	. .	. .	. .	. 0.856
	SARCOMA, STROMAL	2 [45]	1 [40]	1 [41]	1 [41]	0.660 .	0.851 .	0.861 .	0.856 .
	SCHWANNOMA	0 [45]	0 [40]	1 [41]	0 [41]	0.491 .	.	0.477 .	. .
		1 [45]	0 [40]	0 [41]	0 [41]	1.000 .	1.000 .	1.000 .	1.000 .

**Table 3B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Rats (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	0 mg	150 mg	500 mg	1500 mg	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Cont N=65	Low N=65	Med N=65	High N=65				
		[45]	[40]	[41]	[41]	.	.	.	.
zymbal's gland		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, SEBACEOUS CELL	1	0	1	0	0.742	1.000	0.729	1.000
		[45]	[40]	[41]	[41]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

**Table 4A: Intercurrent Mortality Rate  
Male Mice**

Week	CONTROL		150mg		500mg		1500mg	
	NO. OF DEATH	PERCENT						
0-52	7	10.8%	4	6.2%	8	12.3%	8	12.3%
53-78	9	24.6%	13	26.2%	14	33.59%	15	36.4%
79-92	14	46.2%	15	49.2%	14	55.4%	12	53.9%
93-103	14	67.7%	9	63.1%	10	70.8%	9	67.7%
Term. Sac.	21	100.0%	24	100.0%	19	100.0%	21	100.0%

**Table 4B: Intercurrent Mortality Rate  
Female Mice**

Week	CONTROL		1.0mg		3.5mg		12.5mg	
	NO. OF DEATH	PERCENT						
0-52	12	18.5%	8	12.3%	4	6.2%	8	12.3%
53-78	15	41.5%	15	35.4%	16	30.8%	16	36.9%
79-92	13	61.5%	13	55.4%	14	52.3%	11	53.9%
93-97	5	69.2%	4	61.5%	7	63.1%	4	60.0%
Term. Sac.	20	100.0%	25	100.0%	24	100.0%	26	100.0%

**Table 5A: Intercurrent Mortality Comparison  
Male Mice**

Test	P-Value (across four groups)	P-Value (vehicle_contr ol1 vs low)	P-Value (vehicle_con trol1 vs medium)	P-Value (vehicle_contro l1 vs high)
Dose Response	0.6076	0.8425	0.5129	0.7020
Homogeneity	0.6967	0.7097	0.4905	0.5703

**Table 5B: Intercurrent Mortality Comparison  
Female Mice**

Test	P-Value (across four groups)	P-Value (vehicle_contr ol1 vs low)	P-Value (vehicle_con trol1 vs medium)	P-Value (vehicle_contro l1 vs high)
Dose Response	0.5471	0.4717	0.3851	0.3968
Homogeneity	0.5432	0.4182	0.1936	0.2383

**Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Male Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
BONE_MARROW_FEM		(65)	(65)	(65)	(65)	.	.	.	.
	HEMANGIOMA+HEMANGIOSARCOMA	1 [44]	0 [43]	1 [39]	1 [40]	0.365	1.000	0.722	0.729
KIDNEYS		(65)	(65)	(65)	(65)	.	.	.	.
	TUBULAR_CELL_ADENOMA+CARCINOMA	1 [44]	0 [43]	1 [39]	0 [40]	0.727	1.000	0.722	1.000
LIVER		(65)	(65)	(65)	(65)	.	.	.	.
	HEPA_ADENOMA+CARCINOMA	11 [45]	18 [48]	15 [42]	9 [41]	0.829	0.128	0.181	0.701
LUNG		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA+CARCINOMA	22 [50]	17 [47]	22 [44]	19 [45]	0.448	0.840	0.354	0.649
LYMPH_NODE_MESE		(65)	(65)	(65)	(65)	.	.	.	.
	HEMANGIOMA+HEMANGIOSARCOMA	1 [44]	1 [44]	1 [39]	1 [40]	0.482	0.753	0.722	0.729
MULTICENTRIC_NE		(65)	(65)	(65)	(65)	.	.	.	.
	HEMANGIOMA+HEMANGIOSARCOMA	6 [45]	7 [45]	9 [42]	2 [41]	0.933	0.500	0.238	0.961
PANCREAS		(65)	(65)	(65)	(65)	.	.	.	.
	ISLET_CELL_ADENOMA+CARCINOMA	1 [44]	0 [43]	0 [39]	1 [41]	0.432	1.000	1.000	0.735
SPLEEN		(65)	(65)	(65)	(65)	.	.	.	.
	HEMANGIOMA+HEMANGIOSARCOMA	1 [44]	5 [44]	1 [39]	0 [40]	0.952	0.101	0.722	1.000
adrenal glands		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA, CORTICAL	0 [44]	0 [43]	1 [40]	0 [40]	0.479	.	0.476	.
	ADENOMA, SUBCAPSULAR CELL	0 [44]	5 [44]	2 [40]	2 [41]	0.474	0.028	0.224	0.230
	LEUKEMIA, GRANULOCYTIC	2 [45]	0 [43]	0 [39]	0 [40]	1.000	1.000	1.000	1.000
	LYMPHOMA	8 [47]	5 [46]	8 [45]	5 [43]	0.669	0.876	0.570	0.848
	PHEOCHROMOCYTOMA	0	2	0	0	0.792	0.247	.	.

**Table 6A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
		[44]	[44]	[39]	[40]	.	.	.	.
aorta		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOL	1	0	0	0	1.000	1.000	1.000	1.000
		[44]	[43]	[39]	[40]	.	.	.	.
	LYMPHOMA	8	4	7	7	0.354	0.925	0.664	0.647
		[48]	[45]	[45]	[44]	.	.	.	.
bone		(65)	(65)	(65)	(65)	.	.	.	.
	OSTEOMA	0	0	0	1	0.246	.	.	0.482
		[44]	[43]	[39]	[41]	.	.	.	.
	OSTEOSARCOMA	0	1	0	0	0.737	0.500	.	.
		[44]	[44]	[39]	[40]	.	.	.	.
bone marrow, fe		(65)	(65)	(65)	(65)	.	.	.	.
	HEMANGIOMA	1	0	1	0	0.727	1.000	0.722	1.000
		[44]	[43]	[39]	[40]	.	.	.	.
	HEMANGIOSARCOMA	0	0	0	1	0.241	.	.	0.476
		[44]	[43]	[39]	[40]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	2	0	0	0	1.000	1.000	1.000	1.000
bone marrow, fe	LEUKEMIA, GRANULOCYTIC	[45]	[43]	[39]	[40]	.	.	.	.
	LYMPHOMA	13	6	12	6	0.851	0.972	0.611	0.965
		[49]	[46]	[46]	[44]	.	.	.	.
bone marrow, st		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	2	0	0	0	1.000	1.000	1.000	1.000
		[45]	[43]	[39]	[40]	.	.	.	.
	LYMPHOMA	13	6	12	9	0.561	0.972	0.611	0.839
		[49]	[46]	[46]	[45]	.	.	.	.
bone, femur		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[44]	[43]	[39]	[40]	.	.	.	.
	LYMPHOMA	6	5	9	3	0.786	0.726	0.256	0.892
		[47]	[46]	[45]	[42]	.	.	.	.
	OSTEOMA	0	0	0	1	0.241	.	.	0.476
		[44]	[43]	[39]	[40]	.	.	.	.
bone, sternum		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOL	0	1	0	1	0.301	0.500	.	0.482
		[44]	[44]	[39]	[41]	.	.	.	.

**Table 6A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
	LEUKEMIA, GRANULOCYTIC	1 [44]	0 [43]	0 [39]	0 [40]	1.000 .	1.000 .	1.000 .	1.000 .
	LYMPHOMA	11 [49]	6 [46]	12 [45]	9 [44]	0.408 .	0.929 .	0.407 .	0.686 .
brain		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOL	0 [44]	0 [43]	0 [39]	1 [40]	0.241 .	.	.	0.476 .
	LYMPHOMA	6 [47]	4 [45]	5 [42]	2 [42]	0.883 .	0.824 .	0.670 .	0.958 .
cavity, abdomin		(65)	(65)	(65)	(65)	.	.	.	.
	LYMPHOMA	2 [45]	0 [43]	1 [40]	1 [41]	0.540 .	1.000 .	0.856 .	0.861 .
	MESOTHELIOMA	1 [44]	0 [43]	0 [39]	0 [40]	1.000 .	1.000 .	1.000 .	1.000 .
	SARCOMA, UNDIFFERENTIATED	0 [44]	1 [44]	0 [39]	0 [40]	0.737 .	0.500 .	.	.
cavity, thoraci		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOL	0 [44]	0 [43]	0 [39]	1 [41]	0.246 .	.	.	0.482 .
	MESOTHELIOMA	1 [44]	0 [43]	0 [39]	0 [40]	1.000 .	1.000 .	1.000 .	1.000 .
	SARCOMA, UNDIFFERENTIATED	0 [44]	1 [44]	0 [39]	0 [40]	0.737 .	0.500 .	.	.
coagulating gla		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA	1 [44]	0 [43]	0 [39]	0 [40]	1.000 .	1.000 .	1.000 .	1.000 .
epididymides		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA, INTERSTITIAL CELL	0 [44]	0 [43]	0 [39]	1 [40]	0.241 .	.	.	0.476 .
	LEUKEMIA, GRANULOCYTIC	2 [45]	0 [43]	0 [39]	0 [40]	1.000 .	1.000 .	1.000 .	1.000 .
	LYMPHOMA	10 [48]	6 [46]	11 [44]	8 [44]	0.475 .	0.900 .	0.410 .	0.719 .
	SARCOMA, UNDIFFERENTIATED	0 [44]	1 [44]	0 [39]	0 [40]	0.737 .	0.500 .	.	.
	SCHWANNOMA	0 [44]	1 [43]	0 [39]	0 [40]	0.735 .	0.494 .	.	.

**Table 6A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 mg				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
esophagus		(65)	(65)	(65)	(65)	.	.	.	.
	LYMPHOMA	5 [46]	3 [45]	4 [42]	2 [41]	0.797	0.860	0.710	0.925
eyes		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOL	0 [44]	1 [44]	0 [39]	0 [40]	0.737	0.500	.	.
	LEUKEMIA, GRANULOCYTIC	2 [45]	0 [43]	0 [39]	0 [40]	1.000	1.000	1.000	1.000
	LYMPHOMA	8 [47]	4 [45]	8 [44]	3 [42]	0.856	0.930	0.551	0.961
eyes, optic ner		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1 [44]	0 [43]	0 [39]	0 [40]	1.000	1.000	1.000	1.000
	LYMPHOMA	1 [45]	1 [44]	3 [42]	0 [40]	0.774	0.747	0.282	1.000
gallbladder		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA	1 [44]	1 [43]	1 [39]	0 [40]	0.809	0.747	0.722	1.000
	HEMANGIOSARCOMA	1 [44]	0 [43]	0 [39]	0 [40]	1.000	1.000	1.000	1.000
	LEUKEMIA, GRANULOCYTIC	2 [45]	0 [43]	0 [39]	0 [40]	1.000	1.000	1.000	1.000
	LYMPHOMA	11 [49]	4 [46]	8 [44]	6 [44]	0.684	0.985	0.778	0.915
galt		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1 [44]	0 [43]	0 [39]	0 [40]	1.000	1.000	1.000	1.000
	LYMPHOMA	12 [49]	4 [45]	7 [43]	5 [44]	0.851	0.990	0.891	0.973
harderian gland		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA	6 [45]	2 [43]	1 [39]	1 [41]	0.958	0.966	0.990	0.992
heart		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOL	1 [44]	1 [44]	0 [39]	1 [40]	0.513	0.753	1.000	0.729

**Table 6A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Male Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
	LEUKEMIA, GRANULOCYTIC	1 [44]	0 [43]	0 [39]	0 [40]	1.000 .	1.000 .	1.000 .	1.000 .
	LYMPHOMA	10 [49]	5 [46]	10 [45]	9 [45]	0.316 .	0.942 .	0.514 .	0.619 .
joint, tibiofem		(65)	(65)	(65)	(65)	.	.	.	.
	LYMPHOMA	3 [45]	4 [46]	4 [42]	2 [42]	0.715 .	0.512 .	0.461 .	0.798 .
kidneys		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA, RENAL TUBULE	1 [44]	1 [43]	0 [39]	1 [40]	0.515 .	0.747 .	1.000 .	0.729 .
	ADENOMA, TUBULAR CELL	0 [44]	0 [43]	1 [39]	0 [40]	0.476 .	.	0.470 .	.
	CARCINOMA, BRONCHIOLAR ALVEOL	0 [44]	1 [44]	0 [39]	1 [40]	0.296 .	0.500 .	.	0.476 .
	CARCINOMA, TUBULAR CELL	1 [44]	0 [43]	0 [39]	0 [40]	1.000 .	1.000 .	1.000 .	1.000 .
	LEUKEMIA, GRANULOCYTIC	2 [45]	0 [43]	0 [39]	0 [40]	1.000 .	1.000 .	1.000 .	1.000 .
	LYMPHOMA	15 [49]	7 [46]	12 [45]	10 [45]	0.611 .	0.979 .	0.742 .	0.876 .
	SARCOMA, HISTIOCYTIC	0 [44]	1 [43]	0 [39]	0 [40]	0.735 .	0.494 .	.	.
kidneys	SARCOMA, HISTIOCYTIC	[44]	[43]	[39]	[40]	.	.	.	.
lacrimal glands		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	2 [45]	0 [43]	0 [39]	0 [40]	1.000 .	1.000 .	1.000 .	1.000 .
	LYMPHOMA	12 [49]	6 [46]	12 [45]	5 [42]	0.865 .	0.955 .	0.497 .	0.966 .
large intestine		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1 [44]	0 [43]	0 [39]	0 [40]	1.000 .	1.000 .	1.000 .	1.000 .
	LYMPHOMA	2 [44]	3 [45]	3 [41]	0 [40]	0.925 .	0.511 .	0.466 .	1.000 .
		3 [45]	4 [45]	6 [42]	3 [41]	0.525 .	0.500 .	0.208 .	0.616 .
		5 [46]	3 [45]	6 [43]	1 [40]	0.899 .	0.860 .	0.452 .	0.980 .

**Table 6A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 mg				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H	
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65					
larynx		(65)	(65)	(65)	(65)	.	.	.	.	
	CARCINOMA, BRONCHIOLAR ALVEOL	1 [44]	0 [43]	0 [39]	0 [40]	1.000	1.000	1.000	1.000	
	LEUKEMIA, GRANULOCYTTIC	2 [45]	0 [43]	0 [39]	0 [40]	1.000	1.000	1.000	1.000	
	LYMPHOMA	7 [46]	5 [46]	5 [42]	3 [42]	0.857	0.823	0.776	0.939	
liver		(65)	(65)	(65)	(65)	.	.	.	.	
	ADENOMA, HEPATOCELLULAR	6 [45]	15 [48]	10 [41]	7 [41]	0.693	0.034	0.150	0.427	
	CARCINOMA, BRONCHIOLAR ALVEOL	1 [44]	1 [44]	0 [39]	0 [40]	0.932	0.753	1.000	1.000	
	CARCINOMA, HEPATOCELLULAR	6 [44]	3 [43]	5 [41]	2 [40]	0.855	0.916	0.697	0.961	
	FIBROSARCOMA	1 [44]	0 [43]	0 [39]	1 [41]	0.432	1.000	1.000	0.735	
	HEMANGIOMA	1 [44]	0 [43]	1 [39]	0 [40]	0.727	1.000	0.722	1.000	
	HEMANGIOSARCOMA	3 [45]	4 [44]	5 [42]	1 [40]	0.855	0.487	0.318	0.926	
	ITO CELL TUMOR	0 [44]	0 [43]	1 [39]	0 [40]	0.476	.	0.470	.	
	LEUKEMIA, GRANULOCYTTIC	2 [45]	0 [43]	0 [39]	0 [40]	1.000	1.000	1.000	1.000	
	LYMPHOMA	14 [49]	6 [46]	12 [46]	9 [45]	0.622	0.984	0.692	0.886	
	SARCOMA, HISTIOCYTTIC	0 [44]	1 [43]	1 [40]	0 [40]	0.603	0.494	0.476	.	
	SARCOMA, UNDIFFERENTIATED	0 [44]	1 [44]	1 [40]	0 [40]	0.602	0.500	0.476	.	
	lung		(65)	(65)	(65)	(65)	.	.	.	.
		ADENOMA, BRONCHIOLAR ALVEOLAR	14 [48]	17 [47]	16 [43]	12 [42]	0.657	0.306	0.277	0.615
CARCINOMA, BRONCHIOLAR ALVEOL		10 [47]	4 [44]	6 [40]	9 [43]	0.252	0.973	0.849	0.616	
FIBROSARCOMA		0 [44]	0 [43]	0 [39]	1 [41]	0.246	.	.	0.482	
LEUKEMIA, GRANULOCYTTIC		1 [44]	0 [43]	0 [39]	0 [40]	1.000	1.000	1.000	1.000	
LYMPHOMA		14 [44]	6 [43]	15 [39]	8 [40]	0.712	0.984	0.419	0.923	

**Table 6A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
	PAPILLOMA	[49] 0	[46] 0	[46] 0	[44] 1	. 0.241	. .	. .	. 0.476
		[44]	[43]	[39]	[40]	.	.	.	.
lymph node, hep	Lymphoma	(65) 4	(65) 1	(65) 2	(65) 1	. 0.821	. 0.971	. 0.876	. 0.965
		[44]	[43]	[40]	[40]	.	.	.	.
lymph node, ili	Lymphoma	(65) 0	(65) 1	(65) 0	(65) 1	. 0.297	. 0.494	. .	. 0.476
		[44]	[43]	[39]	[40]	.	.	.	.
lymph node, ing	Lymphoma	(65) 0	(65) 0	(65) 1	(65) 0	. 0.479	. .	. 0.476	. .
		[44]	[43]	[40]	[40]	.	.	.	.
lymph node, man	LEUKEMIA, GRANULOCYTIC	(65) 2	(65) 0	(65) 0	(65) 0	. 1.000	. 1.000	. 1.000	. 1.000
		[45]	[43]	[39]	[40]	.	.	.	.
	Lymphoma	(65) 16	(65) 6	(65) 13	(65) 8	. 0.824	. 0.995	. 0.754	. 0.972
		[49]	[46]	[46]	[45]	.	.	.	.
lymph node, med	CARCINOMA, BRONCHIOLAR ALVEOL	(65) 1	(65) 0	(65) 0	(65) 1	. 0.432	. 1.000	. 1.000	. 0.735
		[44]	[43]	[39]	[41]	.	.	.	.
	Lymphoma	(65) 1	(65) 0	(65) 3	(65) 1	. 0.390	. 1.000	. 0.282	. 0.735
		[44]	[43]	[41]	[41]	.	.	.	.
lymph node, mes	CARCINOMA, BRONCHIOLAR ALVEOL	(65) 0	(65) 0	(65) 0	(65) 1	. 0.241	. .	. .	. 0.476
		[44]	[43]	[39]	[40]	.	.	.	.
	HEMANGIOMA	(65) 0	(65) 1	(65) 1	(65) 0	. 0.600	. 0.500	. 0.470	. .
		[44]	[44]	[39]	[40]	.	.	.	.
	HEMANGIOSARCOMA	(65) 1	(65) 0	(65) 0	(65) 1	. 0.425	. 1.000	. 1.000	. 0.729
		[44]	[43]	[39]	[40]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	(65) 2	(65) 0	(65) 0	(65) 0	. 1.000	. 1.000	. 1.000	. 1.000
		[45]	[43]	[39]	[40]	.	.	.	.
	Lymphoma	(65) 16	(65) 5	(65) 15	(65) 9	. 0.701	. 0.998	. 0.616	. 0.948
		[49]	[46]	[47]	[45]	.	.	.	.
	SARCOMA, UNDIFFERENTIATED	(65) 0	(65) 1	(65) 0	(65) 0	. 0.737	. 0.500	. .	. .
		[44]	[44]	[39]	[40]	.	.	.	.

**Table 6A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 mg				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	1500 mg High N=65				
lymph node, ren		(65)	(65)	(65)	(65)	.	.	.	.
	LYMPHOMA	2 [44]	1 [43]	1 [40]	2 [41]	0.381 .	0.875 .	0.861 .	0.665 .
mammary gland		(65)	(65)	(65)	(65)	.	.	.	.
	LYMPHOMA	0 [44]	0 [43]	1 [40]	0 [40]	0.479 .	.	0.476 .	.
mediastinum		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOL	0 [44]	1 [44]	0 [39]	0 [40]	0.737 .	0.500 .	.	.
multicentric ne		(65)	(65)	(65)	(65)	.	.	.	.
	HEMANGIOMA	3 [44]	2 [44]	3 [39]	0 [40]	0.938 .	0.820 .	0.603 .	1.000 .
	HEMANGIOSARCOMA	3 [45]	5 [44]	6 [42]	2 [41]	0.758 .	0.344 .	0.208 .	0.790 .
	LEUKEMIA, GRANULOCYTIC	2 [45]	0 [43]	0 [39]	0 [40]	1.000 .	1.000 .	1.000 .	1.000 .
	LYMPHOMA	16 [49]	7 [46]	17 [47]	13 [46]	0.386 .	0.988 .	0.441 .	0.754 .
	SARCOMA, HISTIOCYTIC	0 [44]	1 [43]	2 [40]	0 [40]	0.620 .	0.494 .	0.224 .	.
nerve, sciatic		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
nerve, sciatic	LEUKEMIA, GRANULOCYTIC	[44]	[43]	[39]	[40]	.	.	.	.
	LYMPHOMA	7 [47]	2 [44]	5 [42]	2 [41]	0.859 .	0.981 .	0.764 .	0.975 .
nose, level a		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1 [44]	0 [43]	0 [39]	0 [40]	1.000 .	1.000 .	1.000 .	1.000 .
	LYMPHOMA	6 [47]	4 [45]	5 [42]	3 [42]	0.762 .	0.824 .	0.670 .	0.892 .
nose, level b		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	2 [45]	0 [43]	0 [39]	0 [40]	1.000 .	1.000 .	1.000 .	1.000 .
	LYMPHOMA	9	4	7	4	0.815	0.958	0.735	0.950

**Table 6A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 mg				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
		[47]	[45]	[43]	[43]	.	.	.	.
nose, level c		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	2	0	0	0	1.000	1.000	1.000	1.000
		[45]	[43]	[39]	[40]	.	.	.	.
	LYMPHOMA	9	4	7	6	0.565	0.954	0.719	0.828
		[48]	[45]	[43]	[44]	.	.	.	.
nose, level d		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	2	0	0	0	1.000	1.000	1.000	1.000
		[45]	[43]	[39]	[40]	.	.	.	.
	LYMPHOMA	8	5	8	4	0.785	0.867	0.532	0.912
		[48]	[46]	[44]	[43]	.	.	.	.
pancreas		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA, ISLET CELL	1	0	0	0	1.000	1.000	1.000	1.000
		[44]	[43]	[39]	[40]	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOL	0	0	0	1	0.241	.	.	0.476
		[44]	[43]	[39]	[40]	.	.	.	.
	CARCINOMA, ISLET CELL	0	0	0	1	0.246	.	.	0.482
		[44]	[43]	[39]	[41]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[44]	[43]	[39]	[40]	.	.	.	.
	LYMPHOMA	13	6	11	8	0.653	0.972	0.701	0.887
		[49]	[46]	[46]	[44]	.	.	.	.
	MESOTHELIOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[44]	[43]	[39]	[40]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.476	.	0.470	.
		[44]	[43]	[39]	[40]	.	.	.	.
parathyroid gla		(65)	(65)	(65)	(65)	.	.	.	.
	LYMPHOMA	2	1	0	0	0.981	0.871	1.000	1.000
		[45]	[43]	[39]	[40]	.	.	.	.
penis		(65)	(65)	(65)	(65)	.	.	.	.
	LYMPHOMA	2	0	0	0	1.000	1.000	1.000	1.000
		[44]	[43]	[39]	[40]	.	.	.	.
pituitary gland		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA, PARS DISTALIS	0	0	2	0	0.479	.	0.218	.
		[44]	[43]	[39]	[40]	.	.	.	.
	LYMPHOMA	5	2	3	2	0.767	0.938	0.836	0.930

**Table 6A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
	OSTEOSARCOMA	[46] 0	[44] 1	[42] 0	[42] 0	.	.	.	.
		[44]	[44]	[39]	[40]	.	.	.	.
preputial gland		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	2	0	0	0	1.000	1.000	1.000	1.000
		[45]	[43]	[39]	[40]	.	.	.	.
	LYMPHOMA	9	5	8	4	0.829	0.921	0.650	0.945
		[47]	[46]	[44]	[42]	.	.	.	.
prostate gland		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[44]	[43]	[39]	[40]	.	.	.	.
	LYMPHOMA	11	5	7	5	0.821	0.964	0.830	0.951
		[49]	[46]	[42]	[43]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	0	0.735	0.494	.	.
		[44]	[43]	[39]	[40]	.	.	.	.
salivary gland,		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[44]	[43]	[39]	[40]	.	.	.	.
	LYMPHOMA	13	6	8	5	0.914	0.972	0.887	0.982
		[44]	[45]	[42]	[42]	.	.	.	.
		4	1	3	1	0.793	0.969	0.733	0.961
		[49]	[46]	[44]	[43]	.	.	.	.
		7	4	5	3	0.826	0.895	0.776	0.939
		[46]	[44]	[41]	[40]	.	.	.	.
seminal vesicle		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	2	0	0	0	1.000	1.000	1.000	1.000
		[45]	[43]	[39]	[40]	.	.	.	.
	LYMPHOMA	11	6	9	7	0.628	0.929	0.686	0.843
		[49]	[46]	[44]	[43]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.476	.	0.470	.
		[44]	[43]	[39]	[40]	.	.	.	.
skeletal muscle		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOL	0	0	0	1	0.241	.	.	0.476
		[44]	[43]	[39]	[40]	.	.	.	.
	LYMPHOMA	4	3	3	2	0.720	0.774	0.733	0.864
		[46]	[45]	[41]	[40]	.	.	.	.

**Table 6A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 mg				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
skin	LYMPHOMA	(65)	(65)	(65)	(65)	.	.	.	.
		12	5	9	6	0.763	0.979	0.779	0.939
		[49]	[46]	[45]	[43]	.	.	.	.
skin, subcutis	FIBROSARCOMA	(65)	(65)	(65)	(65)	.	.	.	.
		1	0	1	2	0.155	1.000	0.722	0.473
	[44]	[43]	[39]	[41]	.	.	.	.	
	HEMANGIOSARCOMA	1	0	0	1	0.425	1.000	1.000	0.729
		[44]	[43]	[39]	[40]	.	.	.	.
	LYMPHOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[44]	[43]	[39]	[40]	.	.	.	.
MESOTHELIOMA	1	0	0	0	1.000	1.000	1.000	1.000	
	[44]	[43]	[39]	[40]	.	.	.	.	
SARCOMA, UNDIFFERENTIATED	0	1	0	0	0.737	0.500	.	.	
	[44]	[44]	[39]	[40]	.	.	.	.	
small intestine	ADENOCARCINOMA	(65)	(65)	(65)	(65)	.	.	.	.
		1	0	0	0	1.000	1.000	1.000	1.000
	[44]	[43]	[39]	[40]	.	.	.	.	
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[44]	[43]	[39]	[40]	.	.	.	.
	LYMPHOMA	1	4	5	3	0.352	0.187	0.096	0.291
		[44]	[45]	[43]	[42]	.	.	.	.
5		3	7	2	0.779	0.860	0.331	0.925	
[46]		[45]	[43]	[41]	.	.	.	.	
[47]	[45]	[42]	[43]	0.548	0.887	0.764	0.777		
[47]	[45]	[42]	[43]	.	.	.	.		
spinal cord, ce	LYMPHOMA	(65)	(65)	(65)	(65)	.	.	.	.
		2	2	0	1	0.738	0.692	1.000	0.861
spinal cord, ce	LYMPHOMA	[44]	[44]	[39]	[40]	.	.	.	.
spinal cord, lu	LYMPHOMA	(65)	(65)	(65)	(65)	.	.	.	.
		1	2	1	3	0.163	0.500	0.729	0.291
[44]	[44]	[40]	[42]	.	.	.	.		
spinal cord, th	LYMPHOMA	(65)	(65)	(65)	(65)	.	.	.	.
		0	1	1	0	0.602	0.500	0.476	.
[44]	[44]	[40]	[40]	.	.	.	.		

**Table 6A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg N=65	150 mg N=65	500 mg N=65	g N=65				
spleen		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOL	0	0	0	1	0.241	.	.	0.476
		[44]	[43]	[39]	[40]	.	.	.	.
	HEMANGIOMA	0	1	0	0	0.735	0.494	.	.
		[44]	[43]	[39]	[40]	.	.	.	.
	HEMANGIOSARCOMA	1	4	1	0	0.931	0.180	0.722	1.000
		[44]	[44]	[39]	[40]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	2	0	0	0	1.000	1.000	1.000	1.000
	[45]	[43]	[39]	[40]	.	.	.	.	
LYMPHOMA		16	7	16	12	0.458	0.988	0.529	0.805
		[49]	[46]	[47]	[45]	.	.	.	.
SARCOMA, HISTIOCYTIC		0	0	1	0	0.479	.	0.476	.
		[44]	[43]	[40]	[40]	.	.	.	.
stomach, glandu		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOL	0	0	0	1	0.241	.	.	0.476
		[44]	[43]	[39]	[40]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	2	0	0	0	1.000	1.000	1.000	1.000
		[45]	[43]	[39]	[40]	.	.	.	.
LYMPHOMA		10	6	9	3	0.949	0.908	0.638	0.988
		[47]	[46]	[44]	[42]	.	.	.	.
SARCOMA, HISTIOCYTIC		0	0	1	0	0.476	.	0.470	.
		[44]	[43]	[39]	[40]	.	.	.	.
stomach, nongla		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, SQUAMOUS CELL	1	0	0	0	1.000	1.000	1.000	1.000
		[44]	[43]	[39]	[40]	.	.	.	.
LYMPHOMA		4	3	3	0	0.975	0.783	0.754	1.000
		[45]	[45]	[42]	[40]	.	.	.	.
tail		(65)	(65)	(65)	(65)	.	.	.	.
	FIBROSARCOMA	0	0	0	1	0.241	.	.	0.476
		[44]	[43]	[39]	[40]	.	.	.	.
	HEMANGIOSARCOMA	0	1	0	0	0.735	0.494	.	.
	[44]	[43]	[39]	[40]	.	.	.	.	
testes		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA, INTERSTITIAL CELL	2	3	0	2	0.543	0.489	1.000	0.655
	[44]	[43]	[39]	[40]	.	.	.	.	

**Table 6A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
	ADENOMA, RETE TESTIS	0 [44]	0 [43]	1 [40]	1 [40]	0.172 .	.	0.476 .	0.476 .
	HEMANGIOMA	1 [44]	0 [43]	0 [39]	0 [40]	1.000 .	1.000 .	1.000 .	1.000 .
	LYMPHOMA	4 [46]	3 [45]	5 [42]	2 [41]	0.720 .	0.774 .	0.442 .	0.870 .
thymus		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOL	1 [44]	0 [43]	0 [39]	1 [41]	0.432 .	1.000 .	1.000 .	0.735 .
	LEUKEMIA, GRANULOCYTIC	1 [44]	0 [43]	0 [39]	0 [40]	1.000 .	1.000 .	1.000 .	1.000 .
	LYMPHOMA	13 [49]	6 [46]	14 [46]	12 [46]	0.268 .	0.972 .	0.423 .	0.611 .
thyroid gland		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA, FOLLICULAR CELL	0 [44]	1 [43]	1 [40]	1 [40]	0.274 .	0.494 .	0.476 .	0.476 .
	LYMPHOMA	9 [47]	3 [45]	5 [41]	4 [42]	0.767 .	0.984 .	0.882 .	0.945 .
tongue		(65)	(65)	(65)	(65)	.	.	.	.
	LYMPHOMA	4 [45]	3 [45]	0 [39]	2 [41]	0.757 .	0.783 .	1.000 .	0.876 .
tooth/teeth		(65)	(65)	(65)	(65)	.	.	.	.
	FIBRO-ODONTOMA, AMELOBLASTIC	0 [44]	0 [43]	0 [39]	1 [41]	0.246 .	.	.	0.482 .
trachea		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1 [44]	0 [43]	0 [39]	0 [40]	1.000 .	1.000 .	1.000 .	1.000 .
	LYMPHOMA	7 [47]	5 [46]	3 [41]	2 [41]	0.941 .	0.812 .	0.929 .	0.975 .
ureters		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	2 [45]	0 [43]	0 [39]	0 [40]	1.000 .	1.000 .	1.000 .	1.000 .
	LYMPHOMA	13 [49]	6 [46]	12 [45]	7 [44]	0.761 .	0.972 .	0.586 .	0.934 .

**Table 6A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Male Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
urinary bladder		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1 [44]	0 [43]	0 [39]	0 [40]	1.000	1.000	1.000	1.000
	Lymphoma	11 [49]	6 [46]	6 [43]	7 [43]	0.629	0.929	0.907	0.843
						.	.	.	.
zymbal's gland		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, SQUAMOUS CELL	0 [44]	1 [44]	0 [39]	0 [40]	0.737	0.500	.	.
	LEUKEMIA, GRANULOCYTIC	1 [44]	0 [43]	0 [39]	0 [40]	1.000	1.000	1.000	1.000
	Lymphoma	8 [47]	6 [46]	7 [43]	2 [41]	0.958	0.795	0.646	0.987

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

**Table 6B : Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
LIVER	HEPA_ADENOMA+CARCINOMA	(65)	(65)	(65)	(65)	.	.	.	.
		2	1	0	0	0.987	0.888	1.000	1.000
		[41]	[43]	[46]	[43]	.	.	.	.
LUNG	ADENOMA+CARCINOMA	(65)	(65)	(65)	(65)	.	.	.	.
		13	11	11	6	0.968	0.802	0.861	0.984
		[43]	[45]	[49]	[44]	.	.	.	.
	HEMANGIOMA+HEMANGIOSARCOMA	0	0	1	1	0.196	.	0.535	0.518
		[40]	[43]	[46]	[43]	.	.	.	.
LYMPH_NODE_MESE	HEMANGIOMA+HEMANGIOSARCOMA	(65)	(65)	(65)	(65)	.	.	.	.
		2	0	2	0	0.828	1.000	0.743	1.000
		[40]	[43]	[46]	[43]	.	.	.	.
MULTICENTRIC_NE	HEMANGIOMA+HEMANGIOSARCOMA	(65)	(65)	(65)	(65)	.	.	.	.
		7	4	6	9	0.180	0.917	0.808	0.493
		[41]	[43]	[47]	[46]	.	.	.	.
OVARIES	HEMANGIOMA+HEMANGIOSARCOMA	(65)	(65)	(65)	(65)	.	.	.	.
		2	1	0	0	0.988	0.893	1.000	1.000
		[40]	[43]	[46]	[43]	.	.	.	.
URINARY_BLADDER	HEMANGIOMA+HEMANGIOSARCOMA	(65)	(65)	(65)	(65)	.	.	.	.
		1	0	0	1	0.445	1.000	1.000	0.776
		[40]	[43]	[46]	[44]	.	.	.	.
UTERUS_WITH_CER	ENDOMETRIAL_STROMAL_POLYP+SARC	(65)	(65)	(65)	(65)	.	.	.	.
		6	10	5	8	0.467	0.266	0.790	0.441
		[42]	[46]	[46]	[45]	.	.	.	.
	LEIOMYOMA+LEIOMYOSARCOMA	2	4	5	2	0.709	0.385	0.279	0.735
		[40]	[44]	[46]	[45]	.	.	.	.
adipose tissue	LYMPHOMA	(65)	(65)	(65)	(65)	.	.	.	.
		1	0	2	0	0.702	1.000	0.553	1.000
		[40]	[43]	[46]	[43]	.	.	.	.
adrenal glands	ADENOMA, CORTICAL	(65)	(65)	(65)	(65)	.	.	.	.
		0	0	1	0	0.517	.	0.535	.
		[40]	[43]	[46]	[43]	.	.	.	.
	ADENOMA, SUBCAPSULAR CELL	0	0	2	1	0.208	.	0.283	0.518
		[40]	[43]	[46]	[43]	.	.	.	.

**Table 6B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
	LEUKEMIA, GRANULOCYTIC	0 [40]	0 [43]	0 [46]	1 [44]	0.254 .	. .	. .	0.524 .
	LYMPHOMA	9 [44]	10 [49]	10 [50]	13 [51]	0.239 .	0.605 .	0.623 .	0.370 .
	SARCOMA, HISTIOCYTIC	0 [40]	1 [43]	1 [47]	2 [44]	0.130 .	0.518 .	0.540 .	0.271 .
aorta		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0 [40]	0 [43]	0 [46]	1 [44]	0.254 .	. .	. .	0.524 .
	LYMPHOMA	14 [48]	9 [48]	8 [49]	10 [49]	0.712 .	0.925 .	0.961 .	0.892 .
bone		(65)	(65)	(65)	(65)	.	.	.	.
	OSTEOMA	0 [40]	0 [43]	0 [46]	2 [44]	0.064 .	. .	. .	0.271 .
bone marrow, fe		(65)	(65)	(65)	(65)	.	.	.	.
	HEMANGIOMA	0 [40]	0 [43]	0 [46]	1 [43]	0.250 .	. .	. .	0.518 .
	LEUKEMIA, GRANULOCYTIC	0 [40]	0 [43]	0 [46]	1 [44]	0.254 .	. .	. .	0.524 .
bone marrow, fe	LEUKEMIA, GRANULOCYTIC	[40]	[43]	[46]	[44]	.	.	.	.
	LYMPHOMA	8 [46]	11 [50]	11 [50]	11 [50]	0.365 .	0.380 .	0.380 .	0.380 .
	SARCOMA, HISTIOCYTIC	0 [40]	0 [43]	1 [46]	1 [43]	0.196 .	. .	0.535 .	0.518 .
bone marrow, st		(65)	(65)	(65)	(65)	.	.	.	.
	HEMANGIOMA	1 [40]	0 [43]	0 [46]	0 [43]	1.000 .	1.000 .	1.000 .	1.000 .
	LEUKEMIA, GRANULOCYTIC	0 [40]	0 [43]	0 [46]	1 [44]	0.254 .	. .	. .	0.524 .
	LYMPHOMA	10 [46]	11 [50]	13 [51]	10 [50]	0.611 .	0.586 .	0.424 .	0.678 .
	SARCOMA, HISTIOCYTIC	0 [40]	0 [43]	2 [46]	1 [43]	0.208 .	. .	0.283 .	0.518 .
bone, femur		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0 [40]	0 [43]	0 [46]	1 [44]	0.254 .	. .	. .	0.524 .
	LYMPHOMA	5 [40]	3 [43]	10 [46]	6 [44]	0.341 .	0.881 .	0.209 .	0.578 .

**Table 6B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
		[43]	[45]	[50]	[48]	.	.	.	.
	OSTEOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[41]	[43]	[46]	[43]	.	.	.	.
bone, maxilla		(65)	(65)	(65)	(65)	.	.	.	.
	OSTEOSARCOMA	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
bone, sternum		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
	LYMPHOMA	14	10	15	13	0.495	0.903	0.579	0.740
		[47]	[49]	[50]	[50]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	1	1	0.310	0.518	0.535	0.518
		[40]	[43]	[46]	[43]	.	.	.	.
brain		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
	LYMPHOMA	3	2	7	5	0.207	0.834	0.229	0.409
		[42]	[44]	[49]	[46]	.	.	.	.
cavity, abdomin		(65)	(65)	(65)	(65)	.	.	.	.
	LIPOSARCOMA	0	1	0	0	0.769	0.524	.	.
		[40]	[44]	[46]	[43]	.	.	.	.
	LYMPHOMA	3	2	0	1	0.854	0.841	1.000	0.945
		[42]	[45]	[46]	[43]	.	.	.	.
	MESOTHELIOMA	0	0	0	2	0.064	.	.	0.271
		[40]	[43]	[46]	[44]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	0	0.767	0.518	.	.
		[40]	[43]	[46]	[43]	.	.	.	.
cavity, thoraci		(65)	(65)	(65)	(65)	.	.	.	.
	LYMPHOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[41]	[43]	[46]	[43]	.	.	.	.
	MESOTHELIOMA	0	0	0	2	0.064	.	.	0.271
		[40]	[43]	[46]	[44]	.	.	.	.
	OSTEOSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[41]	[43]	[46]	[43]	.	.	.	.
clitoral glands		(65)	(65)	(65)	(65)	.	.	.	.
	HEMANGIOMA	0	0	0	1	0.254	.	.	0.524

**Table 6B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
	LYMPHOMA	[40] 5	[43] 5	[46] 12	[44] 7	. 0.337	. 0.688	. 0.111	. 0.462
clitoral glands	LYMPHOMA	[42]	[46]	[50]	[47]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	1	1	0.310	0.518	0.540	0.518
		[40]	[43]	[47]	[43]	.	.	.	.
esophagus		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
	LYMPHOMA	5	3	2	2	0.872	0.889	0.961	0.958
		[41]	[44]	[46]	[45]	.	.	.	.
eyes		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
	LYMPHOMA	5	2	6	8	0.095	0.949	0.578	0.367
		[43]	[44]	[48]	[49]	.	.	.	.
	SARCOMA, HISTIOCYTIC	1	0	1	0	0.771	1.000	0.792	1.000
		[40]	[43]	[47]	[43]	.	.	.	.
eyes, optic ner		(65)	(65)	(65)	(65)	.	.	.	.
	LYMPHOMA	3	3	2	1	0.877	0.684	0.853	0.945
		[42]	[44]	[47]	[43]	.	.	.	.
gallbladder		(65)	(65)	(65)	(65)	.	.	.	.
	LIPOSARCOMA	0	1	0	0	0.769	0.524	.	.
		[40]	[44]	[46]	[43]	.	.	.	.
	LYMPHOMA	11	8	10	10	0.517	0.871	0.745	0.745
		[46]	[48]	[49]	[49]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	1	1	0.310	0.518	0.540	0.518
		[40]	[43]	[47]	[43]	.	.	.	.
galt		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
	LYMPHOMA	6	7	6	5	0.710	0.534	0.666	0.764
		[45]	[47]	[48]	[47]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	0	1	0.250	.	.	0.518
		[40]	[43]	[46]	[43]	.	.	.	.

**Table 6B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
harderian gland		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA	0	1	0	0	0.767	0.518	.	.
		[40]	[43]	[46]	[43]	.	.	.	.
	LYMPHOMA	0	0	1	0	0.517	.	0.535	.
		[40]	[43]	[46]	[43]	.	.	.	.
head		(65)	(65)	(65)	(65)	.	.	.	.
	SARCOMA, UNDIFFERENTIATED	0	0	0	1	0.250	.	.	0.518
		[40]	[43]	[46]	[43]	.	.	.	.
heart		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOL	0	0	1	0	0.517	.	0.535	.
		[40]	[43]	[46]	[43]	.	.	.	.
	HEMANGIOSARCOMA	0	1	0	0	0.767	0.518	.	.
		[40]	[43]	[46]	[43]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
	LYMPHOMA	14	7	14	15	0.187	0.977	0.637	0.552
	[48]	[48]	[50]	[50]	.	.	.	.	
	MESOTHELIOMA	0	0	0	1	0.254	.	.	0.524
	[40]	[43]	[46]	[44]	.	.	.	.	
	SARCOMA, HISTIOCYTIC	0	2	0	2	0.202	0.265	.	0.271
	[40]	[43]	[46]	[44]	.	.	.	.	
joint, tibiofem		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
	LYMPHOMA	2	0	3	2	0.322	1.000	0.575	0.718
	[41]	[43]	[48]	[44]	.	.	.	.	
kidneys		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
	LIPOSARCOMA	0	1	0	0	0.769	0.524	.	.
		[40]	[44]	[46]	[43]	.	.	.	.
	LYMPHOMA	17	11	15	15	0.531	0.942	0.801	0.801
	[49]	[49]	[52]	[52]	.	.	.	.	
	MESOTHELIOMA	0	0	0	1	0.254	.	.	0.524
	[40]	[43]	[46]	[44]	.	.	.	.	
	SARCOMA, HISTIOCYTIC	1	4	1	2	0.570	0.211	0.792	0.536
	[40]	[44]	[47]	[44]	.	.	.	.	

**Table 6B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H	
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65					
lacrimal glands		(65)	(65)	(65)	(65)	.	.	.	.	
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524	
		[40]	[43]	[46]	[44]	.	.	.	.	
	LYMPHOMA	11	7	15	15	0.120	0.914	0.352	0.352	
		[46]	[47]	[51]	[51]	.	.	.	.	
SARCOMA, HISTIOCYTIC		0	0	0	1	0.250	.	.	0.518	
		[40]	[43]	[46]	[43]	.	.	.	.	
	large intestine		(65)	(65)	(65)	(65)	.	.	.	.
		LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
			[40]	[43]	[46]	[44]	.	.	.	.
LYMPHOMA		3	3	4	7	0.074	0.694	0.563	0.208	
		[45]	[47]	[47]	[47]	.	.	.	.	
SARCOMA, HISTIOCYTIC		4	3	3	4	0.443	0.811	0.819	0.682	
		[42]	[45]	[46]	[45]	.	.	.	.	
		5	3	5	5	0.405	0.875	0.711	0.673	
		[43]	[44]	[49]	[46]	.	.	.	.	
		0	0	0	1	0.250	.	.	0.518	
	[40]	[43]	[46]	[43]	.	.	.	.		
larynx		(65)	(65)	(65)	(65)	.	.	.	.	
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524	
		[40]	[43]	[46]	[44]	.	.	.	.	
	LYMPHOMA	5	4	5	5	0.491	0.770	0.699	0.686	
		[43]	[44]	[48]	[47]	.	.	.	.	
liver		(65)	(65)	(65)	(65)	.	.	.	.	
	ADENOMA, HEPATOCELLULAR	2	0	0	0	1.000	1.000	1.000	1.000	
		[41]	[43]	[46]	[43]	.	.	.	.	
	CARCINOMA, HEPATOCELLULAR	0	1	0	0	0.767	0.518	.	.	
		[40]	[43]	[46]	[43]	.	.	.	.	
	HEMANGIOSARCOMA	1	1	2	1	0.518	0.771	0.553	0.771	
		[40]	[43]	[46]	[43]	.	.	.	.	
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524	
		[40]	[43]	[46]	[44]	.	.	.	.	
	LYMPHOMA	16	12	13	16	0.382	0.867	0.827	0.636	
		[50]	[50]	[51]	[52]	.	.	.	.	
MESOTHELIOMA	0	0	0	1	0.254	.	.	0.524		
	[40]	[43]	[46]	[44]	.	.	.	.		
SARCOMA, HISTIOCYTIC	3	4	4	2	0.766	0.526	0.575	0.834		
	[42]	[44]	[48]	[44]	.	.	.	.		

**Table 6B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
lung		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOACANTHOMA	0	1	0	1	0.321	0.524	.	0.518
		[40]	[44]	[46]	[43]	.	.	.	.
	ADENOMA, BRONCHIOLAR ALVEOLAR	9	9	9	4	0.958	0.666	0.720	0.972
		[42]	[45]	[48]	[44]	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOL	4	3	2	2	0.799	0.821	0.928	0.915
lung	CARCINOMA, BRONCHIOLAR ALVEOL	[40]	[44]	[46]	[43]	.	.	.	.
	HEMANGIOMA	0	0	0	1	0.250	.	.	0.518
		[40]	[43]	[46]	[43]	.	.	.	.
	HEMANGIOSARCOMA	0	0	1	0	0.517	.	0.535	.
		[40]	[43]	[46]	[43]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
	LIPOSARCOMA	0	1	0	0	0.769	0.524	.	.
		[40]	[44]	[46]	[43]	.	.	.	.
	LYMPHOMA	18	13	17	17	0.473	0.915	0.738	0.738
		[49]	[50]	[52]	[52]	.	.	.	.
	MESOTHELIOMA	0	0	0	2	0.064	.	.	0.271
	[40]	[43]	[46]	[44]	.	.	.	.	
SARCOMA, ENDOMETRIAL STROMAL	1	0	0	0	1.000	1.000	1.000	1.000	
	[40]	[43]	[46]	[43]	.	.	.	.	
SARCOMA, HISTIOCYTIC	1	2	3	2	0.405	0.527	0.380	0.536	
	[40]	[43]	[48]	[44]	.	.	.	.	
lymph node, axi		(65)	(65)	(65)	(65)	.	.	.	.
	LIPOSARCOMA	0	1	0	0	0.769	0.524	.	.
		[40]	[44]	[46]	[43]	.	.	.	.
	LYMPHOMA	1	0	1	0	0.769	1.000	0.787	1.000
		[40]	[43]	[46]	[43]	.	.	.	.
lymph node, hep		(65)	(65)	(65)	(65)	.	.	.	.
	LIPOSARCOMA	0	1	0	0	0.769	0.524	.	.
		[40]	[44]	[46]	[43]	.	.	.	.
	LYMPHOMA	0	0	4	1	0.310	.	0.080	0.524
		[40]	[43]	[47]	[44]	.	.	.	.
lymph node, ili		(65)	(65)	(65)	(65)	.	.	.	.
	LYMPHOMA	3	2	2	2	0.635	0.834	0.853	0.834
		[42]	[44]	[47]	[44]	.	.	.	.
	SARCOMA, HISTIOCYTIC	1	2	0	0	0.948	0.527	1.000	1.000

**Table 6B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	1500 mg High N=65				
		[40]	[43]	[46]	[43]	.	.	.	.
lymph node, ing		(65)	(65)	(65)	(65)	.	.	.	.
	LYMPHOMA	0	0	1	1	0.200	.	0.535	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
lymph node, man		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
	LYMPHOMA	12	11	13	13	0.409	0.722	0.570	0.570
		[48]	[50]	[51]	[51]	.	.	.	.
	SARCOMA, HISTIOCYTIC	2	0	2	1	0.544	1.000	0.742	0.888
		[41]	[43]	[47]	[43]	.	.	.	.
lymph node, med		(65)	(65)	(65)	(65)	.	.	.	.
	LYMPHOMA	1	2	2	1	0.626	0.536	0.553	0.776
		[40]	[44]	[46]	[44]	.	.	.	.
lymph node, mes		(65)	(65)	(65)	(65)	.	.	.	.
	HEMANGIOMA	1	0	2	0	0.702	1.000	0.553	1.000
		[40]	[43]	[46]	[43]	.	.	.	.
	HEMANGIOSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[40]	[43]	[46]	[43]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
	LYMPHOMA	15	10	16	14	0.450	0.918	0.579	0.715
		[49]	[49]	[52]	[51]	.	.	.	.
	MESOTHELIOMA	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
	SARCOMA, HISTIOCYTIC	2	1	2	2	0.424	0.888	0.734	0.718
lymph node, mes	SARCOMA, HISTIOCYTIC	[41]	[43]	[46]	[44]	.	.	.	.
lymph node, ren		(65)	(65)	(65)	(65)	.	.	.	.
	LYMPHOMA	3	1	2	2	0.556	0.948	0.854	0.841
		[41]	[43]	[46]	[44]	.	.	.	.
mammary gland		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOACANTHOMA	1	1	1	1	0.528	0.776	0.787	0.771
		[40]	[44]	[46]	[43]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524

**Table 6B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
		[40]	[43]	[46]	[44]	.	.	.	.
	LYMPHOMA	12	6	15	14	0.196	0.968	0.446	0.532
		[46]	[46]	[51]	[51]	.	.	.	.
	SARCOMA, HISTIOCYTIC	1	1	0	1	0.537	0.765	1.000	0.765
		[41]	[43]	[46]	[43]	.	.	.	.
multicentric ne		(65)	(65)	(65)	(65)	.	.	.	.
	HEMANGIOMA	3	2	2	6	0.078	0.842	0.860	0.305
		[40]	[43]	[46]	[45]	.	.	.	.
	HEMANGIOSARCOMA	4	2	5	4	0.391	0.910	0.574	0.683
		[41]	[43]	[46]	[44]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
	LYMPHOMA	21	13	20	20	0.355	0.972	0.714	0.714
		[50]	[50]	[52]	[52]	.	.	.	.
	SARCOMA, HISTIOCYTIC	4	6	7	4	0.654	0.400	0.358	0.670
		[42]	[44]	[49]	[44]	.	.	.	.
nerve, sciatic		(65)	(65)	(65)	(65)	.	.	.	.
	LYMPHOMA	8	3	6	6	0.519	0.973	0.842	0.831
		[45]	[44]	[48]	[47]	.	.	.	.
nose, level a		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
	LYMPHOMA	2	1	1	4	0.109	0.892	0.899	0.395
		[41]	[44]	[46]	[46]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	1	0	1	0.327	0.518	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
nose, level b		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
	LYMPHOMA	4	1	5	6	0.117	0.976	0.585	0.444
		[42]	[44]	[48]	[47]	.	.	.	.
	SARCOMA, HISTIOCYTIC	1	1	0	0	0.947	0.771	1.000	1.000
		[40]	[43]	[46]	[43]	.	.	.	.
nose, level c		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
	LYMPHOMA	6	3	7	6	0.366	0.927	0.584	0.667

**Table 6B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
		[44]	[45]	[49]	[47]	.	.	.	.
	OSTEOMA	0	1	0	0	0.767	0.518	.	.
		[40]	[43]	[46]	[43]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
nose, level d		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
	LYMPHOMA	5	3	7	8	0.133	0.881	0.475	0.367
		[43]	[45]	[49]	[49]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	0	1	0.250	.	.	0.518
		[40]	[43]	[46]	[43]	.	.	.	.
ovaries		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA, TUBULOSTROMAL	0	2	1	0	0.752	0.265	0.535	.
		[40]	[43]	[46]	[43]	.	.	.	.
	CYSTADENOMA	2	3	3	1	0.815	0.535	0.567	0.896
		[40]	[43]	[46]	[44]	.	.	.	.
	HEMANGIOMA	0	1	0	0	0.767	0.518	.	.
		[40]	[43]	[46]	[43]	.	.	.	.
	HEMANGIOSARCOMA	2	0	0	0	1.000	1.000	1.000	1.000
		[40]	[43]	[46]	[43]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
	LIPOSARCOMA	0	1	0	0	0.769	0.524	.	.
		[40]	[44]	[46]	[43]	.	.	.	.
	LYMPHOMA	16	8	18	13	0.564	0.984	0.561	0.861
		[47]	[47]	[52]	[50]	.	.	.	.
	SARCOMA, HISTIOCYTIC	1	1	2	2	0.287	0.771	0.561	0.536
		[40]	[43]	[47]	[44]	.	.	.	.
	SEX-CORD/STROMAL TUMOR	2	1	3	2	0.439	0.893	0.567	0.727
		[40]	[43]	[46]	[44]	.	.	.	.
oviducts		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
	LYMPHOMA	10	10	11	10	0.557	0.678	0.586	0.678
		[46]	[50]	[50]	[50]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.517	.	0.535	.
		[40]	[43]	[46]	[43]	.	.	.	.

**Table 6B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
pancreas		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA, ISLET CELL	0	1	1	0	0.644	0.518	0.535	.
		[40]	[43]	[46]	[43]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
	LYMPHOMA	13	10	15	15	0.295	0.859	0.540	0.540
	[46]	[48]	[51]	[51]	.	.	.	.	
	MESOTHELIOMA	0	0	0	2	0.064	.	.	0.271
		[40]	[43]	[46]	[44]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	2	0	2	0.200	0.271	.	0.271
		[40]	[44]	[46]	[44]	.	.	.	.
parathyroid gla		(65)	(65)	(65)	(65)	.	.	.	.
	LYMPHOMA	0	0	1	3	0.022	.	0.535	0.144
		[40]	[43]	[46]	[45]	.	.	.	.
pituitary gland		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA, PARS DISTALIS	1	1	1	1	0.539	0.771	0.787	0.776
		[40]	[43]	[46]	[44]	.	.	.	.
	ADENOMA, PARS INTERMEDIA	0	0	1	0	0.517	.	0.535	.
	[40]	[43]	[46]	[43]	.	.	.	.	
	LYMPHOMA	2	2	5	1	0.743	0.718	0.288	0.892
		[41]	[44]	[48]	[44]	.	.	.	.
salivary gland,		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	.	.	.	.
	LYMPHOMA	2	2	3	7	0.026	0.727	0.567	0.123
		[40]	[44]	[46]	[47]	.	.	.	.
		7	9	12	13	0.123	0.509	0.273	0.190
	[42]	[48]	[50]	[49]	.	.	.	.	
	8	3	7	11	0.094	0.978	0.800	0.443	
		[43]	[44]	[49]	[50]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	0	1	0.250	.	.	0.518
		[40]	[43]	[46]	[43]	.	.	.	.
skeletal muscle		(65)	(65)	(65)	(65)	.	.	.	.
	LIPOSARCOMA	0	1	0	0	0.769	0.524	.	.
		[40]	[44]	[46]	[43]	.	.	.	.
	LYMPHOMA	7	4	9	2	0.931	0.902	0.486	0.985
		[44]	[44]	[49]	[44]	.	.	.	.

**Table 6B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
skin	SARCOMA, HISTIOCYTIC	0 [40]	0 [43]	0 [46]	1 [43]	0.250 .	. .	. .	0.518 .
	LYMPHOMA	(65) 2 [41]	(65) 4 [45]	(65) 5 [48]	(65) 3 [46]	. 0.530 .	. 0.384 .	. 0.288 .	. 0.555 .
skin, subcutis	FIBROSARCOMA	(65) 0 [40]	(65) 1 [43]	(65) 3 [47]	(65) 1 [44]	. 0.397 .	. 0.518 .	. 0.153 .	. 0.524 .
	HEMANGIOMA	(65) 0 [40]	(65) 1 [43]	(65) 0 [46]	(65) 0 [43]	. 0.767 .	. 0.518 .	. . .	. . .
	LIPOSARCOMA	(65) 0 [40]	(65) 1 [44]	(65) 0 [46]	(65) 0 [43]	. 0.769 .	. 0.524 .	. . .	. . .
	SARCOMA, UNDIFFERENTIATED	(65) 1 [40]	(65) 0 [43]	(65) 0 [46]	(65) 0 [43]	. 1.000 .	. 1.000 .	. 1.000 .	. 1.000 .
small intestine	LEUKEMIA, GRANULOCYTIC	(65) 0 [40]	(65) 0 [43]	(65) 0 [46]	(65) 1 [44]	. 0.254 .	. . .	. . .	0.524 . .
	LYMPHOMA	5 [43]	2 [45]	6 [48]	5 [46]	0.340 .	0.952 .	0.578 .	0.673 .
		7 [43]	3 [45]	4 [48]	11 [46]	0.038 .	0.962 .	0.932 .	0.299 .
		8 [43]	7 [45]	7 [48]	8 [46]	0.496 .	0.760 .	0.773 .	0.680 .
		[44]	[47]	[48]	[48]	. .	. .	. .	. .
	SARCOMA, HISTIOCYTIC	[44] 0 [40]	[47] 1 [45]	[48] 0 [43]	[48] 0 [44]	. 0.767 .	. 0.518 .	. . .	. . .
		[44] 0 [44]	[47] 0 [44]	[48] 0 [46]	[48] 2 [44]	. 0.115 .	. 0.518 .	. . .	0.271 . .
		[44] 0 [40]	[44] 2 [43]	[46] 0 [46]	[44] 1 [43]	. 0.456 .	. 0.271 .	. . .	0.524 . .
spinal cord, ce	LEUKEMIA, GRANULOCYTIC	(65) 0 [40]	(65) 0 [43]	(65) 0 [46]	(65) 1 [44]	. 0.254 .	. . .	. . .	0.524 . .
	LYMPHOMA	(65) 1 [40]	(65) 1 [43]	(65) 0 [46]	(65) 0 [43]	. 0.947 .	. 0.771 .	. 1.000 .	. 1.000 .
	SARCOMA, HISTIOCYTIC	(65) 0 [40]	(65) 0 [43]	(65) 1 [47]	(65) 0 [43]	. 0.520 .	. . .	. 0.540 .	. . .
		(65)	(65)	(65)	(65)	. .	. .	. .	. .

**Table 6B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
	LEUKEMIA, GRANULOCYTIC	0 [40]	0 [43]	0 [46]	1 [44]	0.254 .	.	.	0.524 .
	LYMPHOMA	1 [40]	1 [43]	2 [46]	0 [43]	0.805 .	0.771 .	0.553 .	1.000 .
spinal cord, th		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0 [40]	0 [43]	0 [46]	1 [44]	0.254 .	.	.	0.524 .
	LYMPHOMA	1 [40]	1 [43]	0 [46]	0 [43]	0.947 .	0.771 .	1.000 .	1.000 .
	SARCOMA, HISTIOCYTIC	0 [40]	0 [43]	1 [47]	0 [43]	0.520 .	.	0.540 .	.
spleen		(65)	(65)	(65)	(65)	.	.	.	.
	HEMANGIOSARCOMA	0 [40]	1 [43]	1 [46]	0 [43]	0.644 .	0.518 .	0.535 .	.
spleen		(65)	(65)	(65)	(65)	.	.	.	.
	HEMANGIOSARCOMA	0 [40]	0 [43]	0 [46]	1 [44]	0.254 .	.	.	0.524 .
	LYMPHOMA	20 [50]	12 [50]	19 [52]	20 [52]	0.267 .	0.974 .	0.713 .	0.641 .
	SARCOMA, HISTIOCYTIC	0 [40]	2 [43]	2 [46]	1 [43]	0.453 .	0.265 .	0.283 .	0.518 .
stomach, glandu		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0 [40]	0 [43]	0 [46]	1 [44]	0.254 .	.	.	0.524 .
	LYMPHOMA	11 [45]	5 [44]	11 [49]	10 [48]	0.404 .	0.971 .	0.682 .	0.747 .
	MESOTHELIOMA	0 [40]	0 [43]	0 [46]	1 [44]	0.254 .	.	.	0.524 .
	SARCOMA, HISTIOCYTIC	1 [40]	1 [43]	2 [47]	2 [44]	0.287 .	0.771 .	0.561 .	0.536 .
stomach, nongla		(65)	(65)	(65)	(65)	.	.	.	.
	LYMPHOMA	1 [40]	1 [43]	2 [47]	4 [46]	0.066 .	0.771 .	0.561 .	0.227 .
	MESOTHELIOMA	0 [40]	0 [43]	0 [46]	1 [44]	0.254 .	.	.	0.524 .
thymus		(65)	(65)	(65)	(65)	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOL	0 [40]	0 [43]	1 [46]	0 [44]	0.517 .	.	0.535 .	.

**Table 6B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
	HEMANGIOSARCOMA	[40] 0	[43] 0	[46] 1	[43] 0	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	[40] 0	[43] 0	[46] 0	[43] 1	0.254	.	.	0.524
	LYMPHOMA	[40] 18	[43] 12	[46] 18	[44] 19	.	0.946	0.695	.
	MESOTHELIOMA	[48] 0	[49] 0	[52] 0	[51] 1	.	.	.	.
	SARCOMA, HISTIOCYTIC	[40] 0	[43] 1	[46] 1	[44] 1	.	0.518	0.535	0.518
	THYMOMA	[40] 0	[43] 0	[46] 1	[43] 0	.	.	0.535	.
thyroid gland	LYMPHOMA	(65) 9	(65) 1	(65) 6	(65) 5	.	.	.	.
		[45]	[43]	[47]	[46]	.	.	.	.
tongue	LYMPHOMA	(65) 7	(65) 2	(65) 5	(65) 3	.	.	.	.
		[42]	[44]	[47]	[44]	0.796	0.988	0.873	0.963
trachea	LEUKEMIA, GRANULOCYTIC	(65) 0	(65) 0	(65) 0	(65) 1	.	.	.	.
		[40]	[43]	[46]	[44]	0.254	.	.	0.524
	LYMPHOMA	[40] 6	[43] 2	[46] 5	[44] 5	.	0.402	0.975	0.788
		[43]	[45]	[47]	[45]	0.765	.	.	.
ureters	LYMPHOMA	(65) 13	(65) 9	(65) 14	(65) 14	.	.	.	.
		[47]	[47]	[51]	[50]	0.309	0.889	0.599	0.575
	SARCOMA, HISTIOCYTIC	[47] 0	[47] 0	[51] 1	[50] 2	.	.	0.535	0.271
		[40]	[43]	[46]	[44]	0.067	.	.	.
urinary bladder	HEMANGIOMA	(65) 0	(65) 0	(65) 0	(65) 1	.	.	.	.
		[40]	[43]	[46]	[44]	0.254	.	.	0.524
	HEMANGIOSARCOMA	[40] 1	[43] 0	[46] 0	[43] 0	.	1.000	1.000	1.000
	LEUKEMIA, GRANULOCYTIC	[40] 0	[43] 0	[46] 0	[43] 1	.	.	.	.
	LIPOSARCOMA	[40] 0	[43] 1	[46] 0	[44] 0	0.254	.	.	0.524
		[40]	[43]	[46]	[44]	0.769	0.524	.	.

**Table 6B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Mice (Vehicle control, low, medium and high dose groups)**

Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
	LYMPHOMA	[40] 15	[44] 10	[46] 17	[43] 15	.	.	.	.
	SARCOMA, HISTIOCYTIC	[46] 1	[49] 1	[51] 1	[50] 1	.	.	.	.
uterus with cer	ADENOCARCINOMA	(65) 2	(65) 1	(65) 1	(65) 1	.	.	.	.
	ADENOMA	[40] 0	[43] 0	[46] 1	[43] 0	.	.	.	.
	CARCINOMA, SQUAMOUS CELL	[40] 0	[43] 0	[46] 2	[43] 0	.	.	.	.
	FIBROMA	[40] 0	[43] 1	[46] 0	[43] 2	.	.	.	.
	GRANULAR CELL TUMOR	[40] 1	[43] 0	[46] 0	[43] 1	.	.	.	.
	HEMANGIOMA	[40] 1	[43] 0	[46] 0	[43] 3	.	.	.	.
	HEMANGIOSARCOMA	[40] 1	[43] 1	[46] 2	[44] 3	.	.	.	.
	LEIOMYOMA	[40] 1	[43] 2	[46] 4	[43] 0	.	.	.	.
	LEIOMYOSARCOMA	[40] 1	[43] 2	[46] 1	[43] 2	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	[40] 0	[43] 0	[46] 0	[44] 1	.	.	.	.
	LYMPHOMA	[40] 13	[43] 11	[46] 15	[44] 14	.	.	.	.
	MESOTHELIOMA	[46] 0	[48] 0	[51] 0	[50] 1	.	.	.	.
	POLYP, ENDOMETRIAL STROMAL	[40] 4	[43] 8	[46] 4	[44] 6	.	.	.	.
	POLYP, GLANDULAR	[41] 1	[45] 1	[46] 0	[45] 1	.	.	.	.
	SARCOMA, ENDOMETRIAL STROMAL	[40] 2	[43] 2	[46] 2	[43] 2	.	.	.	.
	SARCOMA, HISTIOCYTIC	[40] 4	[43] 5	[46] 4	[43] 4	.	.	.	.
vagina	HEMANGIOSARCOMA	[42] (65) 1	[44] (65) 0	[48] (65) 0	[44] (65) 0	.	.	.	.

**Table 6B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Mice (Vehicle control, low, medium and high dose groups)**

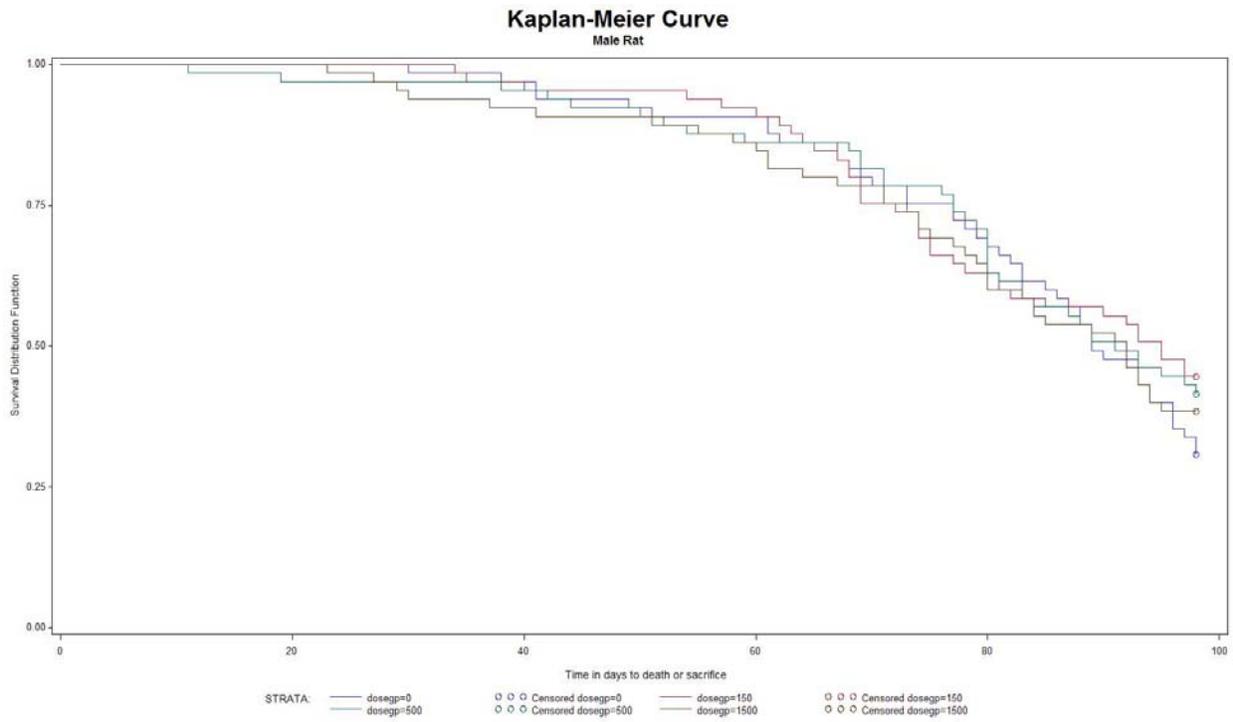
Organ Name	Tumor Name	1500 m				P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		0 mg Cont N=65	150 mg Low N=65	500 mg Med N=65	g High N=65				
	LEIOMYOSARCOMA	[40] 0	[43] 1	[46] 0	[43] 0	. 0.769	. 0.524	. .	. .
	LEUKEMIA, GRANULOCYTIC	[40] 0	[44] 0	[46] 0	[43] 1	. 0.254	. .	. .	. 0.524
	LYMPHOMA	[40] 11	[43] 4	[46] 13	[44] 9	. 0.467	. 0.986	. 0.499	. 0.805
	SARCOMA, HISTIOCYTIC	[47] 0	[45] 1	[51] 1	[49] 2	. 0.130	. 0.518	. 0.540	. 0.271
		[40]	[43]	[47]	[44]	.	.	.	.
zymbal's gland		(65)	(65)	(65)	(65)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	0	1	0.254	.	.	0.524
	LYMPHOMA	[40] 5	[43] 2	[46] 7	[44] 6	. 0.260	. 0.949	. 0.460	. 0.578
		[43]	[44]	[48]	[48]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

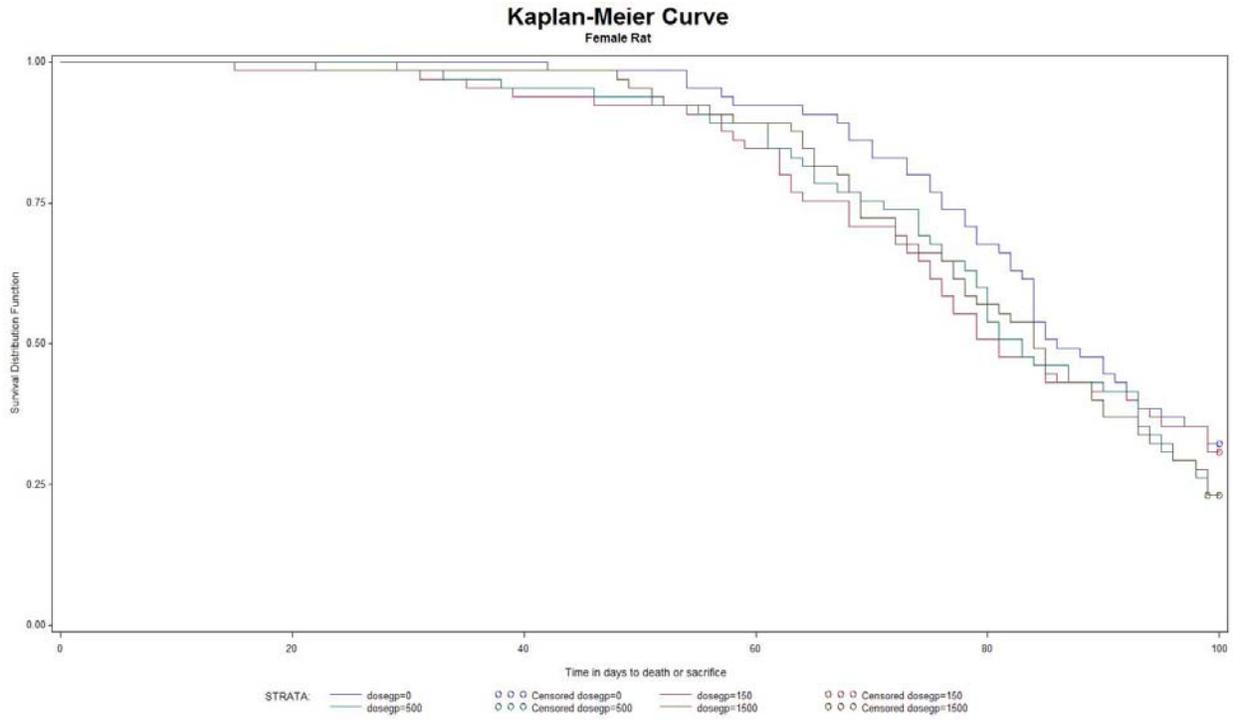
Numbers are the tumor bearing animals

**Figure 1A: Kaplan-Meier Survival Functions for Male Rats**  
Male Rats (Vehicle control, low, medium and high dose groups)



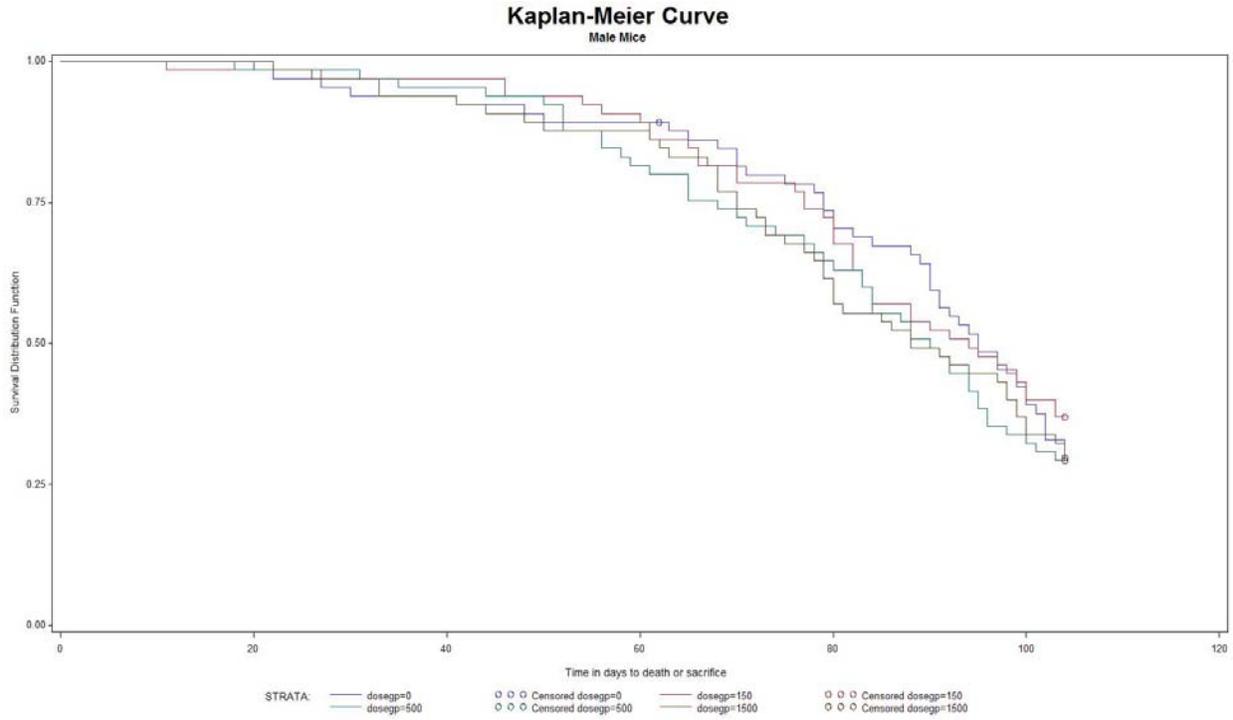
X-Axis: Weeks, Y-Axis: Survival rates

**Figure 1B: Kaplan-Meier Survival Functions for Female Rats**  
Female Rats (Vehicle control, low, medium and high dose groups)



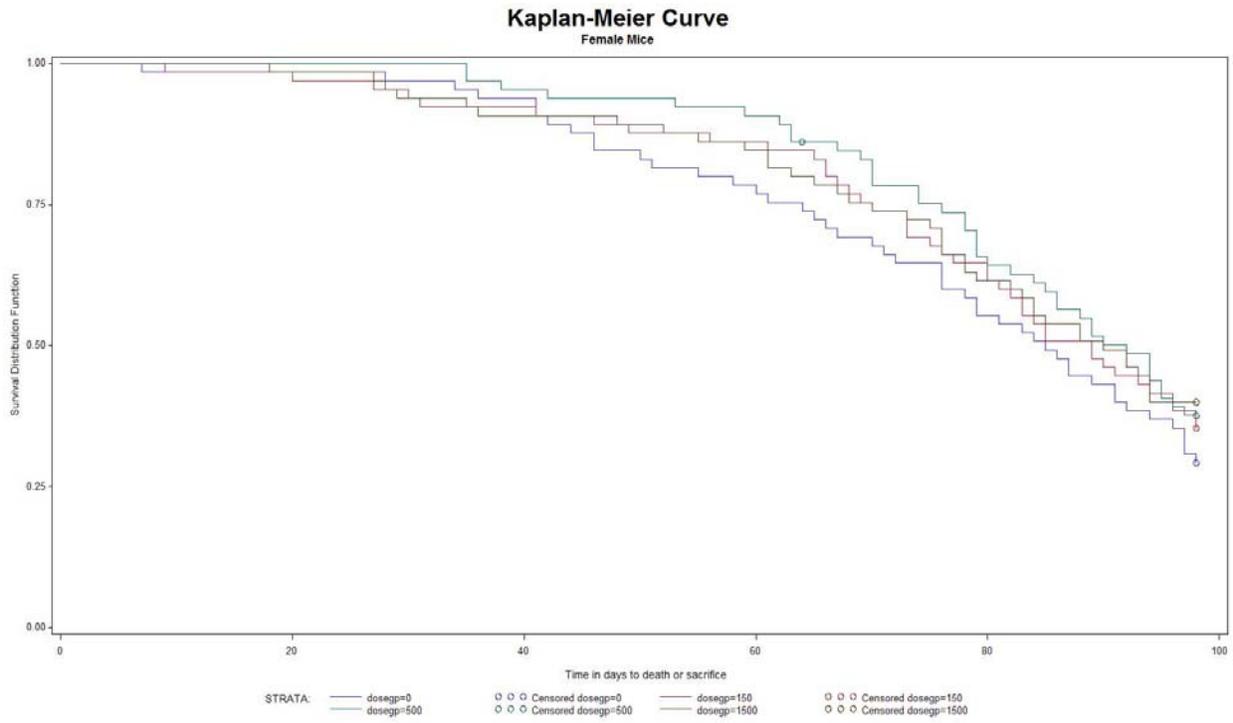
X-Axis: Weeks, Y-Axis: Survival rates

**Figure 2A: Kaplan-Meier Survival Functions for Male Mice**  
Male Mice (Vehicle control, low, medium and high dose groups)



X-Axis: Weeks, Y-Axis: Survival rates

**Figure 2B: Kaplan-Meier Survival Functions for Female Mice**  
Female Mice (Vehicle control, low, medium and high dose groups)



X-Axis: Weeks, Y-Axis: Survival rates

## 7. References:

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2. Bieler, G. S. and Williams, R. L. (1993). "Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity". *Biometrics* 49, 793-801.
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5. Haseman, J (1983), "A re-examination of false-positive rates for carcinogenesis studies", *Fundamental and Applied Toxicology*, 3: 334-339.
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10. U.S. Department of Health and Human Services, "Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals", Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, 2001.

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/s/  
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MIN MIN  
09/24/2014

KARL K LIN  
09/24/2014  
Concur with review

## STATISTICS FILING REVIEW WITH CHECKLIST

<b>NDA Number:</b> 206940	<b>Applicant:</b> Furiex Pharmaceuticals, Inc.	<b>Stamp Date:</b> June 27, 2014
<b>Drug Name:</b> (b) (4) (eluxadoline)	<b>NDA Type:</b> priority	<b>Indication:</b> IBS-d

On **initial** overview of the NDA application for RTF:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1	Index is sufficient to locate necessary reports, tables, data, etc.	×			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	×			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	×			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	×			

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?** \_\_\_ Yes \_\_\_

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

<b>Content Parameter (possible review concerns for 74-day letter)</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
Designs utilized are appropriate for the indications requested.	×			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	×			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	×			Phase 2 Study 2001 had IA conducted but no alpha adjustment. No IA for efficacy was done for two phase 3 studies.
Appropriate references for novel statistical methodology (if present) are included.			×	
Safety data organized to permit analyses across clinical trials in the NDA.	×			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	×			

# STATISTICS FILING REVIEW WITH CHECKLIST

## I. Background

The sponsor submitted this NDA for the study drug, eluxadoline (also known as JNJ-27018966), with a proposed indication for the treatment of abdominal pain and diarrhea in adult patients with diarrhea predominant irritable bowel syndrome (IBS-d). Eluxadoline is claimed to be a locally active, mixed mu opioid receptor ( $\mu$ OR) agonist/delta opioid receptor ( $\delta$ OR) antagonist with low oral bioavailability.

As pharmacologic treatment options are limited, presently there are no unrestricted prescription products on the market that are indicated to provide relief to patients who are suffering from IBS-d. Even though there are approved drugs in treating IBS-d, such as alosetron and loperamide, loperamide allegedly showed limited effectiveness in treating the abdominal pain and global symptoms of IBS-d and both of them may be associated with constipation, which can pose a serious problem for IBS-d patients. Therefore, the sponsor claims that a new agent with favorable safety and tolerability profiles that are effective in providing sustained relief of abdominal discomfort, abdominal pain, and bowel urgency associated with IBS-d is needed.

The sponsor's clinical program for eluxadoline comprises a total of 11 phase 1 clinical trials, one phase 2 dose-ranging clinical trial (IBS-2001) and two phase 3 clinical trials (IBS-3001 and IBS-3002) with diarrhea predominant irritable bowel syndrome (IBS-d).

On March 16, 2010, the sponsor had an End-of-Phase 1 (EOP1) meeting with the FDA to discuss the clinical development program and the proposed phase 2 proof-of-concept (POC) study. Before the phase 3 trials were initiated, an End of Phase 2 (EOP2) meeting was held to reach the agreement on the overall phase 3 study design including primary endpoint, responder definitions and associated analyses, and the overall safety exposures on September 27, 2011.

On September 06, 2013, the sponsor held a Type C Meeting with FDA to discuss their proposed Pediatric Study Plan (PSP) for eluxadoline and to obtain agreement on the design of the planned studies, including age groups proposed and associated timelines for the initiation of these studies and final report submission. Subsequent to that meeting and after incorporating feedback from the FDA on a draft PSP, the sponsor received an agreement on the initial PSP in correspondence dated February 03, 2014.

At the pre-NDA meeting held on April 22, 2014, FDA confirmed the appropriateness of the sponsor's strategy to submit the NDA with the two completed phase 3 studies but all available safety data from the ongoing Study IBS-3001 then had January 24, 2014 as cut-off date. It has been agreed that all remaining safety data from Study IBS-3001 can be provided as a major safety amendment to the NDA via an updated integrated summary of safety (ISS) and associated statistical output no later than 120 days after the NDA submission.

Regarding the format of this NDA submission, it has been submitted in electronic Common Technical Document (eCTD) format to the EDR; for all three studies, the tabulation datasets and analysis datasets were submitted in accordance with CDISC Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM). The link of this submission is: <\\CDSESUB1\evsprod\NDA206940\0000>.

# STATISTICS FILING REVIEW WITH CHECKLIST

## II. Overview of Studies

The efficacy of eluxadoline for the treatment of IBS-d was initially evaluated in the phase 2 study (IBS-2001), which contained four different doses (5 mg twice daily [BID], 25 mg BID, 100 mg BID, and 200 mg BID) and it was titled “A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-27018966 in Treatment of Patients with Irritable Bowel Syndrome with Diarrhea”. The two phase 3 studies were both titled as “A Randomized, Double-Blind, Placebo-Controlled, phase 3 Study to Evaluate the Efficacy, Safety and Tolerability of JNJ-27018966 in the Treatment of Patients with Diarrhea-Predominant Irritable Bowel Syndrome”.

The primary responder definition of the phase 2 study IBS-2001 data was based on a different criterion for the Bristol Stool Scale (BSS) component than that in the FDA recommended overall responder definition, so the dose selected for the phase 3 studies were based on the sponsor’s post hoc analysis. The sponsor concluded that the study demonstrated that patients with IBS-d who were treated with 100 mg BID and 200 mg BID eluxadoline were twice as likely as placebo patients to achieve study response (simultaneous improvement in pain and stool consistency). The sponsor further claimed that even though the 200-mg BID dose also demonstrated statistically significant superiority over placebo from multiple analyses, such as those for the percentage of patients reporting adequate relief and BSS response rate, increasing the dose did not improve the post hoc response rates over the 100-mg BID dose and it resulted in more adverse events (AEs) at 200 mg BID, particularly gastrointestinal AEs. Therefore, the sponsor decided to choose 100 mg BID as the top dose from the phase 2 study to carry into the phase 3 program; although the efficacy of 75 mg BID was not specifically explored in the phase 2 study, this dose was included as one of the therapeutic arms in the phase 3 studies. Of note, for this phase 2 study although four doses were included, due to its exploratory nature, no alpha adjustment were made for adjusting multiple dose comparisons and the missing data were simply imputed by the baseline observation carried forward (BOCF) method. This statistical reviewer had confirmed the sponsor’s results for those using the FDA recommended definition, and the results are shown in Table 2 (b).

For both IBS-3001 and IBS-3002 studies, the primary endpoint for the US approval was the proportion of composite responders over the interval from Weeks 1-12 while for the EU approval was the proportion of composite responders over the interval from Weeks 1-26. A patient was counted as a composite responder if he/she met the daily response criteria for at least 50% of the days with diary entries during the interval of interest (Weeks 1-12 or Weeks 1-26). A patient must have met both of the following criteria on a given day to be a daily responder:

- Daily pain response: worst abdominal pain scores in the past 24 hours improved by  $\geq 30\%$  compared to baseline (average of daily worst abdominal pain the week prior to randomization).
- Daily stool consistency response: BSS score  $< 5$  (i.e., score of 1, 2, 3 or 4) or the absence of a bowel movement if accompanied by  $\geq 30\%$  improvement in worst abdominal pain compared to baseline pain.

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To be eligible to be a responder, a patient must have had a minimum of 60 days of diary entries over the 12-week interval and a minimum of 110 days of diary entries over the 26-week interval. Any patient with fewer than the minimum number of days of diary entries was considered a non-responder for that interval, including patients in the intent-to-treat (ITT) analysis who had not yet recorded post-baseline diary data.

If no diary entry was made for a given day then it was considered a missing day. If a diary entry was made and BSS was missing (e.g., because no bowel movement was reported on a given day), but worst abdominal pain score was entered then so long as the pain criteria was met the patient was considered a responder for that day.

The primary analysis assessed treatment effect via pair-wise, two-sided Cochran-Mantel-Haenszel (CMH) tests for eluxadoline (75 mg BID or 100 mg BID) versus placebo. The proportions of composite responders in the eluxadoline groups (75 mg BID and 100 mg BID) were compared to the proportion of composite responders in the placebo group.

To control for multiple tests for the multiple doses of the primary composite endpoint, each active treatment group was tested against placebo and the family-wise error rate was controlled by a classic Bonferroni adjustment. In particular, the family-wise  $\alpha$ -level ( $\alpha = 0.05$ ) is divided by the number of primary hypotheses, i.e., two active doses were assessed against placebo using the nominal  $\alpha = 0.025$  and thus, the null hypotheses relating to the primary composite endpoint were deemed statistically significant at the  $P < 0.025$  level. Success was determined by evaluating the resulting significance of the Bonferroni-adjusted multiple tests for either active treatment group. The following Tables 1 to 4 summarized the designs for all three studies and the sponsor's analysis results for the single phase 2 and two phase 3 studies.

Table 1. Description of Clinical Efficacy and Safety Studies

Study ID and Number of Study Centers Locations(s)	Study Dates Enrollment Completion Study Status Total Enrollment/ Enrollment Goal	Study Objectives	Design Control Type	Study & Ctrl Drugs Dose, Route, & Regimen	No. Pts by Arm Entered/ Compl. <sup>a</sup>	Duration of Treatment	Gender M/F Median Age (Range) <sup>a</sup>	Diagnosis Inclusion Criteria	Primary Efficacy Endpoint(s) <sup>b</sup>
<b>Phase 2 Study<sup>c</sup></b>									
<b>IBS-2001</b> 208 US	Apr 2010 to Jul 2011 Apr 2011 Complete 807/850	Efficacy, safety, and PK	Randomized, double-blind, parallel Placebo control	Eluxadoline: 5 mg PO BID 25 mg PO BID 100 mg PO BID 200 mg PO BID Placebo	111/50 174/131 176/123 174/103 172/118	12 weeks + 2-week post-treatment follow-up	246/561 46 yrs (18-65)	IBS-d 1 wk prior to random: -average daily pain scores $\geq 3.0$ -average BSS $\geq 5.5$ -diary compliance	Study composite response over Weeks 1-12 ( <i>post hoc</i> )
<b>Phase 3 Studies</b>									
<b>IBS-3001</b> 295 US, Canada, UK	May 2012 to ongoing Jul 2013 Efficacy complete, safety assessments are ongoing 1282/1125	Efficacy and Safety Long-term safety	Randomized, double-blind, parallel Placebo control	Eluxadoline: 75 mg PO BID 100 mg PO BID Placebo	429/91 (183) 426/79 (193) 427/94 (186) () = ongoing	52 weeks + 2-week post-treatment follow-up	444/838 45 yrs (18-80)	IBS-d 1 wk prior to random: -average daily worst abdominal pain $> 3.0$ -average BSS score $\geq 5.5$ & $\geq 5$ days with a BSS score $\geq 5$ -IBS-d global symptom score $\geq 2$ -diary compliance	Proportion of composite responders for Weeks 1-12 (FDA) and Weeks 1-26 (EMA)

## STATISTICS FILING REVIEW WITH CHECKLIST

Study ID and Number of Study Centers Locations(s)	Study Dates Enrollment Completion Study Status Total Enrollment/ Enrollment Goal	Study Objectives	Design Control Type	Study & Ctrl Drugs Dose, Route, & Regimen	No. Pts by Arm Entered/ Compl. <sup>a</sup>	Duration of Treatment	Gender M/F Median Age (Range) <sup>a</sup>	Diagnosis Inclusion Criteria	Primary Efficacy Endpoint(s) <sup>b</sup>
IBS-3002 261 US, Canada, UK	May 2012 to Jan 2014 Jun 2013 Complete 1146/1125	Efficacy and Safety	Randomized, double-blind, parallel Placebo control	Eluxadoline: 75 mg PO BID 100 mg PO BID Placebo	381/250 383/264 382/273	26 weeks + 4-weeks single-blinded withdrawal	378/768 45.5 yrs (18-77)	IBS-d 1 wk prior to random: -average daily worst abdominal pain >3.0 -average BSS score ≥5.5 & ≥5 days with a BSS score ≥5 -IBS-d global symptom score ≥2 -diary compliance	Proportion of composite responders for Weeks 1-12 (FDA) and Weeks 1-26 (EMA)

Abbreviations: BID = twice daily; BSS = Bristol Stool Scale; Compl = completed; Ctrl = control; EMA = European Medicines Agency; F = female; FDA = Food and Drug Administration; IBS-d = diarrhea-predominant irritable bowel syndrome; ID = identification; M = male; No. = number; PK = pharmacokinetic; PO = oral; Pts = patients; UK = United Kingdom; US = United States; yrs = years

<sup>a</sup> Number of patients enrolled in each individual study.

<sup>b</sup> Efficacy endpoints are defined in ISE in-text Table 5-1.

<sup>c</sup> In the Phase 2 CSR, 18 patients from Site 191 (reported to the FDA for potential scientific misconduct) were excluded from the summary tables provided with the CSR. However, data listings for these patients were included in Section 16.6 of the CSR. The number of patients presented above, include all patients enrolled (N=807) in this study, including the 18 patients from Site 191.

Source: Sponsor's Table 2.7.3.2-1 of summary-clin-efficacy-ibs-d.pdf from M2 (Page 10/99)

Table 2 Sponsor's Analysis Results for Study IBS-2001

(a) Based on Primary Responder Definition (ITT Analysis Set)

	JNJ-27018966 5 mg BID (N = 105)	JNJ-27018966 25 mg BID (N = 167)	JNJ-27018966 100 mg BID (N = 163)	JNJ-27018966 200 mg BID (N = 160)	Placebo (N = 159)
<b>Week 4</b>					
Overall response rate	12.4%	12.0%	11.0%	13.8%	5.7%
Odds ratio	2.457	2.383	2.079	2.797	
(95% CI)	(0.994, 6.077)	(1.036, 5.478)	(0.893, 4.842)	(1.227, 6.376)	
P value	0.052	0.041	0.090	0.015	
<b>Week 12</b>					
Overall response rate	8.6%	13.2%	20.2%	15.0%	11.3%
Odds ratio	0.719	1.208	2.014	1.395	
(95% CI)	(0.306, 1.689)	(0.615, 2.373)	(1.069, 3.795)	(0.717, 2.716)	
P value	0.449	0.583	0.030	0.326	

Source: Sponsor's Table 11-6 of CSR.

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(b) Based on FDA Guidance Subset Definition (ITT Analysis Set)

	JNJ-27018966 5 mg BID (N=73)	JNJ-27018966 25 mg BID (N=130)	JNJ-27018966 100 mg BID (N=119)	JNJ-27018966 200 mg BID (N=124)	Placebo (N=108)
<b>Week 4</b>					
Overall response rate	27.4%	30%	30.3%	31.5%	24.1%
Odds ratio (95% CI)	1.177 (0.589, 2.352)	1.339 (0.742, 2.420)	1.381 (0.756, 2.525)	1.416 (0.781, 2.565)	
p-value	0.643	0.332	0.293	0.251	
<b>Week 12</b>					
Overall response rate	24.7%	29.2%	41.2%	31.5%	25%
Odds ratio (95% CI)	0.952 (0.471, 1.921)	1.246 (0.692, 2.247)	2.133 (1.191, 3.822)	1.342 (0.744, 2.420)	
p-value	0.890	0.462	0.011	0.328	

Source: Sponsor's Table 14.2.1.10, 14.2.1.10.1, 14.2.1.11 and 14.2.1.11.1

Table 3 Sponsor's CMH Analysis of Composite Responders for Study IBS-3001 (ITT Analysis Set)

Interval Treatment	Number (%)		P value <sup>a</sup>
	Responder	Non-Responder	
<b>Weeks 1-12 (FDA primary endpoint)</b>			
Eluxadoline 75 mg BID (N=427)	102 (23.9)	325 (76.1)	0.014
Eluxadoline 100 mg BID (N=426)	107 (25.1)	319 (74.9)	0.004
Placebo BID (N=427)	73 (17.1)	354 (82.9)	--
<b>Weeks 1-26 (EMA primary endpoint)</b>			
Eluxadoline 75 mg BID (N=427)	100 (23.4)	327 (76.6)	0.112
Eluxadoline 100 mg BID (N=426)	125 (29.3)	301 (70.7)	<0.001
Placebo BID (N=427)	81 (19.0)	346 (81.0)	--

Abbreviations: BID = twice daily; EMA = European Medicines Agency; FDA = Food and Drug Administration; ITT = intent to treat

Source: Sponsor's Table 2.7.3.2-3 of summary-clin-efficacy-ibs-d.pdf from M2 (Page 17/99)

Table 4 Sponsor's CMH Analysis of Composite Responders for Study IBS-3002 (ITT Analysis Set)

Interval Treatment	Number (%)		P value <sup>a</sup>
	Responder	Non-Responder	
<b>Weeks 1-12 (FDA primary endpoint)</b>			
Eluxadoline 75 mg BID (N=381)	110 (28.9)	271 (71.1)	<0.001
Eluxadoline 100 mg BID (N=382)	113 (29.6)	269 (70.4)	<0.001
Placebo BID (N=382)	62 (16.2)	320 (83.8)	--
<b>Weeks 1-26 (EMA primary endpoint)</b>			
Eluxadoline 75 mg BID (N=381)	116 (30.4)	265 (69.6)	0.001
Eluxadoline 100 mg BID (N=382)	125 (32.7)	257 (67.3)	<0.001
Placebo BID (N=382)	77 (20.2)	305 (79.8)	--

Abbreviations: BID = twice daily; EMA = European Medicines Agency; FDA = Food and Drug Administration; ITT = intent to treat

Source: Sponsor's Table 2.7.3.2-4 of summary-clin-efficacy-ibs-d.pdf from M2 (Page 22/99)

Finally, based on the significant findings shown above for Studies IBS-3001 and IBS-3002, the sponsor concluded that the effectiveness of eluxadoline has been demonstrated.

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/s/  
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YEH FONG CHEN  
08/15/2014

FREDA COONER  
08/15/2014