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STATISTICAL REVIEW(S)

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

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 206-627
Drug Name:	Hydrocodone bitartrate
Applicant:	Sponsor: Purdue Pharma L. P. Nonclinical Drug Safety Evaluation 6 Cedar Brook Drive Cranbury, New Jersey 08512 Test Facility (b) (4)
Documents Reviewed:	Electronic data submitted on April 24, 2014, Also include the sponsor's reports submitted.
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -6
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Project Manager:	
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 hydrocodone bitartrate when administered daily by oral gavage to rats for at least 104 weeks.
Results of this review have been discussed with the reviewing pharmacologist Dr. Bolan 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 two control groups. Male and female Crl:CD®(SD)IGS BR rats were assigned to one of five toxicity phase groups (70/sex/group). Groups 1 and 2 were control animals and received distilled water at a dose volume of 10 mL/kg. Groups 3, 4 and 5 animals received hydrocodone (administered as hydrocodone bitartrate) at dose levels of 4, 12 and 25 mg/kg/day, respectively. Group 6 (9 sex/group) was the counterpart toxicokinetic group to Groups 1 and 2 and received distilled water. Animals in Groups 7, 8, and 9 (12/sex/group) received hydrocodone and were the counterpart toxicokinetic evaluation animals to Groups 3, 4 and 5, respectively. Group 10 (25/sex/group) animals were untreated and served as sentinel animals to monitor health status of the animals received and maintained during the study. Male and female Crl:CD®(SD)IGS BR rats were assigned to groups, and doses were administered as indicated in the following table. Rats were dosed via oral gavage.

TABLE 5.3.1 Study Design

Group	No. of Animals[a]		Dose Level (mg/kg/day)[b]	Concentration (mg/mL)
	Male	Female		
Main Study				
1 (Control)	70	70	0	0
2 (Control)	70	70	0	0
3 (Low)	70	70	4	0.4
4 (Mid)	70	70	12	1.2
5 (High)	70	70	25	2.5
Toxicokinetic Study[b]				
6 (Control)	9	9	0	0
7 (Low)	12	12	4	0.4
8 (Mid)	12	12	12	1.2
9 (High)	12	12	25	2.5
Sentinels				
10 (Untreated)	25	25	0	0

a Twenty-five animals/sex (in addition to main and toxicokinetic animals) were assigned as sentinel animals. Five rats/sex were bled prestudy and at Weeks 26 and 52 and four rats/sex were bled (due to survival) at Weeks 78 and 104 for viral screening purposes.
b Toxicokinetic animals were bled on Day 1 and during Weeks 26 and 52 at the following time points: predose and 0.5, 1, 2, 6, and 24 hours postdose.

2.1. Sponsor's analyses

2.1.1. Survival analysis

Evaluations of trend and heterogeneity of survival data were performed using the Cox-Tarone binary regression on life tables and Gehan-Breslow nonparametric methods using the National Cancer Institute (NCI) Life Table Package (Thomas et al., 1977). The Cox-Tarone method is more sensitive to late deaths, and the Gehan-Breslow method is more sensitive to early deaths due to treatment. As a result, they are both important tools to evaluate observable incidence data. Week 106 and Week 105 were treated as the end of the study in the NCI package for males and females, respectively. Those animals sacrificed at the scheduled interval and animals sacrificed for other reasons (gavagerelated or aggressive behavior) were censored in the analyses. Continuity-corrected onesided tail probabilities for trend and group comparisons were evaluated at <5.0% significance level.

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. At the point of the initiating terminal necropsy during Week 105, the number of surviving males was 28, 22, 31, 36, and 41 for the Control Group 1, Control Group 2, and those that received 4, 12, and 25 mg/kg/day hydrocodone bitartrate, respectively. Also at the point of the initiating terminal necropsy during Week 105, the number of surviving females was 17, 17, 19, 27, and 41 for the Control Group 1, Control Group 2, and those that received the 4, 12, and 25 mg/kg/day hydrocodone bitartrate, respectively.
The significantly lower mortality was noted for males given 12 or 25 mg of Hydrocodone Bitartrate/kg of body weight/day (mg/kg/day) when compared with the controls separately as well as combined. This significant mid and high-dose effect caused significant negative trend against each control separately and combined. Also the significantly lower mortality was noted for females given 12 or 25 mg/kg/day when compared with the controls separately as well as combined. This significant mid and high-dose effect caused significant negative trend against each control separately and combined.

Treatment with Hydrocodone Bitartrate caused significant increased survival in both sexes in a dose-related fashion. The effect was prominent in both males and females given 12 or 25 mg/kg/day.

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

FIGURE 17.1. Summary of Survival Data

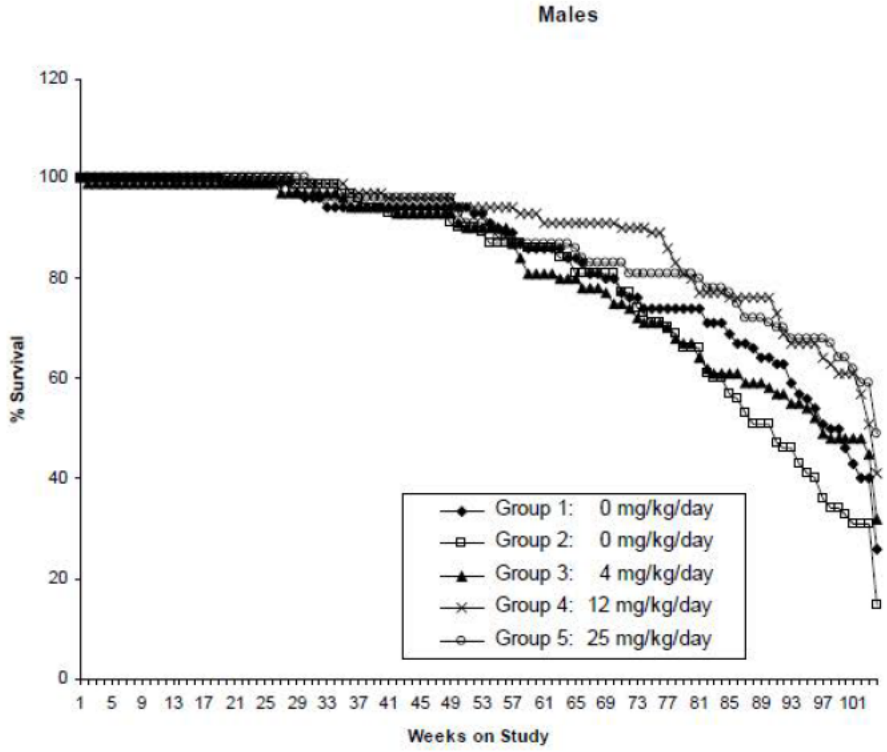
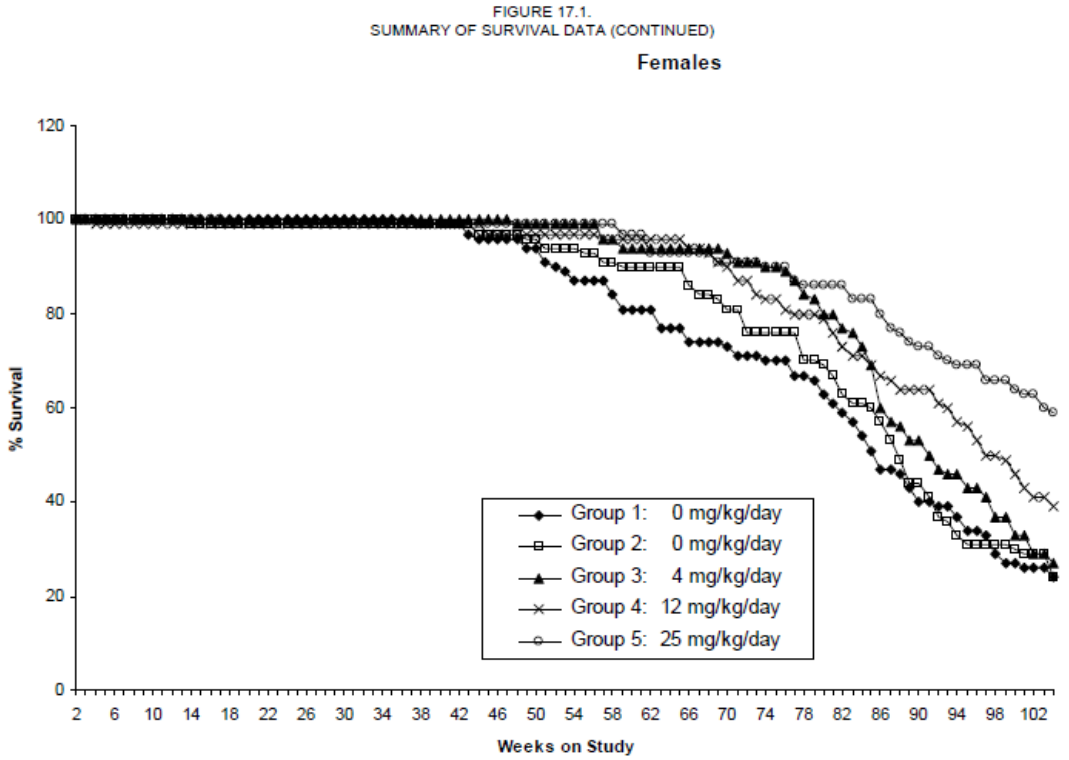


Figure 2: Kaplan-Meier plot of Survival in Female Rats



2.1.2. Tumor data analysis

Neoplastic lesions were chosen for statistical analyses if the incidence in at least one of the treated groups was increased or decreased by at least two occurrences over either control group. The incidental tumors (i.e., tumors not assigned to be the cause of death of the animals by the study pathologist) were analyzed by linear logistic regression of tumor prevalence (Dinse and Lagakos, 1983). The fatal and palpable (superficial) tumors were analyzed by the Cox-Tarone binary regression method using the death time or the first palpation time (as applicable) as a surrogate for the tumor onset time. In the case of any particular tumor type where the study pathologist assigned the tumor in question as being the cause of death of a subset of the animals and the rest of the animals were assumed to be dead of other competing risks, IARC-type (Peto et al., 1980) cause of death analysis was performed. Specifically, the subset of the tumors assigned to be the cause of death by the study pathologist was analyzed by Cox-Tarone logistic regression under life table techniques. The subset, which was considered incidental by the pathologist, was analyzed by logistic regression of tumor prevalence. Tumor types in which the cause of death was undetermined were treated as incidental for statistical purposes. The score statistics and their respective variances from the previously listed tests were then used to compute the combined evidence as described by Gart et al. (1986). If only one tumor belonging to one of the two categories (fatal and incidental) in a test was noted, they were combined with the other category for the purpose of statistical analyses. In addition, for incidental tumors only, in the cases where a lack of convergence for the asymptotic test of the logistic regression method was observed or when the tables were sparse (<5), the exact probability of significance was obtained by using LogXact-Turbo (Cytel Software Corporation, 1993).

One-sided positive trends in common (background incidence rate >1%) and rare (background incidence <1%) tumors (if applicable) defined by the study pathologist were evaluated at the 0.005 and 0.025 significance levels, respectively. High-dose group comparisons in common and rare tumors were evaluated at the 0.01 and 0.05 significance levels (FDA Draft Guidance for Industry, 2001). Other intermediate pairwise one-sided group comparisons were evaluated at the 5.0% significance level. The benign and malignant neoplastic incidences were evaluated both separately and combined, where appropriate. The criteria for combination were based on the work of McConnell et al. (1986). The incidences of multiple-organ and combined neoplastic findings such as hemangioma, lipoma, fibroma, fibrosarcoma, osteosarcoma, endometrial stromal polyp, endometrial stromal sarcoma, and liver hepatocellular adenoma/carcinoma were counted by animal, not by tissue type. They were evaluated statistically if they met the selection criterion for the analysis. The statistical results for these cases may be biased because not all the animals were examined for every tissue. Further, in the cases where the intermediate dose groups did not have a complete histopathology examination, they were excluded from statistical analyses, and only control versus high-dose group comparisons were performed. Dose levels 0, 0, 4, 12 and 25 were used in the analyses for Groups 1, 2, 3, 4, and 5. Continuity correction was done for all asymptotic tests.

Sponsor's findings: For males, no statistically significant positive trend or increase in incidence rate was noted for any of the treated groups for males in this study when compared with the controls separately and combined. Several cases of statistically significant negative trend and decreases in certain neoplastic incidences were noted in the males. For females, no statistically significant positive trend was noted for any of the treated groups for females in this study when compared with the control groups separately and combined. For 2 cases, significant positive increases were noted. For endometrial stromal polyp found in the uterus, a significant increase in the incidence rate for females given 12 mg/kg/day was noted when compared with Control 1. For malignant thymoma found in the thymus, an isolated instance of a significant increase was noted for females given 12 mg/kg/day when compared with the combined controls. The incidence was not significant versus the two controls separately and no significant trend was noted versus the controls separately or combined. Several cases of statistically significant negative trend and decreases in certain neoplastic incidences were noted in the females.

Many instances of significantly decreased neoplastic lesions were noted in both sexes. Several of them were dose-related. No treatment-related significant increase in any neoplastic incidence in either sex was noted, except for the borderline increase in the incidence rates of endometrial stromal polyp of the uterus (versus Control 1 only, not versus the second control or combined controls) and malignant thymoma of the thymus (versus the combined controls, not versus any of the two controls individually) of females given 12 mg/kg/day. These increases were considered not to be treatment-related because they were not found versus both controls separately, the incidence rates for females given 25 mg/kg/day did not show these effects, and no significant positive trend was noted versus the two controls separately or combined.

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. Survival and tumor analysis were done in the reviewer's analysis including the combined controls with three treated groups.

2.2.1. Survival analysis

The survival distributions of animals in all five treatment groups (three treated groups and two control groups)

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 five 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 five 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 three sets of data in males and females, respectively.

Reviewer's findings: The tests showed statistically significant dose-response in survivals across the combined controls and treated groups in both males and females. Also the tests showed statistically significant pair-wise differences between medium dose group and the combined control groups, between high dose group and the combined control groups in survivals in both males and females. 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.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships and pair-wise comparisons of the combined control groups 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 the following tumor combinations:

Rat

- Hemangioma and hemagiosarcoma for the whole body (all sites) for male rats only.
- Malignant lymphomas and leukemia for the whole body (all sites) for male rats only.
- Adrenal cortex adenoma and carcinoma.
- Adrenal medulla benign and malignant pheochromocytomas.
- Cavity oral squamous cell papilloma and carcinoma for female rats only.
- Hemato neoplasia leukemia and lymphoma.
- Liver hepatocellular adenoma and carcinoma for male rats only.
- Liver hepatocellular adenoma and metastatic carcinoma for female rats only.
- LN mesenteric hemangioma and hemangiosarcoma.
- Pancreas acinar cell adenoma and carcinoma.
- Pancreas islet cell adenoma and carcinoma.
- Pituitary adenoma and carcinoma for female rats only.
- Skin squamous cell papilloma, carcinoma and keratoacanthomas.
- Thyroid C cell adenoma and carcinoma.
- Thyroid follicular cell adenoma and carcinoma.

Mouse

- Harderian gland adenoma and carcinoma for males only.
- Liver hepatocellular adenoma and carcinoma.
- Lung bronchiolar adenoma and carcinoma.
- Thyroid follicular cell adenoma and carcinoma for males only.

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 α=0.025 for rare tumors and α=0.005 for common tumors for a submission with two species, and a significance level α=0.05 for rare tumors and α=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 α=0.05 for rare tumors and α=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: Tests did not show statistically significant positive dose response relationship or increased tumor incidence in the treated groups compared to the combined controls in any tumor type in both males and females.

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 two control groups. Male and female Crl:CD-1® (ICR) BR mice were assigned to one of five main study groups to assess carcinogenicity of the test article, hydrocodone, when administered by oral gavage daily for 104 weeks. Groups 1 (60/sex) and 2 (70/sex) were control animals and received distilled water at a dose volume of 10 mL/kg. Males (70/group) in Groups 3, 4 and 5 received hydrocodone (administered as hydrocodone bitartrate) at free base dose levels of 20, 60 and 200 mg/kg/day, respectively. Females (70/group) in Groups 3, 4 and 5 received hydrocodone at dose levels of 10, 30 and 100 mg/kg/day, respectively. Group 6 (12/sex/group) was the counterpart toxicokinetic group to Groups 1 and 2 and received distilled water. Animals in Groups 7, 8, and 9 (36/sex/group) received hydrocodone and were the counterpart toxicokinetic evaluation animals to Groups 3, 4 and 5, respectively. Group 10 animals (25/sex/group) were untreated and served as sentinel mice to monitor the viral health status of animals received and maintained during the study.
Male and female Crl:CD-1® (ICR) BR mice were assigned to groups, and doses were administered as indicated in the following table. Rats were dosed via oral gavage.

TABLE 6.4.1 Study Design

Group	No. of Animals		Dose Level (mg/kg/day)		Concentration (mg/mL)	
	Male	Female	Male	Female	Male	Female
Main Study						
1 (Control 1)	60	60	0	0	0	0
2 (Control 2)	70	70	0	0	0	0
3 (Low)	70	70	20	10	2	1
4 (Mid)	70	70	60	30	6	3
5 (High)	70	70	200	100	20	10
TK Study[a]						
6 (Control)	12	12	0	0	0	0
7 (Low)	36	36	20	10	2	1
8 (Mid)	36	36	60	30	6	3
9 (High)	36	36	200	100	20	10
10 (Sentinel)[b]	25	25	0	0	0	0

a Toxicokinetic animals in Groups 7-9 were bled on Day 1 and during Week 26 at the following time points: predose, 0.5, 1, 2, 6, and 24 hours postdose. Toxicokinetic mice in Group 6 were bled on Day 1 and Week 26 at 0.5 hour postdose.

b Five (5) mice/sex were bled for viral screening purposes prestudy, and at Weeks 26, 52, 78, and 104, except for during Week 78 when 4 males and 3 females were bled and Week 104 when two/sex were bled.

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). Based on graphical depiction of survival across time, and confirmed by statistical evaluation, mortality among the groups of males administered control material and those given 20 or 60 mg/kg/day hydrocodone appeared similar throughout the study, whereas the group administered 200 mg/kg/day had a greater rate of mortality, most notable after approximately Week 20. Due to high mortality, high-dose males receiving 200 mg/kg/day were suspended from dosing during Week 94 for the remainder of the study, and surviving males were necropsied during Weeks 102 and 103.

At the point of the initiating terminal necropsy during Week 102, the number of surviving males was 26, 27, 30, 30, and 15 for Control Group 1, Control Group 2, and those that received 20, 60, and 200 mg/kg/day hydrocodone, respectively. Based on graphical depiction of survival across time, and confirmed by statistical evaluation, mortality among the groups of females administered control material and 10, 30, or 100 mg/kg/day were similar throughout the study. At the point of the initiating terminal necropsy during Week 105, the number of surviving females was 23, 28, 24, 28, and 27 for Control Group 1, Control Group 2, and those that received 10, 30, and 100 mg/kg/day hydrocodone bitartrate groups, respectively.

The significantly higher mortality was noted for males given 200 mg of Hydrocodone Bitartrate/kg of body weight/day (mg/kg/day) when compared with the controls separately as well as combined. This significant high-dose effect caused significant positive trend against each control separately and combined. The other two treated groups for the males did not show significant mortality. In addition, no statistically significant change in mortality was noted for any of the treated groups for the females in this study.

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

FIGURE 17.1. Summary of Survival Data

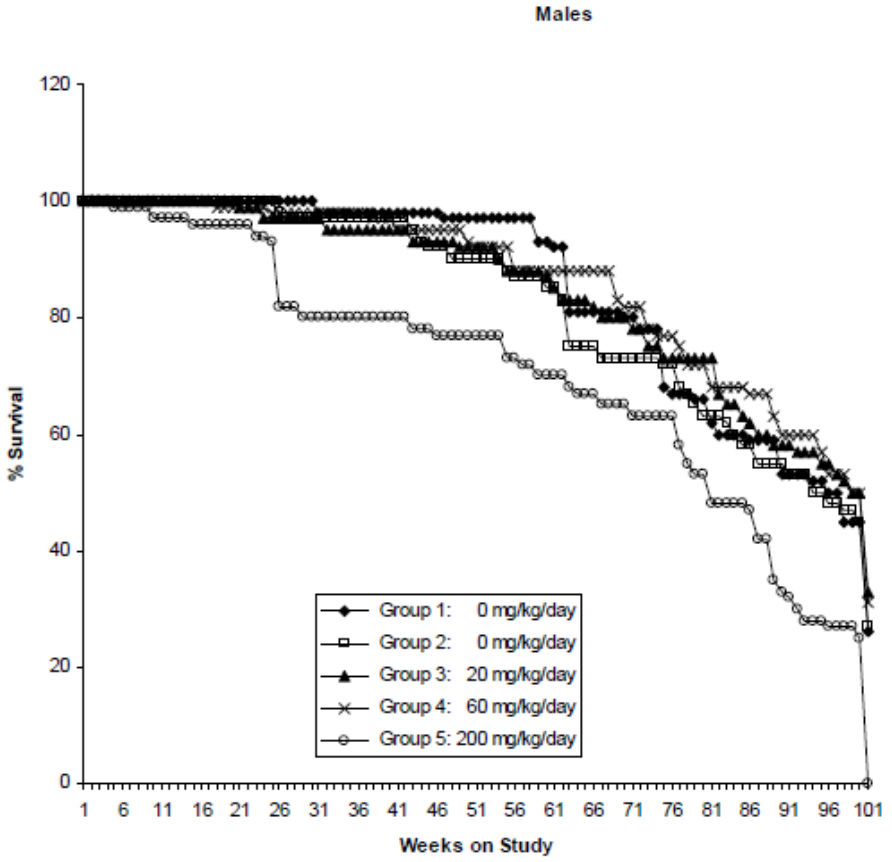
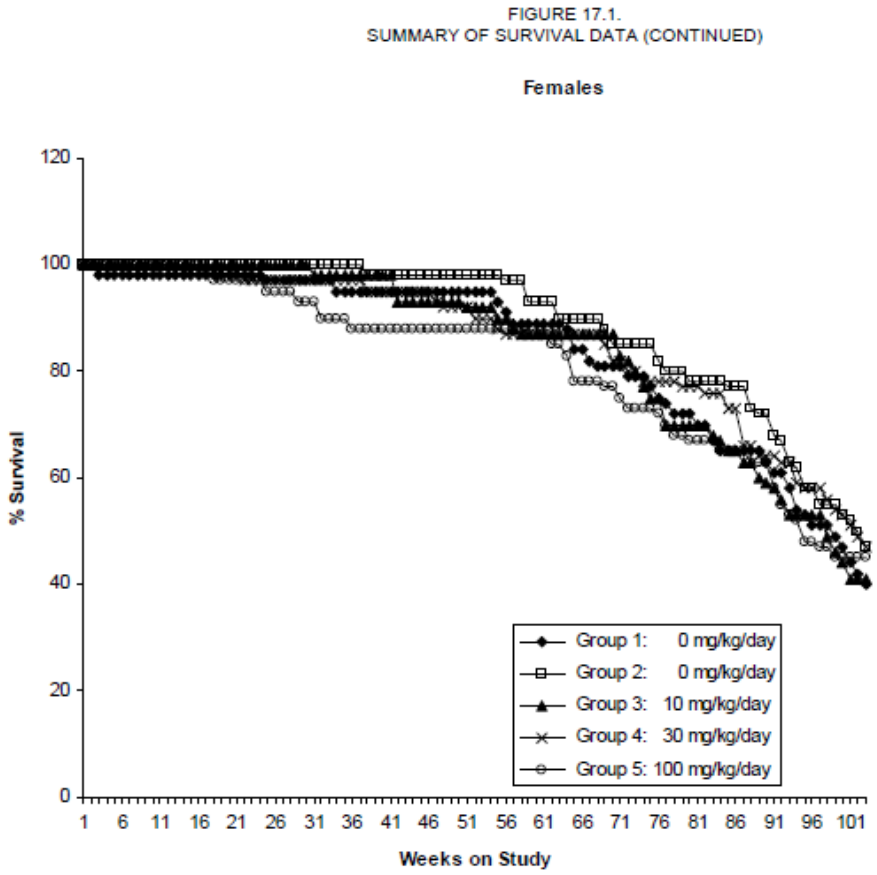


Figure 4: Kaplan-Meier plot of Survival in Female Mice



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 statistically significant positive trend or increase in incidence rate was noted for any of the treated groups for males in this study when compared with the controls separately and combined. Several cases of statistically significant decreases in certain neoplastic incidences were noted in the males. No statistically significant positive trend of neoplastic lesions was noted for any of the treated groups for males or females in this study when compared with the controls separately and combined. For papillary cystadenoma found in multiple organs, a significant increase in the incidence rate for females given 30 mg/kg/day was noted when compared with Control Group 1, but a significant decrease was noted in the incidence rate when compared to Control Group 2. The overall conclusion was that hydrocodone administration was not associated with increased neoplasia. Several instances of significantly lower incidences of neoplastic findings were noted in some treated groups compared to either one or both controls or combined controls in both sexes.
In conclusion, none of the dose levels tested (20, 60, and 200 mg/kg/day in males; 10, 30 and 100 mg/kg/day in females) were associated with evidence of carcinogenicity. Thus, the highest dose levels of 200

mg/kg/day (males) and 100 mg/kg/day (females) are considered to be the no-observed-effect levels (NOEL) with respect to the carcinogenicity end point in males and females, respectively in this study.

3.2. Reviewer's analyses

This reviewer independently performed survival and tumor data analyses for 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.

3.2.1. Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for five 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 tests showed statistically significant dose-response in survivals across the combined controls and treated groups in males. Also the tests showed statistically significant pair-wise differences between high dose group and the combined control groups in survivals in males. 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 the combined control groups 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. Bolan.

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 the combined controls and each of individual treated groups, respectively.

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

			0 mg	10 mg	30 mg	100 mg				
			Cont	Low	Med	High	P_Value	P_Value	P_Value	P_Value
Organ Name		Tumor Name	N=130	N=70	N=70	N=70	Dos Resp	C vs. L	C vs. M	C vs. H
Female										
	MAMMARY, FEMALE									
		M-CARCINOMA	2	1	0	3	0.030	0.697	1.000	0.187
		#EXAMINED ANIMALS	(95)	(49)	(44)	(55)				
		ADJUSTED N	[54]	[28]	[26]	[17]				
		PERCENTAGE	1.54%	1.43%	0%	4.29%				

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 combined control groups was considered to be statistically significant in either sex for increased tumor incidence in the treated group.

4. Evaluation of validity of the designs of the rat and mouse studies

As having been noted, the tumor data analyses from rat and mouse studies including the combined control groups 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 B6C3Fl 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 consider 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 Hydrocodone bitartrate rat and mouse studies, 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	90%	80%	69%
Female	99%	86%	71%

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

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

Percent Difference in Mean body Weight Gain
From combined controls

Male			Female		
4mg	12mg	25mg	4mg	12mg	25mg
-6.94	-24.08	-37.35	-10.67	-24.70	-35.67

Therefore, relative to the combined control groups, there had been up to 38% loss in body weight gain in the treated groups in both males and females.

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

Mortality Rates at the End of the Experiment

	Combined Cont.	**Low**	**Medium**	**High**
Male	64%	56%	49%	41%
Female	76%	73%	61%	41%

This shows that the morality rate of in the high dose group in females is 23% lower than the combined control groups and 34% lower in males. Thus, from the body weight gain and mortality data it can be concluded that for males and females the used high dose level might have reached or exceeded 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.

4.2. Mouse 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	66%	50%	27%
Female	76%	60%	50%

Based on the survival criterion Haseman proposed, it could be concluded that there were not enough mice exposed to the high dose for a sufficient amount of time in males.

Percent Difference in Mean body Weight Gain
From combined controls

Male			Female		
20mg	60mg	200mg	10mg	30mg	100mg
-41.67	-50	-2.08	-15.83	-35.83	-41.67

Therefore, relative to the combined control groups, there had been up to 50% loss in body weight gain in the treated groups in both males and females.

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

Mortality Rates at the End of the Experiment

	Combined			
	Cont.	**Low**	**Medium**	**High**
Male	59%	57%	57%	79%
Female	61%	66%	60%	61%

This shows that the morality rate of in the high dose group in males is 20% higher than the combined control groups but in females is the same as in the combined control groups. Thus, from the body weight gain and mortality data it can be concluded that for both males and females the used high dose level might have reached or exceeded the MTD. For a final determination of the adequacy of the doses used in mice, 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 hydrocodone bitartrate when administered daily by oral gavage to rats for at least 104 weeks.

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 two control groups. Male and female Crl:CD®(SD)IGS BR rats were assigned to one of five toxicity phase groups (70/sex/group). Groups 1 and 2 were control animals and received distilled water at a dose volume of 10 mL/kg. Groups 3, 4 and 5 animals received hydrocodone (administered as hydrocodone bitartrate) at dose levels of 4, 12 and 25 mg/kg/day, respectively.
The tests showed statistically significant dose-response in survivals across the combined controls and treated groups in both males and females. Also the tests showed statistically significant pair-wise differences between medium dose group and the combined control groups, between high dose group and the combined control groups in survivals in both males and females. 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.
Tests did not show statistically significant positive dose response relationship or increased tumor incidence in the treated groups compared to the combined controls in any tumor type in both males and females. From the body weight gain and mortality data it can be concluded that for males and females the used high dose level might have reached or exceeded 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 two control groups. Male and female Crl:CD-1® (ICR) BR mice were assigned to one of five main study groups to assess carcinogenicity of the test article, hydrocodone, when administered by oral gavage daily for 104 weeks. Groups 1 (60/sex) and 2 (70/sex) were control animals and received distilled water at a dose volume of 10 mL/kg. Males (70/group) in Groups 3, 4 and 5 received hydrocodone (administered as hydrocodone bitartrate) at free base dose levels of 20, 60 and 200 mg/kg/day, respectively. Females (70/group) in Groups 3, 4 and 5 received hydrocodone at dose levels of 10, 30 and 100 mg/kg/day, respectively.
The tests showed statistically significant dose-response in survivals across the combined controls and treated groups in males. Also the tests showed statistically significant pair-wise differences between high dose group and the combined control groups in survivals in males. 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 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 combined control groups 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 both males and females the used high dose level might have reached or exceeded the MTD. For a final determination of the adequacy of the doses used in mice, other clinical signs and histopathological toxic effects must be considered.

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6. Appendix

Table 1A: Intercurrent Mortality Rate
Male Rats

Week	CONTROL1 NO.OF DEATH	PERCENT	CONTROL2 NO.OF DEATH	PERCENT	LOW NO.OF DEATH	PERCENT	MEDIUM NO.OF DEATH	PERCENT	HIGH NO.OF DEATH	PERCENT
0-52	4	5.7%	7	10.0%	8	11.4%	4	5.7%	7	10.0%
53-78	14	25.7%	14	30.0%	14	31.4%	6	14.3%	7	20.0%
79-92	8	37.1%	16	52.9%	9	44.3%	9	27.0%	8	31.4%
93-104	16	60.0%	11	68.6%	8	55.7%	15	48.6%	7	41.4%
Term. Sac.	28	100.0%	22	100.0%	31	100.0%	36	100.0%	41	100.0%

Table 1B: Intercurrent Mortality Rate
Female Rats

Week	CONTROL1 NO.OF DEATH	PERCENT	CONTROL2 NO.OF DEATH	PERCENT	LOW NO.OF DEATH	PERCENT	MEDIUM NO.OF DEATH	PERCENT	HIGH NO.OF DEATH	PERCENT
0-52	7	10.0%	4	5.7%	1	1.4%	2	2.9%	1	1.4%
53-78	16	32.9%	17	30.0%	10	15.7%	12	20.0%	9	14.3%
79-92	20	61.4%	23	62.9%	26	52.9%	13	38.6%	10	28.6%
93-104	10	75.7%	9	75.7%	14	72.9%	16	61.4%	9	41.4%
Term. Sac.	17	100.0%	17	100.0%	19	100.0%	27	100.0%	41	100.0%

Table 2A: Intercurrent Mortality Comparison
Male Rats

Test	P-Value (across four groups)	P-Value (combined controls vs low)	P-Value (combined controls vs medium)	P-Value (combined controls vs high)
Dose Response	0.0029	0.3939	0.0146	0.0054
Homogeneity	0.0045	0.3373	0.0075	0.0019

Table 2B: Intercurrent Mortality Comparison
Female Rats

Test	P-Value (across four groups)	P-Value (combined controls vs low)	P-Value (combined controls vs medium)	P-Value (combined controls vs high)
Dose Response	< .0001	0.2776	0.0308	< .0001
Homogeneity	< .0001	0.1688	0.0066	< .0001

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Rats (Combined controls, low, medium and high dose goups)

		0 mg	4 mg	12 mg	25 mg				
		Cont	Low	Med	High	P_Value	P_Value	P_Value	P_Value
Organ Name	Tumor Name	N=140	N=70	N=70	N=70	Dos Resp	C vs. L	C vs. M	C vs. H
ADRENAL, CORTEX		(140)	(70)	(70)	(70)	.	.	.	.
	B-ADENOMA	2	1	0	1	0.534	0.707	1.000	0.747
		[73]	[27]	[36]	[31]	.	.	.	.
	M-CARCINOMA	2	0	0	0	1.000	1.000	1.000	1.000
		[73]	[27]	[36]	[31]	.	.	.	.
ADRENAL, MEDULL		(139)	(70)	(70)	(70)	.	.	.	.
	B-PHEOCHROMOCYTOMA	16	9	11	7	0.453	0.451	0.411	0.805
		[74]	[28]	[37]	[31]	.	.	.	.
	M-MALIGNANT GANGLIONEUROMA	0	0	0	1	0.187	.	.	0.367
		[72]	[27]	[36]	[31]	.	.	.	.
	M-MALIGNANT PHEOCHROMOCYTOMA	3	1	0	3	0.167	0.801	1.000	0.382
		[73]	[27]	[36]	[32]	.	.	.	.
ADRENAL_CORTEX		(140)	(70)	(70)	(70)	.	.	.	.
	ADENOMA+CARCINOMA	4	1	0	1	0.778	0.873	1.000	0.901
		[73]	[27]	[36]	[31]	.	.	.	.
ADRENAL_MEDULLA		(140)	(70)	(70)	(70)	.	.	.	.
	B+M_PHEOCHROMOCYTOMAS	19	10	11	10	0.327	0.511	0.600	0.664
		[74]	[28]	[37]	[32]	.	.	.	.
ALL_SITES		(140)	(70)	(70)	(70)	.	.	.	.
	HEMANGIOMA+HEMANGIOSARCOMA	3	1	0	0	0.964	0.804	1.000	1.000
		[74]	[27]	[36]	[31]	.	.	.	.
	LYMPHOMA+LEUKEMIA	3	2	1	0	0.896	0.537	0.847	1.000
		[74]	[27]	[36]	[31]	.	.	.	.
	SCHWANNOMAS	4	1	2	2	0.404	0.868	0.719	0.712
		[75]	[27]	[36]	[32]	.	.	.	.
AUDITORY SEB GL		(133)	(61)	(52)	(69)	.	.	.	.
	M-CARCINOMA, SEBACEOUS-SQUAM	2	0	0	0	1.000	1.000	1.000	1.000
		[73]	[27]	[36]	[31]	.	.	.	.
BONE, FEMUR		(140)	(70)	(70)	(70)	.	.	.	.
	M-HEMANGIOSARCOMA	0	1	0	0	0.566	0.336	.	.
		[72]	[27]	[36]	[31]	.	.	.	.
BRAIN		(140)	(70)	(70)	(70)	.	.	.	.
	M-ASTROCYTOMA	1	0	0	1	0.338	1.000	1.000	0.598
		[73]	[27]	[36]	[31]	.	.	.	.
	M-MENINGEAL SARCOMA	0	1	0	0	0.569	0.336	.	.
		[72]	[28]	[36]	[31]	.	.	.	.

Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (Combined controls, low, medium and high dose goups)

		0 mg	4 mg	12 mg	25 mg				
		Cont	Low	Med	High	P_Value	P_Value	P_Value	P_Value
Organ Name	Tumor Name	N=140	N=70	N=70	N=70	Dos Resp	C vs. L	C vs. M	C vs. H
CORD, THORACIC		(138)	(70)	(70)	(70)	.	.	.	.
	M-GLIOMA	0	0	1	0	0.404	.	0.376	.
		[72]	[27]	[36]	[31]	.	.	.	.
EYE		(140)	(70)	(70)	(70)	.	.	.	.
	M-AMELANOTIC MELANOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[73]	[27]	[36]	[31]	.	.	.	.
HEART		(140)	(70)	(70)	(70)	.	.	.	.
	M-ENDOCARDIAL SCHWANNOMA	0	0	1	0	0.404	.	0.376	.
		[72]	[27]	[36]	[31]	.	.	.	.
HEMATO NEOPLASI		(140)	(70)	(70)	(70)	.	.	.	.
	M-LEUKEMIA, LARGE GRANULAR L	1	0	1	0	0.643	1.000	0.609	1.000
		[73]	[27]	[36]	[31]	.	.	.	.
	M-LYMPHOMA	2	2	0	0	0.912	0.407	1.000	1.000
		[73]	[27]	[36]	[31]	.	.	.	.
	M-SARCOMA, HISTIOCYTIC	0	1	0	1	0.177	0.336	.	0.367
		[72]	[27]	[36]	[31]	.	.	.	.
HEMATO_NEOPLASI		(140)	(70)	(70)	(70)	.	.	.	.
	LYMPHOMA+LEUKEMIA	3	2	1	0	0.896	0.537	0.847	1.000
		[74]	[27]	[36]	[31]	.	.	.	.
ILEUM		(129)	(65)	(67)	(65)	.	.	.	.
JEJUNUM		(128)	(65)	(67)	(66)	.	.	.	.
	M-CYSTADENOCARCINOMA	3	0	0	0	1.000	1.000	1.000	1.000
		[73]	[27]	[36]	[31]	.	.	.	.
LIVER		(140)	(70)	(70)	(70)	.	.	.	.
	B-ADENOMA, HEPATOCELLULAR	2	1	0	0	0.920	0.704	1.000	1.000
		[72]	[27]	[36]	[31]	.	.	.	.
	HEPA_ADENOMA+CARCINOMA	3	1	0	0	0.966	0.804	1.000	1.000
		[72]	[27]	[36]	[31]	.	.	.	.
	M-CARCINOMA, HEPATOCELLULAR	1	0	0	0	1.000	1.000	1.000	1.000
		[72]	[27]	[36]	[31]	.	.	.	.
LN, MESENTERIC		(140)	(70)	(70)	(70)	.	.	.	.
	B-HEMANGIOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[72]	[27]	[36]	[31]	.	.	.	.
	M-HEMANGIOSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[73]	[27]	[36]	[31]	.	.	.	.

Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (Combined controls, low, medium and high dose goups)

		0 mg	4 mg	12 mg	25 mg				
		Cont	Low	Med	High	P_Value	P_Value	P_Value	P_Value
Organ Name	Tumor Name	N=140	N=70	N=70	N=70	Dos Resp	C vs. L	C vs. M	C vs. H
LUNG		(140)	(70)	(70)	(70)	.	.	.	.
	B-ADENOMA, BRONCHIOLAR-ALVEO	1	0	0	0	1.000	1.000	1.000	1.000
		[72]	[27]	[36]	[31]	.	.	.	.
	M-NEUROFIBROSARCOMA	0	0	1	0	0.404	.	0.376	.
		[72]	[27]	[36]	[31]	.	.	.	.
MAMMARY, MALE		(124)	(64)	(67)	(63)	.	.	.	.
	B-ADENOMA	0	0	1	0	0.404	.	0.376	.
		[72]	[27]	[36]	[31]	.	.	.	.
	B-FIBROADENOMA	0	1	0	1	0.177	0.336	.	0.367
		[72]	[27]	[36]	[31]	.	.	.	.
	M-CARCINOMA	0	0	1	0	0.404	.	0.376	.
		[72]	[27]	[36]	[31]	.	.	.	.
MESENTERIC_LN		(140)	(70)	(70)	(70)	.	.	.	.
	HEMANGIOMA+HEMANGIOSARCOMA	2	0	0	0	1.000	1.000	1.000	1.000
		[73]	[27]	[36]	[31]	.	.	.	.
PANCREAS		(140)	(70)	(70)	(70)	.	.	.	.
	ACINAR_CELL_ADENOMA+CARCINOM	4	3	0	0	0.982	0.429	1.000	1.000
		[73]	[28]	[36]	[31]	.	.	.	.
	B-ADENOMA, ACINAR CELL	3	0	0	0	1.000	1.000	1.000	1.000
		[73]	[27]	[36]	[31]	.	.	.	.
	B-ADENOMA, ISLET CELL	7	2	2	1	0.894	0.865	0.912	0.976
		[73]	[27]	[36]	[31]	.	.	.	.
	ISLET_CELL_ADENOMA+CARCINOMA	7	3	2	1	0.908	0.710	0.912	0.976
		[73]	[27]	[36]	[31]	.	.	.	.
	M-CARCINOMA, ACINAR CELL	0	1	0	0	0.566	0.336	.	.
		[72]	[27]	[36]	[31]	.	.	.	.
	M-CARCINOMA, ISLET CELL	1	3	0	0	0.883	0.110	1.000	1.000
		[72]	[28]	[36]	[31]	.	.	.	.
PARATHYROID		(127)	(60)	(60)	(58)	.	.	.	.
	B-ADENOMA	1	0	1	0	0.643	1.000	0.612	1.000
		[73]	[27]	[36]	[31]	.	.	.	.
PITUITARY		(140)	(68)	(69)	(70)	.	.	.	.
	B-ADENOMA, PARS DISTALIS	67	20	19	18	0.992	0.997	1.000	1.000
		[92]	[33]	[40]	[34]	.	.	.	.
	B-ADENOMA, PARS INTERMEDIA	1	0	0	0	1.000	1.000	1.000	1.000
		[72]	[27]	[36]	[31]	.	.	.	.
	M-MALIGNANT SCHWANNOMA	0	1	0	0	0.566	0.336	.	.
		[72]	[27]	[36]	[31]	.	.	.	.

Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (Combined controls, low, medium and high dose goups)

		0 mg	4 mg	12 mg	25 mg				
		Cont	Low	Med	High	P_Value	P_Value	P_Value	P_Value
Organ Name	Tumor Name	N=140	N=70	N=70	N=70	Dos Resp	C vs. L	C vs. M	C vs. H
SKIN		(140)	(70)	(70)	(70)	.	.	.	.
	B-KERATOACANTHOMA	1	2	3	3	0.054	0.258	0.147	0.138
		[73]	[27]	[37]	[32]	.	.	.	.
	B-PAPILLOMA, SQUAMOUS CELL	2	1	0	0	0.920	0.704	1.000	1.000
		[72]	[27]	[36]	[31]	.	.	.	.
	B-TRICHOEPITHELIOMA	0	0	1	0	0.404	.	0.376	.
		[72]	[27]	[36]	[31]	.	.	.	.
	M-CARCINOMA, BASAL CELL	0	0	0	1	0.187	.	.	0.367
		[72]	[27]	[36]	[31]	.	.	.	.
	M-CARCINOMA, SQUAMOUS CELL	1	0	1	0	0.646	1.000	0.612	1.000
		[72]	[27]	[36]	[31]	.	.	.	.
	SQUMOUS_CELL_PAPILLOMA+CARCI	4	3	4	3	0.255	0.429	0.342	0.503
		[73]	[27]	[37]	[32]	.	.	.	.
SPLEEN		(140)	(70)	(70)	(70)	.	.	.	.
	M-HEMANGIOSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[73]	[27]	[36]	[31]	.	.	.	.
STOMACH, NONGL		(140)	(70)	(70)	(70)	.	.	.	.
	B-SQUAMOUS CELL PAPILLOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[72]	[27]	[36]	[31]	.	.	.	.
TESTIS		(140)	(69)	(70)	(70)	.	.	.	.
	B-INTERSTITIAL CELL TUMOR	5	0	1	1	0.774	1.000	0.945	0.940
		[73]	[27]	[36]	[31]	.	.	.	.
	B-MESOTHELIOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[73]	[27]	[36]	[31]	.	.	.	.
THYMUS		(138)	(64)	(68)	(67)	.	.	.	.
	M-MALIGNANT SCHWANNOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[73]	[27]	[36]	[31]	.	.	.	.
THYROID		(140)	(70)	(70)	(70)	.	.	.	.
	B-"C" CELL ADENOMA	7	4	5	3	0.486	0.531	0.486	0.778
	B-"C" CELL ADENOMA	[73]	[27]	[36]	[31]	.	.	.	.
	B-FOLLICULAR CELL ADENOMA	2	1	1	0	0.804	0.701	0.757	1.000
		[73]	[27]	[36]	[31]	.	.	.	.
	M-"C" CELL CARCINOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[72]	[27]	[36]	[31]	.	.	.	.
	C_CELL_ADENOMA+CARCINOMA	8	4	5	3	0.566	0.614	0.575	0.837
		[73]	[27]	[36]	[31]	.	.	.	.

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 (Combined controls, low, medium and high dose groups)

Organ Name	Tumor Name	0 mg Cont N=140	4 mg Low N=70	12 mg Med N=70	25 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ADRENAL, CORTEX		(140)	(70)	(69)	(70)	.	.	.	.
	B-ADENOMA	3	2	0	1	0.793	0.610	1.000	0.878
		[83]	[45]	[48]	[48]	.	.	.	.
	M-CARCINOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[82]	[45]	[48]	[48]	.	.	.	.
ADRENAL, MEDULL		(140)	(70)	(66)	(69)	.	.	.	.
	B-PHEOCHROMOCYTOMA	2	2	1	1	0.625	0.475	0.766	0.795
		[82]	[45]	[48]	[48]	.	.	.	.
	M-MALIGNANT PHEOCHROMOCYTOMA	0	0	1	0	0.433	.	0.385	.
		[82]	[45]	[49]	[48]	.	.	.	.
	M-OSTEOSARCOMA	0	0	0	1	0.215	.	.	0.411
		[82]	[45]	[48]	[48]	.	.	.	.
ADRENAL_CORTEX		(140)	(70)	(70)	(70)	.	.	.	.
	ADENOMA+CARCINOMA	4	2	0	1	0.870	0.720	1.000	0.929
		[83]	[45]	[48]	[48]	.	.	.	.
ADRENAL_MEDULLA		(140)	(70)	(70)	(70)	.	.	.	.
	ADENOMA+CARCINOMA	2	2	2	1	0.572	0.475	0.500	0.795
		[82]	[45]	[49]	[48]	.	.	.	.
ALL_SITES		(140)	(70)	(70)	(70)	.	.	.	.
	SCHWANNOMAS	1	0	1	1	0.308	1.000	0.618	0.650
		[82]	[45]	[48]	[48]	.	.	.	.
AUDITORY SEB GL		(126)	(67)	(68)	(67)	.	.	.	.
	M-CARCINOMA, SEBACEOUS-SQUAM	0	0	1	0	0.431	.	0.381	.
		[82]	[45]	[48]	[48]	.	.	.	.
CERVIX		(139)	(70)	(68)	(69)	.	.	.	.
	B-FIBROMA	0	0	1	0	0.431	.	0.381	.
		[82]	[45]	[48]	[48]	.	.	.	.
	B-GRANULAR CELL TUMOR	0	1	0	0	0.632	0.366	.	.
		[82]	[45]	[48]	[48]	.	.	.	.
CORD, CERVICAL		(140)	(70)	(69)	(70)	.	.	.	.
	M-MALIGNANT RETICULOSIS	0	0	1	0	0.433	.	0.385	.
		[82]	[45]	[49]	[48]	.	.	.	.
HEMATO NEOPLASI	M-LEUKEMIA, LARGE GRANULAR L	0	1	0	0	0.632	0.366	.	.
		[82]	[45]	[48]	[48]	.	.	.	.
	M-LYMPHOMA	1	1	0	0	0.866	0.606	1.000	1.000
		[82]	[45]	[48]	[48]	.	.	.	.
	M-SARCOMA, HISTIOCYTIC	2	0	0	0	1.000	1.000	1.000	1.000
		[83]	[45]	[48]	[48]	.	.	.	.

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

Organ Name	Tumor Name	0 mg Cont N=140	4 mg Low N=70	12 mg Med N=70	25 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
HEMATO_NEOPLASI		(140)	(70)	(70)	(70)	.	.	.	.
	LYMPHOMA+LEUKEMIA	1	2	0	0	0.870	0.310	1.000	1.000
		[82]	[45]	[48]	[48]	.	.	.	.
KIDNEY		(140)	(70)	(69)	(70)	.	.	.	.
	B-ADENOMA, TUBULAR CELL	0	0	1	0	0.431	.	0.381	.
		[82]	[45]	[48]	[48]	.	.	.	.
	M-CARCINOMA, TRANSITIONAL CE	0	0	1	0	0.431	.	0.381	.
		[82]	[45]	[48]	[48]	.	.	.	.
LIVER		(140)	(70)	(69)	(70)	.	.	.	.
	ADENOMA+CARCINOMA	3	0	0	0	1.000	1.000	1.000	1.000
		[83]	[45]	[48]	[48]	.	.	.	.
	B-ADENOMA, HEPATOCELLULAR	2	0	0	0	1.000	1.000	1.000	1.000
		[83]	[45]	[48]	[48]	.	.	.	.
	B-CHOLANGIOMA	0	1	0	0	0.634	0.371	.	.
		[82]	[46]	[48]	[48]	.	.	.	.
	M-METASTATIC CARCINOMA, UNCE	1	0	0	0	1.000	1.000	1.000	1.000
		[82]	[45]	[48]	[48]	.	.	.	.
LUNG		(140)	(70)	(69)	(70)	.	.	.	.
	B-ADENOMA, BRONCHIOLAR-ALVEO	0	0	0	1	0.215	.	.	0.407
		[82]	[45]	[48]	[48]	.	.	.	.
MAMMARY, FEMALE		(140)	(70)	(69)	(70)	.	.	.	.
	B-ADENOMA	10	6	5	3	0.871	0.576	0.738	0.949
		[85]	[46]	[50]	[48]	.	.	.	.
	B-FIBROADENOMA	51	34	30	18	0.986	0.227	0.538	0.998
		[96]	[53]	[54]	[50]	.	.	.	.
	M-CARCINOMA	36	18	20	9	0.987	0.723	0.586	0.999
		[97]	[50]	[52]	[50]	.	.	.	.
	M-SARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[83]	[45]	[48]	[48]	.	.	.	.
ORAL_CAVITY		(140)	(70)	(70)	(70)	.	.	.	.
	SQUAMOUS_CELL_PAPILLOMA+CARC	1	0	0	1	0.383	1.000	1.000	0.647
ORAL_CAVITY	SQUAMOUS_CELL_PAPILLOMA+CARC	[83]	[45]	[48]	[48]	.	.	.	.
OVARY		(139)	(70)	(69)	(70)	.	.	.	.
	B-LUTEOMA	0	1	0	0	0.632	0.366	.	.
		[82]	[45]	[48]	[48]	.	.	.	.
	M-GRANULOSA/THECA CELL TUMOR	1	0	0	1	0.385	1.000	1.000	0.650
		[82]	[45]	[48]	[48]	.	.	.	.
OVIDUCT		(140)	(70)	(69)	(70)	.	.	.	.

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

Organ Name	Tumor Name	0 mg Cont N=140	4 mg Low N=70	12 mg Med N=70	25 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
PANCREAS		(139)	(70)	(69)	(70)	.	.	.	.
	ADENOMA+CARCINOMA	6	0	0	0	1.000	1.000	1.000	1.000
		[83]	[45]	[48]	[48]	.	.	.	.
	B-ADENOMA, ISLET CELL	4	0	0	0	1.000	1.000	1.000	1.000
		[83]	[45]	[48]	[48]	.	.	.	.
	M-CARCINOMA, ISLET CELL	2	0	0	0	1.000	1.000	1.000	1.000
		[82]	[45]	[48]	[48]	.	.	.	.
PARATHYROID		(121)	(53)	(42)	(54)	.	.	.	.
	B-ADENOMA	0	0	1	0	0.431	.	0.381	.
		[82]	[45]	[48]	[48]	.	.	.	.
PINNA		(138)	(69)	(69)	(70)	.	.	.	.
	M-SCHWANNOMA	0	0	1	0	0.431	.	0.381	.
		[82]	[45]	[48]	[48]	.	.	.	.
PITUITARY		(139)	(68)	(69)	(69)	.	.	.	.
	ADENOMA+CARCINOMA	119	55	52	47	0.914	0.973	0.998	1.000
		[129]	[62]	[64]	[54]	.	.	.	.
	B-ADENOMA, PARS DISTALIS	113	52	50	47	0.762	0.936	0.992	0.995
		[127]	[61]	[64]	[54]	.	.	.	.
	M-CARCINOMA	6	3	2	0	0.984	0.706	0.873	1.000
		[84]	[46]	[49]	[48]	.	.	.	.
SALIV GL, PAROT		(136)	(67)	(65)	(67)	.	.	.	.
	M-CARCINOMA	0	0	0	1	0.215	.	.	0.407
		[82]	[45]	[48]	[48]	.	.	.	.
SKIN		(140)	(70)	(69)	(70)	.	.	.	.
	B-KERATOACANTHOMA	2	0	0	1	0.556	1.000	1.000	0.795
		[82]	[45]	[48]	[48]	.	.	.	.
	B-PAPILLOMA, SQUAMOUS CELL	0	1	0	0	0.632	0.371	.	.
		[82]	[45]	[48]	[48]	.	.	.	.
	KERATOACANTHOMA+PAPILLOMA	2	1	0	1	0.616	0.755	1.000	0.795
		[82]	[45]	[48]	[48]	.	.	.	.
THYMUS		(131)	(65)	(66)	(65)	.	.	.	.
	M-THYMOMA	1	1	3	3	0.061	0.600	0.159	0.184
		[82]	[45]	[49]	[48]	.	.	.	.
THYROID		(140)	(70)	(69)	(69)	.	.	.	.
	B-"C" CELL ADENOMA	13	5	7	5	0.731	0.862	0.683	0.915
		[86]	[46]	[50]	[48]	.	.	.	.
	B-FOLLICULAR CELL ADENOMA	2	1	2	1	0.505	0.751	0.487	0.792
		[83]	[45]	[49]	[48]	.	.	.	.

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

Organ Name	Tumor Name	0 mg Cont N=140	4 mg Low N=70	12 mg Med N=70	25 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
THYROID	M-"C" CELL CARCINOMA	3	0	1	0	0.910	1.000	0.857	1.000
		[82]	[45]	[48]	[48]	.	.	.	.
	M-FOLLICULAR CELL CARCINOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[82]	[45]	[48]	[48]	.	.	.	.
THYROID_GLAND		(140)	(70)	(70)	(70)	.	.	.	.
	C_CELL_ADENOMA+CARCINOMA	16	5	8	5	0.849	0.944	0.751	0.971
		[86]	[46]	[50]	[48]	.	.	.	.
	F_CELL_ADENOMA+CARCINOMA	3	1	2	1	0.638	0.845	0.627	0.878
		[83]	[45]	[49]	[48]	.	.	.	.
URINARY BLADDER		(139)	(69)	(69)	(67)	.	.	.	.
	M-LEIOMYOSARCOMA	0	0	0	1	0.215	.	.	0.407
		[82]	[45]	[48]	[48]	.	.	.	.
UTERUS		(140)	(70)	(69)	(70)	.	.	.	.
	B-ENDOMETRIAL STROMAL POLYP	4	2	5	2	0.450	0.720	0.224	0.785
		[83]	[45]	[49]	[48]	.	.	.	.
	M-HEMANGIOSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[82]	[45]	[48]	[48]	.	.	.	.
VAGINA		(140)	(70)	(69)	(70)	.	.	.	.
	B-GRANULAR CELL TUMOR	1	0	0	0	1.000	1.000	1.000	1.000
		[82]	[45]	[48]	[48]	.	.	.	.
	B-POLYP	1	0	1	0	0.677	1.000	0.615	1.000
		[82]	[45]	[48]	[48]	.	.	.	.
	M-SARCOMA	0	0	1	0	0.433	.	0.381	.
		[82]	[45]	[49]	[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

Table 4A: Intercurrent Mortality Rate
Male Mice

Week	CONTROL1 NO.OF DEATH	PERCENT	CONTROL2 NO.OF DEATH	PERCENT	LOW NO.OF DEATH	PERCENT	MEDIUM NO.OF DEATH	PERCENT	HIGH NO.OF DEATH	PERCENT
0-52	2	3.3%	16	22.9%	15	21.0%	15	21.0%	24	34.0%
53-78	19	35.0%	13	41.4%	11	37.0%	10	36.0%	11	50.0%
79-92	8	48.3%	9	54.3%	9	50.0%	9	49.0%	16	73.0%
93-101	5	56.7%	5	61.4%	5	57.0%	6	57.0%	4	79.0%
Term. Sac.	26	100.0%	27	100.0%	30	100.0%	30	100.0%	15	100.0%

Table 4B: Intercurrent Mortality Rate
Female Mice

Week	CONTROL1 NO.OF DEATH	PERCENT	CONTROL2 NO.OF DEATH	PERCENT	LOW NO.OF DEATH	PERCENT	MEDIUM NO.OF DEATH	PERCENT	HIGH NO.OF DEATH	PERCENT
0-52	6	10.0%	11	15.7%	15	21.0%	15	21.0%	17	24.0%
53-78	12	30.0%	11	31.4%	13	40.0%	8	33.0%	11	40.0%
79-92	7	41.7%	7	41.4%	8	51.0%	9	46.0%	7	50.0%
93-104	12	61.7%	13	60.0%	10	66.0%	10	60.0%	8	61.0%
Term. Sac.	23	100.0%	28	100.0%	24	100.0%	28	100.0%	27	100.0%

Table 5A: Intercurrent Mortality Comparison
Male Mice

Test	P-Value (across four groups)	P-Value (combined controls vs low)	P-Value (combined controls vs medium)	P-Value (combined controls vs high)
Dose Response	0.0003	0.8396	0.8228	0.0004
Homogeneity	0.0032	0.6759	0.5690	0.0031

Table 5B: Intercurrent Mortality Comparison
Female Mice

Test	P-Value (across four groups)	P-Value (combined controls vs low)	P-Value (combined controls vs medium)	P-Value (combined controls vs high)
Dose Response	0.7175	0.4455	0.8806	0.6019
Homogeneity	0.8847	0.6003	0.7000	0.7794

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

Organ Name	Tumor Name	0 mg Cont N=130	20 mg Low N=70	60 mg Med N=70	200 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ADRENAL, CORTEX		(120)	(58)	(59)	(60)	.	.	.	.
	B-ADENOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[48]	[15]	[19]	[12]	.	.	.	.
	B-ADENOMA, SUBCAPSULAR CELL	1	1	0	0	0.742	0.572	1.000	1.000
		[48]	[15]	[19]	[12]	.	.	.	.
GALLBLADDER		(103)	(47)	(49)	(41)	.	.	.	.
	B-ADENOMA	2	1	1	0	0.697	0.721	0.728	1.000
		[48]	[15]	[19]	[12]	.	.	.	.
HARDERIAN GLAND		(119)	(59)	(59)	(60)	.	.	.	.
	B-ADENOMA	13	5	6	4	0.327	0.810	0.726	0.759
		[50]	[15]	[20]	[12]	.	.	.	.
	M-CARCINOMA	0	0	0	1	0.128	.	.	0.281
		[48]	[15]	[19]	[12]	.	.	.	.
HARDERIAN_GLAND		(130)	(70)	(70)	(70)	.	.	.	.
	ADENOMA+CARCINOMA	13	5	6	5	0.167	0.810	0.726	0.603
		[50]	[15]	[20]	[12]	.	.	.	.
HEMATO NEOPLASI		(120)	(59)	(60)	(60)	.	.	.	.
	M-LYMPHOMA	6	5	1	1	0.768	0.302	0.950	0.896
		[53]	[17]	[19]	[13]	.	.	.	.
	M-SARCOMA, HISTIOCYTIC	3	0	0	0	1.000	1.000	1.000	1.000
		[49]	[15]	[19]	[12]	.	.	.	.
KIDNEY		(120)	(59)	(60)	(60)	.	.	.	.
	M-CARCINOMA, TUBULAR CELL	1	0	0	0	1.000	1.000	1.000	1.000
		[48]	[15]	[19]	[12]	.	.	.	.
LIVER		(120)	(59)	(60)	(60)	.	.	.	.
	B-ADENOMA, HEPATOCELLULAR	4	2	1	1	0.532	0.665	0.883	0.808
		[50]	[15]	[19]	[12]	.	.	.	.
	HEPA_ADENOMA+CARCINOMA	19	2	3	1	0.984	0.999	0.995	0.999
		[54]	[15]	[19]	[12]	.	.	.	.
	M-CARCINOMA, HEPATOCELLULAR	15	0	2	0	0.998	1.000	0.995	1.000
		[52]	[15]	[19]	[12]	.	.	.	.
	M-CHOLANGIOCARCINOMA	0	0	1	0	0.330	.	0.354	.
		[48]	[15]	[19]	[12]	.	.	.	.
	M-HEMANGIOSARCOMA	8	0	0	0	1.000	1.000	1.000	1.000
		[49]	[15]	[19]	[12]	.	.	.	.
LUNG		(120)	(59)	(60)	(60)	.	.	.	.
	ADENOMA+CARCINOMA	26	8	16	8	0.206	0.960	0.380	0.822
		[54]	[16]	[22]	[14]	.	.	.	.

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

Organ Name	Tumor Name	0 mg Cont N=130	20 mg Low N=70	60 mg Med N=70	200 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
	B-ADENOMA, BRONCHIOLAR-ALVEO	14	6	12	7	0.053	0.756	0.161	0.370
		[50]	[16]	[21]	[14]	.	.	.	.
	M-CARCINOMA, BRONCHIOLAR-ALV	12	2	4	1	0.889	0.981	0.876	0.988
		[51]	[16]	[20]	[13]	.	.	.	.
PANCREAS		(119)	(58)	(59)	(60)	.	.	.	.
	B-ADENOMA, ISLET CELL	1	0	0	0	1.000	1.000	1.000	1.000
		[48]	[15]	[19]	[12]	.	.	.	.
SPLEEN		(120)	(59)	(59)	(59)	.	.	.	.
	M-HEMANGIOSARCOMA	2	0	0	0	1.000	1.000	1.000	1.000
		[49]	[15]	[19]	[12]	.	.	.	.
STOMACH, NONGL		(117)	(59)	(57)	(60)	.	.	.	.
	B-SQUAMOUS CELL PAPILLOMA	0	0	0	1	0.128	.	.	0.281
		[48]	[15]	[19]	[12]	.	.	.	.
TESTIS		(120)	(59)	(59)	(59)	.	.	.	.
	B-INTERSTITIAL CELL TUMOR	1	0	0	1	0.240	1.000	1.000	0.484
		[48]	[15]	[19]	[12]	.	.	.	.
THYROID		(119)	(57)	(56)	(60)	.	.	.	.
	B-FOLLICULAR CELL ADENOMA	0	1	0	0	0.489	0.349	.	.
		[48]	[15]	[19]	[12]	.	.	.	.
	F_CELL_ADENOMA+CARCINOMA	1	1	0	0	0.742	0.578	1.000	1.000
		[48]	[15]	[19]	[12]	.	.	.	.
	M-FOLLICULAR CELL CARCINOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[48]	[15]	[19]	[12]	.	.	.	.

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 (Combined controls, low, medium and high dose groups)

Organ Name	Tumor Name	0 mg Cont N=130	10 mg Low N=70	30 mg Med N=70	100 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ADRENAL, CORTEX		(120)	(59)	(60)	(59)	.	.	.	.
	B-ADENOMA	0	0	1	0	0.344	.	0.339	.
		[53]	[27]	[26]	[16]	.	.	.	.
	B-ADENOMA, SUBCAPSULAR CELL	1	0	0	0	1.000	1.000	1.000	1.000
		[53]	[27]	[26]	[16]	.	.	.	.
ADRENAL, MEDULL		(117)	(57)	(57)	(58)	.	.	.	.
	B-PHEOCHROMOCYTOMA	0	0	1	0	0.344	.	0.339	.
		[53]	[27]	[26]	[16]	.	.	.	.
CERVIX		(100)	(50)	(56)	(57)	.	.	.	.
	B-GRANULAR CELL TUMOR	1	0	0	0	1.000	1.000	1.000	1.000
		[53]	[27]	[26]	[16]	.	.	.	.
	B-LEIOMYOMA	1	1	0	1	0.269	0.547	1.000	0.540
		[54]	[27]	[26]	[16]	.	.	.	.
	B-POLYP,ENDOMETRIAL STROMAL	1	0	2	0	0.443	1.000	0.264	1.000
		[53]	[27]	[26]	[16]	.	.	.	.
	M-CARCINOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[54]	[27]	[26]	[16]	.	.	.	.
	M-LEIOMYOSARCOMA	4	1	0	1	0.589	0.866	1.000	0.860
		[54]	[27]	[26]	[16]	.	.	.	.
DUODENUM		(116)	(59)	(55)	(58)	.	.	.	.
	B-ADENOMA	0	0	1	0	0.344	.	0.339	.
		[53]	[27]	[26]	[16]	.	.	.	.
HARDERIAN GLAND		(117)	(60)	(60)	(56)	.	.	.	.
	B-ADENOMA	8	2	0	1	0.875	0.893	1.000	0.972
		[55]	[28]	[26]	[16]	.	.	.	.
HEMATO NEOPLASI		(120)	(60)	(60)	(59)	.	.	.	.
	M-LYMPHOMA	24	13	15	5	0.840	0.483	0.391	0.988
		[60]	[33]	[33]	[19]	.	.	.	.
	M-SARCOMA, HISTIOCYTIC	6	2	1	2	0.425	0.792	0.945	0.783
		[56]	[28]	[26]	[16]	.	.	.	.
LIVER		(120)	(60)	(60)	(59)	.	.	.	.
	B-HEMANGIOMA	0	0	0	1	0.131	.	.	0.323
		[53]	[27]	[26]	[16]	.	.	.	.
	HEMANGIOMA+HEMANGIOSARCOMA	2	1	0	1	0.388	0.697	1.000	0.690
		[54]	[28]	[26]	[16]	.	.	.	.
	M-CARCINOMA, HEPATOCELLULAR	0	1	0	1	0.131	0.328	.	0.323
		[53]	[27]	[26]	[16]	.	.	.	.
	M-HEMANGIOSARCOMA	2	1	0	0	0.920	0.697	1.000	1.000
		[54]	[28]	[26]	[16]	.	.	.	.

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

Organ Name	Tumor Name	0 mg Cont N=130	10 mg Low N=70	30 mg Med N=70	100 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
LUNG		(120)	(60)	(60)	(59)	.	.	.	.
	ADENOMA+CARCINOMA	18	13	10	8	0.212	0.173	0.489	0.636
		[57]	[31]	[28]	[18]	.	.	.	.
	B-ADENOMA, BRONCHIOLAR-ALVEO	12	10	7	4	0.473	0.155	0.477	0.817
		[55]	[30]	[27]	[16]	.	.	.	.
	M-CARCINOMA, BRONCHIOLAR-ALV	6	3	4	4	0.093	0.603	0.455	0.412
		[55]	[28]	[26]	[17]	.	.	.	.
MAMMARY, FEMALE		(95)	(49)	(44)	(55)	.	.	.	.
	B-FIBROADENOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[53]	[27]	[26]	[16]	.	.	.	.
	M-CARCINOMA	2	1	0	3	0.030	0.697	1.000	0.187
		[54]	[28]	[26]	[17]	.	.	.	.
OVARY		(116)	(57)	(57)	(56)	.	.	.	.
	B-ANGIOMA	2	0	1	0	0.728	1.000	0.711	1.000
		[54]	[27]	[26]	[16]	.	.	.	.
	B-PAPILLARY CYSTADENOMA	5	3	3	0	0.879	0.515	0.554	1.000
		[54]	[28]	[26]	[16]	.	.	.	.
	B-SERTOLIFORM ADENOMA	1	1	0	0	0.816	0.550	1.000	1.000
		[53]	[28]	[26]	[16]	.	.	.	.
	M-GRANULOSA/THECA CELL TUMOR	0	0	1	0	0.344	.	0.339	.
		[53]	[27]	[26]	[16]	.	.	.	.
	M-HEMANGIOSARCOMA	0	0	0	1	0.138	.	.	0.323
		[53]	[27]	[26]	[17]	.	.	.	.
	M-SARCOMA, NOS	1	0	0	0	1.000	1.000	1.000	1.000
		[53]	[27]	[26]	[16]	.	.	.	.
OVIDUCT		(115)	(57)	(58)	(58)	.	.	.	.
OVIDUCT	B-PAPILLARY CYSTADENOMA	0	0	1	0	0.344	.	0.339	.
		[53]	[27]	[26]	[16]	.	.	.	.
PANCREAS		(118)	(60)	(60)	(59)	.	.	.	.
	B-ADENOMA, ISLET CELL	0	0	0	1	0.131	.	.	0.323
		[53]	[27]	[26]	[16]	.	.	.	.
PITUITARY		(108)	(60)	(56)	(53)	.	.	.	.
	B-ADENOMA	3	2	0	0	0.946	0.526	1.000	1.000
		[54]	[27]	[26]	[16]	.	.	.	.
SPLEEN		(120)	(60)	(60)	(58)	.	.	.	.
	M-HEMANGIOSARCOMA	0	2	1	0	0.472	0.106	0.339	.
		[53]	[28]	[26]	[16]	.	.	.	.

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

Organ Name	Tumor Name	0 mg Cont N=130	10 mg Low N=70	30 mg Med N=70	100 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
STOMACH, GL		(120)	(59)	(60)	(59)	.	.	.	.
	M-OSTEOSARCOMA	0	1	0	0	0.569	0.328	.	.
		[53]	[28]	[26]	[16]	.	.	.	.
URINARY BLADDER		(117)	(57)	(58)	(57)	.	.	.	.
	B-MESENCHYMAL TUMOR	1	0	0	1	0.246	1.000	1.000	0.543
		[53]	[27]	[26]	[16]	.	.	.	.
UTERUS		(120)	(59)	(60)	(58)	.	.	.	.
	B-ADENOMA	2	2	2	0	0.695	0.398	0.417	1.000
		[53]	[28]	[26]	[16]	.	.	.	.
	B-ENDOMETRIAL STROMAL POLYP	1	1	0	1	0.272	0.550	1.000	0.543
		[53]	[27]	[26]	[16]	.	.	.	.
	M-CARCINOMA	0	0	0	1	0.131	.	.	0.323
		[53]	[27]	[26]	[16]	.	.	.	.
	M-ENDOMETRIAL STROMAL SARCOM	0	1	0	0	0.569	0.328	.	.
		[53]	[28]	[26]	[16]	.	.	.	.
	M-HEMANGIOSARCOMA	1	1	0	2	0.077	0.550	1.000	0.251
		[53]	[28]	[26]	[18]	.	.	.	.
	M-LEIOMYOSARCOMA	2	0	1	0	0.728	1.000	0.711	1.000
		[54]	[27]	[26]	[16]	.	.	.	.

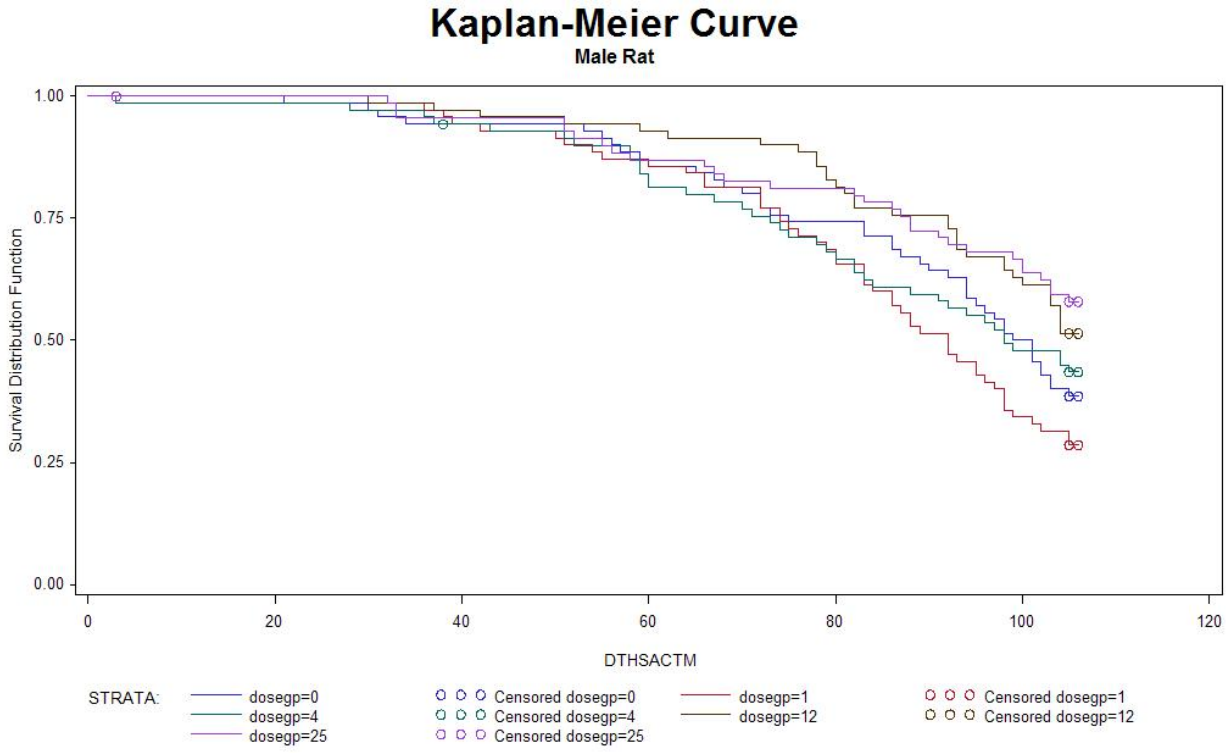
Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

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

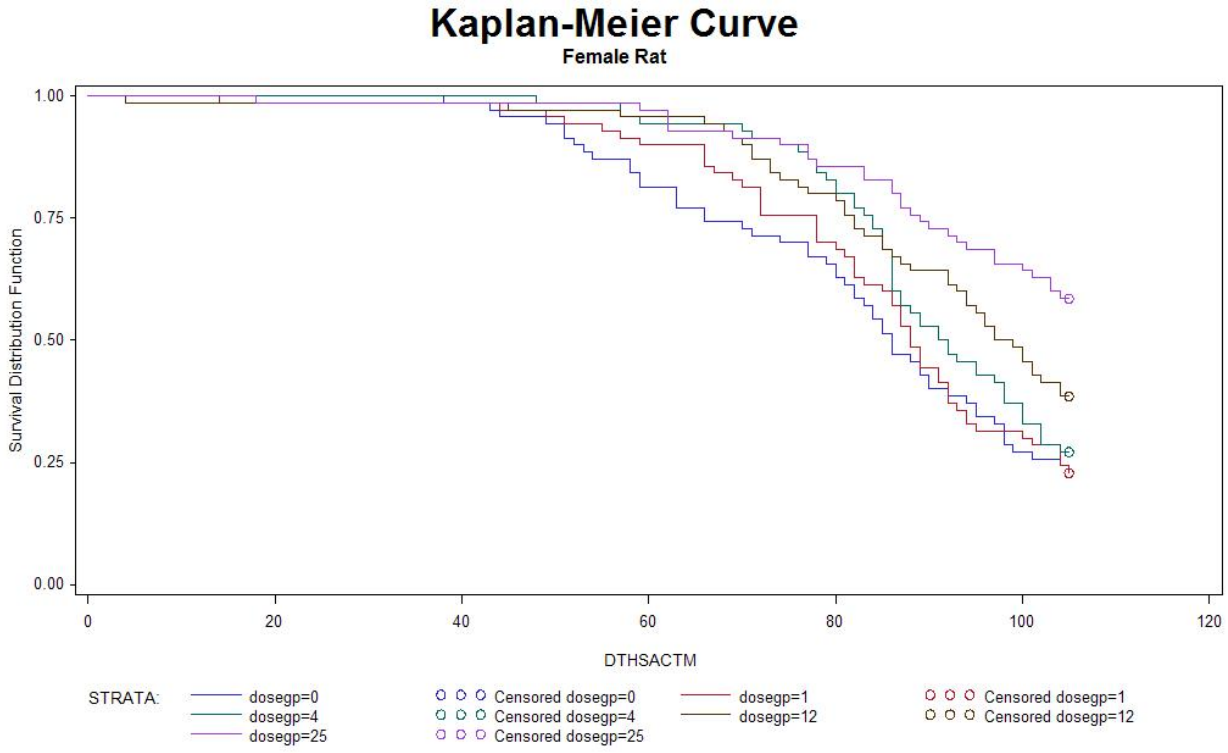
Male Rats (two controls, low, medium and high dose groups)



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

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

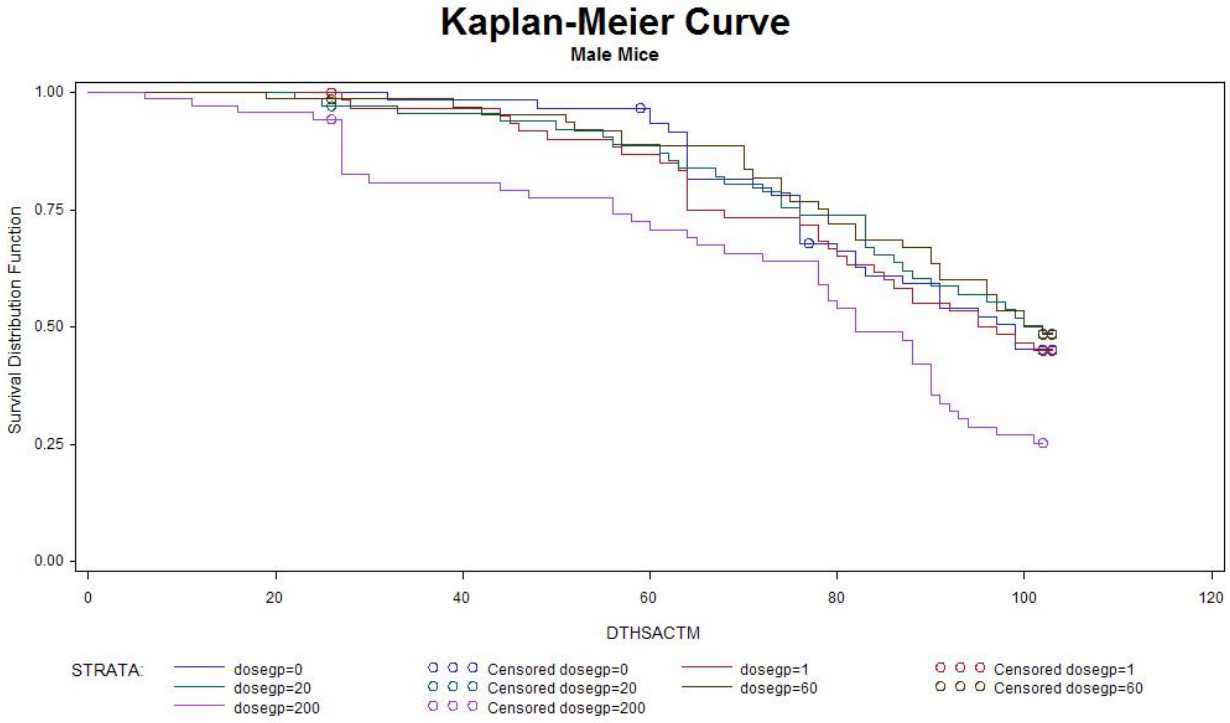
Female Rats (two controls, low, medium and high dose groups)



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

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

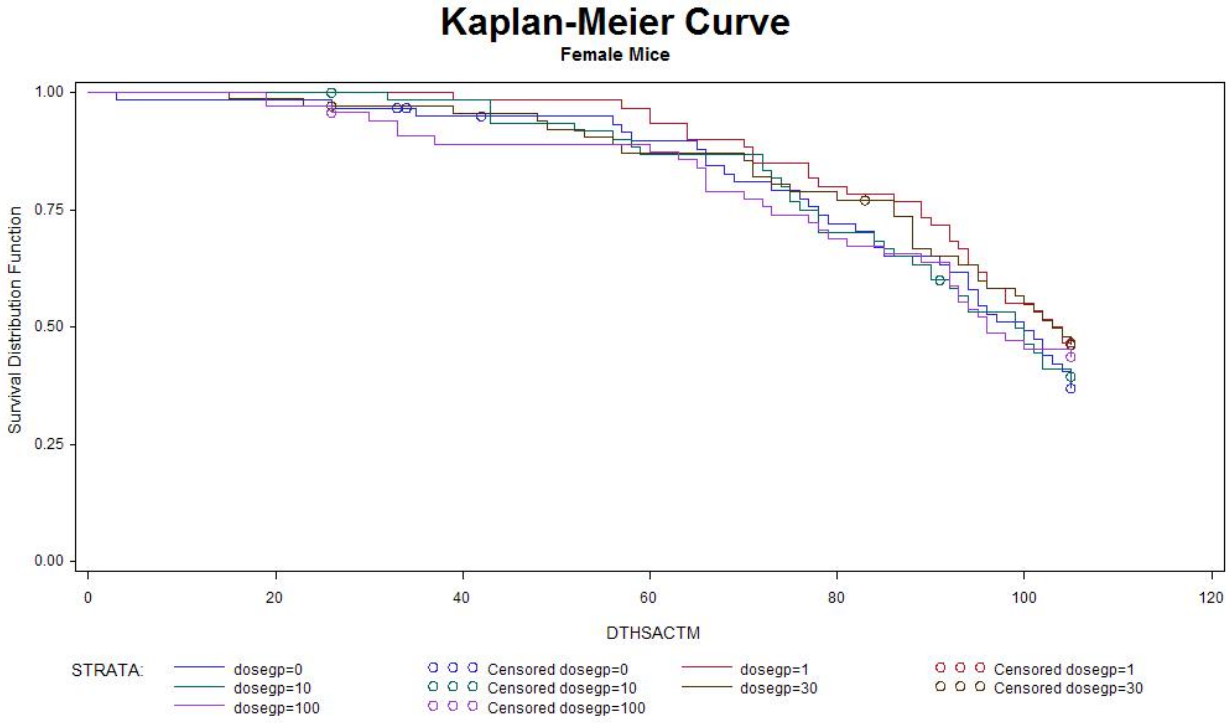
Male Mice (two controls, low, medium and high dose groups)



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

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

Female Mice (two controls, low, medium and high dose groups)



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

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/s/

MIN MIN
09/24/2014

KARL K LIN
09/24/2014
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 #:	206-627
Drug Name:	Hysingla ER (hydrocodone bitartrate) extended-release tablet
Indication(s):	Management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time
Applicant:	Purdue Pharma. L.P.
Date(s):	Letter date: April 28, 2014 PDUFA date: October 28, 2014
Review Priority:	Priority
Biometrics Division:	II
Statistical Reviewer:	Yan Zhou, Ph.D.
Concurring Reviewer:	Janice Derr, Ph.D.
Medical Division:	Division of Anesthesia , Analgesia and Addiction Products
Clinical Team:	Medical Officer: Jackie Spaulding, M.D. Medical Team Leader: Ellen Fields, M.D. Deputy Division Director: Sharon Hertz, M.D.
Project Manager:	Dominic Chiapperino
Keywords:	NDA review, clinical studies

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1. EXECUTIVE SUMMARY

Purdue Pharma. L.P. has submitted a New Drug Application (NDA) for Hysingla (hydrocodone bitartrate) extended-release (ER) tablets seeking an indication for management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. Based on my review, I believe that the results from the Phase 3 study provided evidence that Hysingla ER has an analgesic effect in the desired indication in comparison to placebo.

The submission contained 14 Phase 1 studies and two Phase 3 studies. My review focuses only on one Phase 3 study (Study HYD3002) which was a multicenter, double-blind, placebo-controlled, randomized-withdrawal design study evaluating the efficacy and safety of Hysingla ER in subjects with moderate to severe chronic low back pain. Subjects who tolerated and achieved adequate analgesia with Hysingla ER by the end of the open-label run-in period were then randomized either to continue on their optimal dose of Hysingla ER or to take placebo for 12 weeks. The Hysingla ER doses included in this study were 20, 40, 60, 80 and 120 mg once daily. Supplemental analgesic medication (immediate-release (IR) oxycodone) was permitted during the period of the study.

The primary efficacy variable was the weekly mean pain intensity (PI) score during the double-blind (DB) period. The causal estimand (i.e., primary efficacy parameter) was the difference in weekly mean PI score between the placebo and Hysingla ER treatment groups at week 12 for subjects in the full analysis population (FAP), while the FAP included all randomized subjects who took at least 1 dose of DB study drug.

Usually, in chronic pain studies, there are high percentages of subjects who discontinue the study early due to various reasons. In Study HYD3002, there were 23% and 28% of subjects in the Hysingla ER and placebo arm who discontinued the study early in the DB period. The current approach favored by the division is that a drug intended to treat chronic pain is not efficacious if subjects cannot stay on the treatment for the trial duration. Thus, strategies to handle missing data should not attribute any treatment benefit to subjects discontinuing from the study. In July 2010, the National Academy of Sciences (NAS) released a report on the prevention and treatment of missing data. The NAS report discourages single imputation methods. In light of the NAS report, the applicant's primary analysis utilized a mixed effects model with repeated measures (MMRM) incorporating a pattern mixture model (PMM) framework to account for missing data. Using the proposed framework, the week 12 treatment estimate was derived based on three patterns defined by the disposition status of patients: completing the study, discontinuing the study due to an adverse event (AE) or American Speech-Language Hearing Association (ASHA) related event, or discontinuing the study due to other reasons. The primary comparison between Hysingla ER and placebo was then based on a weighted average of the estimated mean PI scores for three patterns of subjects, while weight was the proportion of each pattern of subjects within a treatment. The primary analysis method had a desirable feature in that a bad outcome was attributed to subjects that discontinued the study due to AEs. The method additionally account for sources of variability introduced by different patterns of missing data. The week 12 mean PI score for the group of subjects who discontinued due to an AE or ASHA related event was estimated by the least square (LS) mean at the screening baseline from the MMRM model. This can be considered analogous to the baseline observation carried forward

(BOCF) imputation method. Similarly, the week 12 mean PI score for the group of subjects who discontinued due to other reasons was estimated by the average of the LS means at weeks 4 through 8 from the MMRM model. This can be considered analogous to the last observation carried forward (LOCF) imputation method. Overall, the primary analysis method can be viewed as a hybrid BOCF/LOCF imputation method. Therefore, the results were similar in the primary analysis and the sensitivity analysis where the BOCF/LOCF was utilized to handle the missing PI scores.

In my review, I also conducted a cumulative responder analysis of the change in PI from the screening baseline to the end of the DB period. This methodology may address some of the concerns outlined in the NAS report.

In the study, subjects were allowed to continue staying in the study and collecting their PI scores through week 12 regardless of whether they discontinued taking their randomized study drug (defined as retrieved dropouts). To address concerns that the use of subsequent analgesic medications after discontinuation for retrieved dropouts may result in better pain scores at week 12 compared to those that continue the study treatment, the retrieved dropout data were used in the sensitivity analyses, instead of the primary analysis.

Based on my review, I concluded that Hysingla ER reduced the pain intensity in subjects with low back pain when compared to placebo.

2. INTRODUCTION

2.1 Overview

Hydrocodone bitartrate (HYD) is currently marketed in the United States of American in combination with nonopiate analgesic drugs (e.g., acetaminophen, aspirin, and ibuprofen). Immediate-release hydrocodone combination products (e.g., Vicodin) contribute significantly to the epidemic of prescription opioid abuse. Purdue Pharma. L.P. is currently developing Hysingla ER, an extended-release HYD product with abuse deterrent properties. The extended-release formulation will allow dosing every 24 hours which supports improved convenience and compliance for patients taking HYD. As a single-entity opioid formulation, HYD dosing will not be limited by a nonopioid component, thus permitting treatment of chronic pain that requires higher total daily HYD doses. The applicant believes that the multiple dosage strengths planned for HYD will allow for easy titration to effective pain control.

The clinical development program of Hysingla ER was discussed between the agency and the applicant under IND 59,175.

In the End-of-Phase 2 meeting dated May 4, 2011, the agency stated the following:

- From Weeks 3 through 12 of the double-blind treatment phase, subjects in both treatment arms will be allowed a maximum daily IR hydrocodone dose of 10 mg (5 mg twice daily) as rescue medication for breakthrough low back pain. Restricting rescue medication use to this limit for patients with chronic moderate to severe pain will likely result in a substantial number of dropouts. As noted in the National

Academy of Sciences (NAS) Report on Prevention and Treatment of Missing Data in Clinical Trial (http://www nap.edu/catalog.php) efforts should be made to retain patients in clinical studies in order to minimized dropouts and missing data. Therefore, we strongly urge you to re-consider the limitation on rescue medication use.

- Your defined estimand of the difference in means for "average pain over the last 24 hours" score between the placebo and HYD treatment groups at Week 12 for all randomized subjects is acceptable. We acknowledge that this estimand reflects the initially assigned treatment as well as subsequent treatments received after discontinuation for retrieved dropouts.
- The proposed analysis approach appears to have a desirable feature in that a bad outcome is attributed to patients that discontinue the study due to AEs. The method additionally appears to account for sources of variability introduced by missing data. Although we cannot be certain which methodologies will be most appropriate for analgesic trials at this time, your proposed seems reasonable and we encourage you to proceed.

  Address the following:

  1. Provide a justification for your assumption, though not explicitly stated, that patients who drop out due to reasons other than AEs have responses similar to the average response at Week 2 and Week 4.
  2. You must thoroughly ascertain and document the reason for discontinuation for dropouts and also thoroughly document medications received after discontinuation for retrieved dropouts.
  3. Currently, a patient who discontinues the study treatment due to an AE may be included in the analysis as a completer if Week 12 data is collected after he/she drops out. Thus, your weighted average estimate will implicitly assign the mean pain score at Week 12 to this patient. This strategy is consistent with the intention-to-treat principle. However, concern will arise if the data from the study suggest that the use of subsequent analgesic medications after discontinuation for retrieved dropouts results in better pain scores at Week 12 compared to those that continue the study treatment.
- Based on the assumptions, the sample size calculation appears reasonable. However, we notice that the sample size is larger than normally seen in analgesic trials and caution that the magnitude of the beneficial effect will be weighed against risk.

In the advice/information request (IR) letter dated September 27, 2012, the agency made the following comments:

- The protocol states that the sample size may be adjusted if the assumptions underlying the simulations are thought to be substantially different. Clarify when the sample size will be adjusted.

In the Pre-NDA meeting dated July 10, 2013, the agency made the following comments:

- Similar to our responses in the End-of-Phase 2 meeting dated May 4, 2011, you should provide a justification for that patients who drop out due to reasons other than AEs have responses similar to the average at Week 3, Week 4 and Week 5.
- You have proposed to conduct subgroup analyses based on age (< 65 and ≥ 65 years), dose level (HYD 20 mg, 40 mg, 60 mg, 80 mg and 120 mg), baseline opioid status (naïve and experienced) and prior hydrocodone product. Also conduct subgroup analyses for gender and race.

The submission contained 14 Phase 1 studies and two Phase 3 studies. As Study HYD3003 is a Phase 3, open-label, safety study, my review focuses only on the Phase 3 study (Study HYD3002) which was a multicenter, DB, placebo-controlled, randomized-withdrawal design study evaluating the efficacy and safety of Hysingla ER in subjects with moderate to severe chronic low back pain.

Table 1: List of studies included in this review

Study Number (Dates Conducted)	Number of Centers (Locations)	Sample Size	Type of Control	Design
HYD3002 (03/2012 – 09/2013)	US: 94 sites	Enrolled/screened: 1927 Run-in period: 905 Randomization: Hysingla ER: n=296 Placebo: n=292	Placebo	multicenter, randomized, DB, placebo-controlled study with an open-label run-in period in subjects with moderate to severe chronic low back pain

Source: Reviewer's analysis

2.2 Data Sources

All data was supplied electronically as SAS transport files and can be found at the following location in the CDER electronic document room:
\\Cdsesub1\evsprod\NDA206627\0000\m5\datasets\hyd3002

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The electronic data and define documents submitted by the applicant were of sufficient quality to allow a thorough review. I was able to locate the primary outcome as well as the secondary variables of interest.

3.2 Evaluation of Efficacy

My efficacy review focuses on the Study HYD3002 which was submitted as part of the current NDA.

Study Design and Endpoints

Study HYD3002 was a Phase 3, multicenter, randomized, DB, placebo-controlled, enriched study evaluating the efficacy and safety of Hysingla ER 20 to 120 mg once daily in subjects with moderate to severe chronic low back pain uncontrolled by their current analgesic regimen. The study consisted of a baseline period, an open-label run-in period, a DB period and a follow-up period. After the baseline period, subjects received open-label Hysingla ER titrated to an optimal dose up to 45 days. To achieve adequate pain control, Hysingla ER dose was allowed to be increased once every 3 to 5 days until a stabilized and tolerable dose was identified. Subjects who demonstrated adequate analgesic benefit and acceptable tolerability with HYD treatment during the open-label run-in period were then randomized in a 1:1 ratio to receive their optimal Hysingla ER dose or placebo for 12 weeks. Randomization was stratified by subjects' opioid experience prior to the study and the stable HYD dose they received at the end of the open-label run-in period. Study visits occurred at weeks 1, 2, 4, 8 and 12 of the DB period. In order to

minimize/prevent opioid withdrawal symptoms, subjects who were randomized to the placebo treatment group were tapered from their titrated dose to placebo during the first 2 weeks of the DB period. For tolerability reasons, 1 down titration was permitted subsequent to the 2-week taper period for subjects randomized to HYD 40 mg, 60 mg, 80 mg, 120 mg, or the corresponding matching placebo. If after a down titration subjects did not achieve adequate analgesia, 1 up titration back to the randomized dose was allowed. Supplemental medication (IR oxycodone) was permitted in the study.

The primary efficacy variable was the weekly mean PI score using the daily diary "average pain over the last 24 hours" scores recorded by the subject (on an 11-point NRS) each evening during the DB period. Secondary efficacy endpoints included medical outcome study sleep scale, patient global impression of change, responder to the treatment and other efficacy variables. None of them was identified as a key secondary endpoint.

Statistical Methodologies

In the study, the causal estimand (i.e., primary efficacy parameter) was defined as the difference in weekly mean PI score between the placebo and Hysingla ER treatment groups at week 12 for subjects in the full analysis population (FAP), while the FAP included all randomized subjects who took at least 1 dose of DB study drug.

The applicant utilized a mixed effects model with repeated measures (MMRM) analysis of the primary efficacy variable incorporating a pattern mixture model (PMM) framework to account for missing data. The method can be described as the following four steps: (1) all observed data collected while subjects were exposed to the DB treatment were firstly analyzed using a MMRM model. The MMRM model included treatment, time and prior opioid experience status as fixed effects. The baseline and pre-randomization mean PI scores were incorporated as the dependent variables; (2) within each treatment, subjects were categorized into three patterns: completing the study; discontinuing the DB treatment due to an AE or ASHA related event; or discontinuing the DB treatment due to all other reasons. For each pattern, the mean PI score at week 12 was then estimated differently. For subjects discontinuing the DB treatment due to an AE or ASHA related event, missing mean PI score was replaced with the least square (LS) mean PI score at the screening baseline that was estimated from the MMRM model. For subjects discontinuing due to other reasons, missing mean PI score was replaced with an arithmetic mean of the weekly LS mean PI scores at week 4, 5, 6, 7 and 8 that were estimated from the MMRM model. For completers, the estimated LS mean at week 12 was used; (3) within each treatment, the week 12 treatment estimate was a weighted average of the estimated mean PI scores for subjects categorized by the three patterns, while weight was the proportion of each group of subjects within a treatment; (4) Finally, the week 12 treatment estimates between two treatment groups were compared.

The current approach favored by the division is that a drug intended to treat chronic pain is not efficacious if subjects cannot stay on the treatment for the trial duration. Thus, strategies to handle missing data should not attribute any treatment benefit to subjects discontinuing from the study. The primary analysis method had a desirable feature in that a bad outcome was attributed to subjects that discontinued the study due to AEs. The method additionally account for sources

of variability introduced by different patterns of missing data. The week 12 mean PI score for the group of subjects who discontinued due to an AE or ASHA related event was estimated by the LS mean at the screening baseline from the MMRM model. This can be considered analogous to the BOCF imputation method. Similarly, the week 12 mean PI score for the group of subjects who discontinued due to other reasons was estimated by the average of the LS means at weeks 4 through 8 from the MMRM model. This can be considered analogous to the LOCF imputation method. Therefore, in my opinion, the primary analysis method can be viewed as a hybrid BOCF/LOCF imputation method. To compare the primary analysis method with the method using the BOCF/LOCF imputation method, I also conducted sensitivity analyses in which the week 12 mean PI scores were analyzed by the analysis of covariance (ANCOVA) model with treatment and prior opioid experience status as factors and screening baseline and randomization baseline as covariates.

In my review, I also conducted a cumulative responder analysis of the change in PI from the screening baseline to the end of the DB period and dropouts were classified as non-responders. This methodology may address some of the concerns outlined in the NAS report as it defines an outcome that can be ascertained in a high proportion of participants by incorporating dropout as part of the outcome. I conducted two rank-based non-parametric tests: Wilcoxon Rank Sum and Van der Waerden test. Both tests are more sensitive to the differences in the left tails of the distributions of pain improvements, in which we have more interests.

In the study, subjects were allowed to continue staying in the study and collecting their PI scores through week 12 regardless of whether they discontinued taking their randomized study drug (defined as retrieved dropouts). To address concerns that the use of subsequent analgesic medications after discontinuation for retrieved dropouts may result in better pain scores at week 12 compared to those that continue the study treatment, the retrieved dropout data were used in the sensitivity analyses, instead of the primary analysis.

Patient Disposition, Demographic and Baseline Characteristics

The demographic and baseline characteristics for all treated subjects are presented in the appendix. The majority of the subjects were white (68%), and approximately 57% of all subjects were female. The mean age was 49 years. The demographic and baseline characteristics were generally balanced between two treatment groups.

The disposition of subjects is shown in Table 2. The reasons for discontinuation are shown by phase. There were 35% of the subjects who discontinued early in the open-label titration phase. In the DB maintenance phase, the dropout rates of the Hysingla ER and placebo groups were 23% and 28% respectively. The most common reasons for early discontinuation in the Hysingla ER group were adverse event followed by lack of efficacy, while the most common reason for study discontinuation in the placebo group was lack of efficacy.

Table 2: Subject disposition in Study HYD3002 – Number (%) of Subjects

	Run-in Period (N=905)			Double-blind Period (N=592)		
	Non-randomized (NN=312)	Randomized (NN=593)	Overall (NN=905)	Placebo[a] (NN=292)	HYD (NN=296)	Overall (NN=592)
Completed Period on Study Drug[b], n (%)		**592 (100)**	**592 (65)**	**210 (72)**	**229 (77)**	**439 (74)**
Discontinued Study Drug - All Cases, n (%)[c]	**312 (100)**	**1 (< 1)**	**313 (35)**	**82 (28)**	**67 (23)**	**153 (26)**
Adverse Event	94 (30)	0	94 (10)	10 (3)	17 (6)	28 (5)
ASHA-Related Event[e]	3 (1)	0	3 (< 1)	1 (< 1)	1 (< 1)	2 (< 1)
Subject's Choice	49 (16)	0	49 (5)	14 (5)	15 (5)	29 (5)
Lost to Follow-up	19 (6)	0	19 (2)	3 (1)	5 (2)	9 (2)
Lack of Therapeutic Effect	46 (15)	0	46 (5)	44 (15)	16 (5)	60 (10)
Confirmed or Suspected Diversion	23 (7)	0	23 (3)	3 (1)	2 (1)	6 (1)
Administrative	20 (6)	1 (< 1)	21 (2)	7 (2)	11 (4)	19 (3)
Did Not Qualify for Double-blind Period	59 (19)	–	59 (7)	–	–	–
Discontinued Study Drug and Study Simultaneously, n (%)				**51 (17)**	**46 (16)**	**101 (17)**
Adverse Event				6 (2)	8 (3)	15 (3)
ASHA-Related Event[e]				0	1 (< 1)	1 (< 1)
Subject's Choice				12 (4)	15 (5)	27 (5)
Lost to Follow-up				3 (1)	5 (2)	9 (2)
Lack of Therapeutic Effect				21 (7)	7 (2)	28 (5)
Confirmed or Suspected Diversion				3 (1)	2 (1)	6 (1)
Administrative				6 (2)	8 (3)	15 (3)
Discontinued Study Drug and Stayed in Study, n (%)[d]				**31 (11)**	**21 (7)**	**52 (9)**
Adverse Event				4 (1)	9 (3)	13 (2)
ASHA-Related Event[e]				1 (< 1)	0	1 (< 1)
Subject's Choice				2 (1)	0	2 (< 1)
Lack of Therapeutic Effect				23 (8)	9 (3)	32 (5)
Confirmed or Suspected Diversion				0	0	0
Administrative				1 (< 1)	3 (1)	4 (1)

Source: Clinical Study Report Table 14.1.1.2.1

In the DB phase, there were 7% of subjects in the Hysingla ER group and 11% of subjects in the placebo group who discontinued study drug but stayed in the study. There were 5% of the Hysingla ER group and 4% of the placebo group who discontinued study drug and study simultaneously due to the reason of subject's choice. An IR dated June 16, 2014 was sent out to request the specific reasons for subject's choice. The applicant responded on June 18, 2014 and provided the following table which summarized sub-categories for the reason of subject's choice.

Table 3: Subjects discontinued study drug and study simultaneously due to the reason of "subject's choice" (Study HYD3002, DB phase)

	Total	HYD	Placebo
Number of subjects in any sub-category	27	15	12
Withdrew consent	9	6	3
Family matter	4	2	2
Moved away	4	1	3
Schedule conflict	3	2	1
Out of town	3	2	1
Transportation	2	1	1
Wanted to return to prior pain medication	2	1	1

Source: response to IR, sequence 0006 Table 1

Another IR dated June 26, 2014 was sent out to request additional information for subjects discontinuing study drug due to the reason of subject's choice, including the last pain score, the last observed AE and drug accountability issues. The applicant responded on July 8, 2014 and stated that an adjudication committee reviewed all cases designated as "subject's choice" to assess whether they should be reclassified as AE or lack of efficacy. In all but 4 cases (Table 4), the committee agreed with the reason entered by the investigator on the clinical report form. As there was only one subject whose reason of discontinuation should be reclassified from subject's choice to lack of efficacy, it would not change the efficacy analysis results significantly.

Table 4: Discrepancies in reasons for discontinuation (Study HYD3002, DB phase)

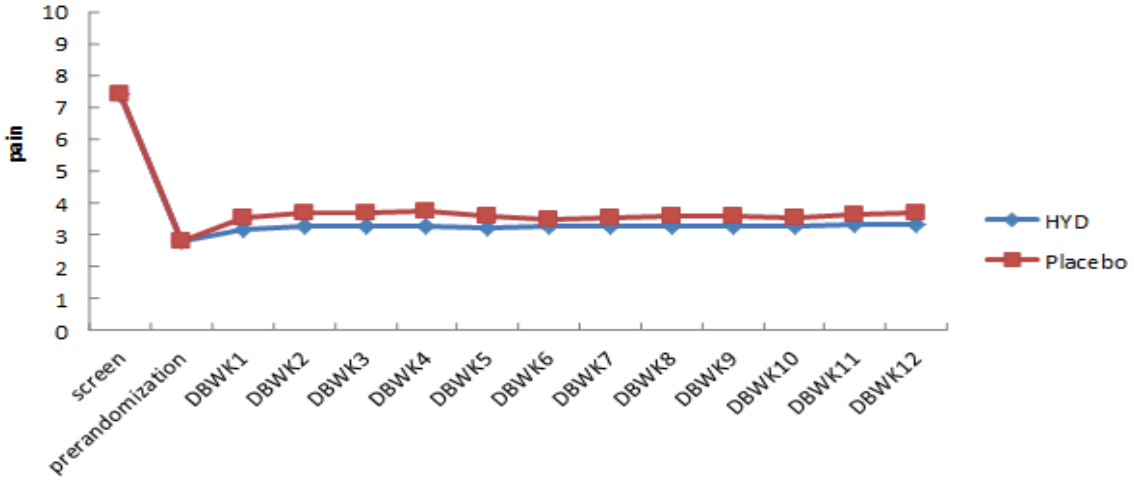
	Reason for Discontinuation	
USUBJID	CRF	Review Panel Consensus
HYD3002-0437A-2059002	Administrative	Confirmed or suspected diversion
HYD3002-0884A-2005023	Lost to follow-up	Subject's choice
HYD3002-2197A-2086001	Subject's choice	Lack of therapeutic effect
HYD3002-2382A-2070014	Administrative	Confirmed or suspected diversion

Source: response to IR, sequence 0008

Results and Conclusions

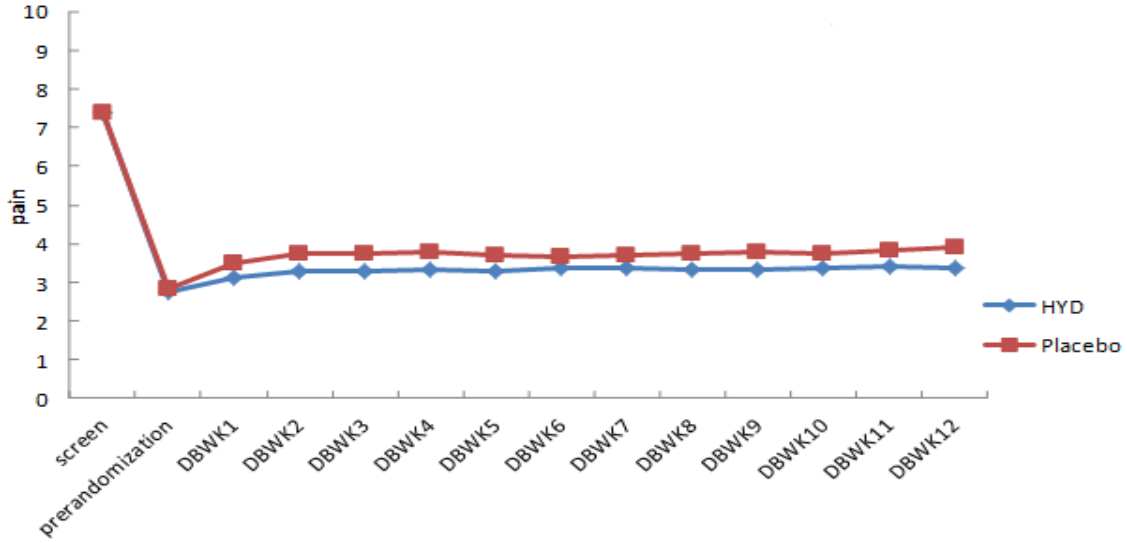
The average of the observed pain scores over time for each treatment group without retrieved dropouts is displayed in Figure 1. The overall trend of the observed PI over time is plateau after randomization and the pain curves of two treatment groups did not separate too much. Similar results demonstrated when retrieved dropouts were included to calculate average PI over time (Figure 2).

Figure 1: Average pain over time (observed pain scores without retrieved dropouts)



Source: Reviewer's analyses

Figure 2: Average pain over time (observed pain scores with retrieved dropouts)



Source: Reviewer's analyses

Of the 593 subjects randomized into the DB phase, 588 subjects received DB treatment (292 randomized to placebo and 296 randomized to Hysingla ER). Table 5 lists the number of randomized subjects in each dosage group.

Table 5: Number of randomized subjects in each dosage group

	optimal dose at the end of run-in period					total
	20 mg	**40 mg**	**60 mg**	**80 mg**	**120 mg**	
Hysingla ER	63	88	55	48	42	296
placebo	62	86	59	45	40	292
total	125	174	114	93	82	588

Source: Reviewer's analysis

I replicated the applicant's results for the primary efficacy analyses. Table 6 shows the results from the primary efficacy analyses. Using the proposed framework, the week 12 treatment estimate was derived based on three patterns defined by the disposition status of patients: completing the study, discontinuing the study due to an AE or ASHA related event, or discontinuing the study due to other reasons. The primary comparison between Hysingla ER and placebo was then based on a weighted average of the estimated mean PI scores for three patterns of subjects, while weight was the proportion of each pattern of subjects within a treatment. The primary efficacy results demonstrated Hysingla ER is statistically significant different from and superior to placebo. However, the treatment difference of 0.53 on the PI scale (0 to 10) will need to be evaluated from a clinical perspective as the significance of the test is mainly due to the large sample size.

In addition, I also conducted four sensitivity analyses:

> Sensitivity analysis 1 (all observed data): similar to the primary efficacy analysis, but retrieved dropouts were included in the analysis;
>
> Sensitivity analysis 2 (partial AE penalty): similar to the primary efficacy analysis, except for using the average of pre-randomization and screening baseline estimates for subjects who dropped out due to an AE or ASHA related event;
>
> Sensitivity analysis 3 (BOCF/LOCF without retrieved dropouts): the week 12 mean PI scores were analyzed by an ANCOVA model with treatment and prior opioid experience status as factors and screening baseline and randomization baseline as covariates. Retrieved dropouts were not included in the analysis;
>
> Sensitivity analysis 4 (BOCF/LOCF with retrieved dropouts): similar to sensitivity analysis 3, but retrieved dropouts were included in the analysis;

Sensitivity analyses results are shown in Table 7. Results are similar across all four sensitivity analyses and primary efficacy analysis. Only 9% of subjects were retrieved dropouts. Therefore, whether to include retrieved dropouts would not affect the results significantly. Furthermore, in the primary analysis, the week 12 mean PI score for the group of subjects who discontinued due to an AE or ASHA related event was estimated by the LS mean at the screening baseline from the MMRM model. This can be considered analogous to the BOCF imputation method. Similarly, the week 12 mean PI score for the group of subjects who discontinued due to other reasons was estimated by the average of the LS means at weeks 4 through 8 from the MMRM model. This can be considered analogous to the LOCF imputation method. Therefore, in my opinion, the primary analysis method can be viewed as a hybrid BOCF/LOCF imputation method and the results were similar in the primary analysis and the sensitivity analysis where the BOCF/LOCF was utilized to handle the missing PI scores.

Table 6: Primary efficacy analysis

Study Period/Week Mean Pain Intensity	Placebo[a] (N=292)	HYD (N=296)
Baseline		
n	292	296
Mean (SD)	7.4 (1.19)	7.4 (1.13)
Prerandomization		
n	291	296
Mean (SD)	2.8 (1.15)	2.8 (1.16)
Double-blind Week 12		
n	199	218
Mean (SD)	3.7 (2.04)	3.3 (1.93)
Pattern 1: Completed Week 12**		
n (%)	210 (72)	229 (77)
LS Mean (SE)	4.17 (0.131)	3.47 (0.128)
Pattern 2: Discontinued Study Drug due to Adverse Event or ASHA Related Event**		
n (%)	11 (4)	18 (6)
LS Mean (SE)	7.40 (0.048)	7.40 (0.048)
Pattern 3: Discontinued Study Drug due to Other Reasons**		
n (%)	71 (24)	49 (17)
LS Mean (SE)	3.90 (0.114)	3.38 (0.112)
Repeated Measures Analysis/Least Squares Means (SE) at Double-blind Week 12 from PMM		
LS Mean (SE)	4.23 (0.126)	3.70 (0.128)
Treatment Comparison at Double-blind Week 12		
Difference in LS means from Placebo (Mean (SE))		-0.53 (0.180)
P value vs Placebo		0.0016
95% CI for difference from Placebo		(-0.882, -0.178)

Source: Clinical Study Report Table 14.2.1.1.1 and Table 14.2.1.1.2.

To further explore the pain response profile, I also generated the continuous responder curves by treatment groups. All non-completers were classified as non-responders. My results confirmed the applicant's results. As shown in Figure 3, Hysingla ER treated subjects had consistently higher responder rates than placebo treated subjects. The applicant only compared the responder rates at 30% and 50% respectively. I conducted non-parametric tests to compare the overall responder curves between two treatment groups. In the two non-parametric tests I conducted, only subjects discontinuing from the study were assigned zero improvement while negative values were attributed to subjects who worsened. The two curves were significantly different when applying the non-parametric tests (Wilcoxon rank sums test: p-value = 0.023; Van der Waerden test: p-value = 0.026).

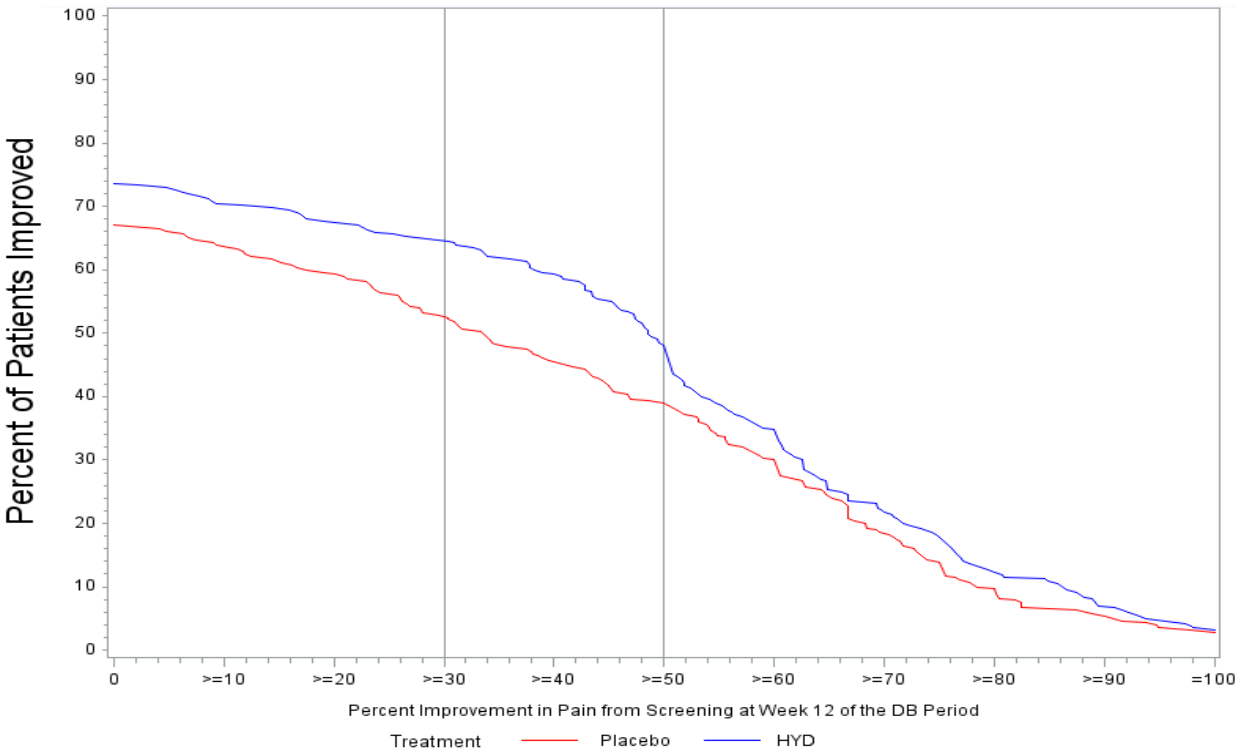
Table 7: Sensitivity analysis results

	statistics	HYD (n=296)	Placebo (n=292)	95% CI	p-value
method					
Sensitivity analysis 1	LS mean (SE)	3.5 (0.1)	4.2 (0.1)		
(all observed data)	difference (SE)	-0.6 (0.2)		(-0.9, -0.2)	0.001
Sensitivity analysis 2	LS mean (SE)	3.6 (0.1)	4.1 (0.1)		
(partial AE penalty)	difference (SE)	-0.6 (0.2)		(-0.9, -0.3)	<0.001

Sensitivity analysis 3					
(BOCF/LOCF	LS mean (SE)	3.7 (0.1)	4.3 (0.1)		
without retrieved dropouts)	difference (SE)	-0.5 (0.2)		(-0.9, -0.2)	0.002
Sensitivity analysis 4					
(BOCF/LOCF	LS mean (SE)	3.7 (0.1)	4.2 (0.1)		
with retrieved dropouts)	difference (SE)	-0.5 (0.2)		(-0.9, -0.2)	0.002

Source: Clinical Study Report Table 14.2.1.2.1, Table 14.2.1.4.1, Reviewer's results

Figure 3: Percent improvement in pain from screening baseline at week 12 of the DB period



Source: Reviewer's analyses

In the DB phase, subjects were allowed to use rescue medication (IR oxycodone 5 mg) up to 6 tablets per day depending on their randomized Hysingla ER dose. Table 8 summarizes the use of IR oxycodone tablets during the DB period by treatment group and dose group. The use of IR oxycodone medication correlated with the dosage stabilized in the end of the run-in period, with greater usage in higher dosage.

Analyses results of the other secondary efficacy endpoints were supportive to the primary analyses.

3.3 Evaluation of Safety

The evaluation of the safety data was conducted by Dr. Jackie Spaulding. The reader is referred to Dr. Spaulding's review for detailed information regarding the adverse event profile.

Table 8: Mean daily number of IR oxycodone tablets used in the DB period

	Titrated Dose					
	20 mg	**40 mg**	**60 mg**	**80 mg**	**120 mg**	**Total**
HYD (weeks 1-12)						
N	63	88	55	48	42	296
Mean (SD)	0.1 (0.3)	0.3 (0.5)	0.5 (0.7)	0.9 (1.1)	2.1 (1.7)	0.7 (1.1)
Median	0	0.1	0.1	0.5	1.9	0.1
Min, Max	0, 1.2	0, 2.4	0, 3.2	0, 3.7	0, 5.6	0, 5.6
Placebo (weeks 1-12)						
N	62	86	59	45	40	292
Mean (SD)	0.2 (0.4)	0.4 (0.6)	1.0 (0.9)	1.5 (1.4)	2.3 (1.8)	0.9 (1.2)
Median	0	0.1	0.6	1.0	2.4	0.3
Min, Max	0, 2.0	0, 2.1	0, 2.7	0, 5.4	0, 5.8	0, 5.8

Source: Clinical Study Report Table 14.2.6.2.2

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The applicant conducted the subgroup analyses by age, race, gender and body mass index (BMI) using an MMRM model. I conducted subgroup analyses with the ANCOVA model that was used in the sensitivity analysis. A hybrid BOCF/LOCF method was used to impute the missing PI scores. My subgroup analyses didn't reveal any issues that were concerning.

4.1 Gender, Race, Age, and Prior Opioid Experience

Table 9 presents subgroup analyses results. Treatment differences were consistently in favor of Hysingla ER across subgroups.

Table 9: Reviewer's subgroup analyses

	HYD		**Placebo**	
	n	**Mean (SD)**	**n**	**Mean (SD)**
Week 12 Mean Pain Intensity				
Gender				
Female	165	3.7 (2.2)	160	4.2 (2.3)
Male	120	3.7 (2.0)	120	4.3 (2.0)
Age (years)				
< 65	250	3.8 (2.1)	250	4.2 (2.2)
>= 65	35	3.0 (1.9)	30	4.4 (2.0)
Race				
White	189	4.1 (2.2)	197	4.6 (2.1)
Black	63	3.4 (1.8)	49	3.8 (2.3)
Other	33	2.1 (1.5)	34	2.8 (1.8)
Prior Opioid Experience				
Naïve	158	3.3 (2.2)	156	3.8 (2.3)
Experienced	127	4.2 (1.9)	124	4.7 (1.9)

Source: Reviewer's analyses

4.2 Other Special/Subgroup Populations

No other subgroup analyses were performed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The main statistical issue is the direct impact of dropouts on the efficacy results. The applicant applied a MMRM model incorporating a PMM framework to account for missing data. Using the proposed framework, the week 12 treatment estimate was derived based on three patterns defined by the disposition status of patients: completing the study, discontinuing the study due to an AE or ASHA related event, or discontinuing the study due to other reasons. The primary comparison between Hysingla ER and placebo was then based on a weighted average of the estimated mean PI scores for three patterns of subjects, while weight was the proportion of each pattern of subjects within a treatment. The primary analysis method had a desirable feature in that a bad outcome was attributed to subjects that discontinued the study due to AEs. The method additionally account for sources of variability introduced by different patterns of missing data. However, in my opinion, the primary analysis method can be viewed as a hybrid BOCF/LOCF imputation method.

In the study, subjects were allowed to continue staying in the study and collecting their PI scores through week 12 regardless of whether they discontinued taking their randomized study drug (defined as retrieved dropouts). As there were only 9% of subjects were retrieved dropouts in the study, whether to include retrieved dropouts or not would not affect the results significantly as shown in the sensitivity analyses.

A cumulative responder analysis was also conducted where dropouts were classified as non-responders. This methodology may address concerns outlined in the NAS report as it defines an outcome that can be ascertained in a high proportion of participants by incorporating dropout as part of the outcome. I conducted two rank-based non-parametric tests: Wilcoxon Rank Sum and Van der Waerden test. Both of these tests are more sensitive to the differences in the left tails of the distributions of responders, in which we have more interests.

5.2 Collective Evidence

The collective evidence from Study HYD3002 was in support of the efficacy of Hysingla ER in comparison to placebo. In the study, there was a statistically significant difference between the two treatment groups. This conclusion was supported by the similarity of the results from various sensitivity analyses. The secondary efficacy endpoints were also in favor of Hysingla ER. However, the treatment difference of 0.53 on the PI scale (0 to 10) will need to be evaluated from a clinical perspective.

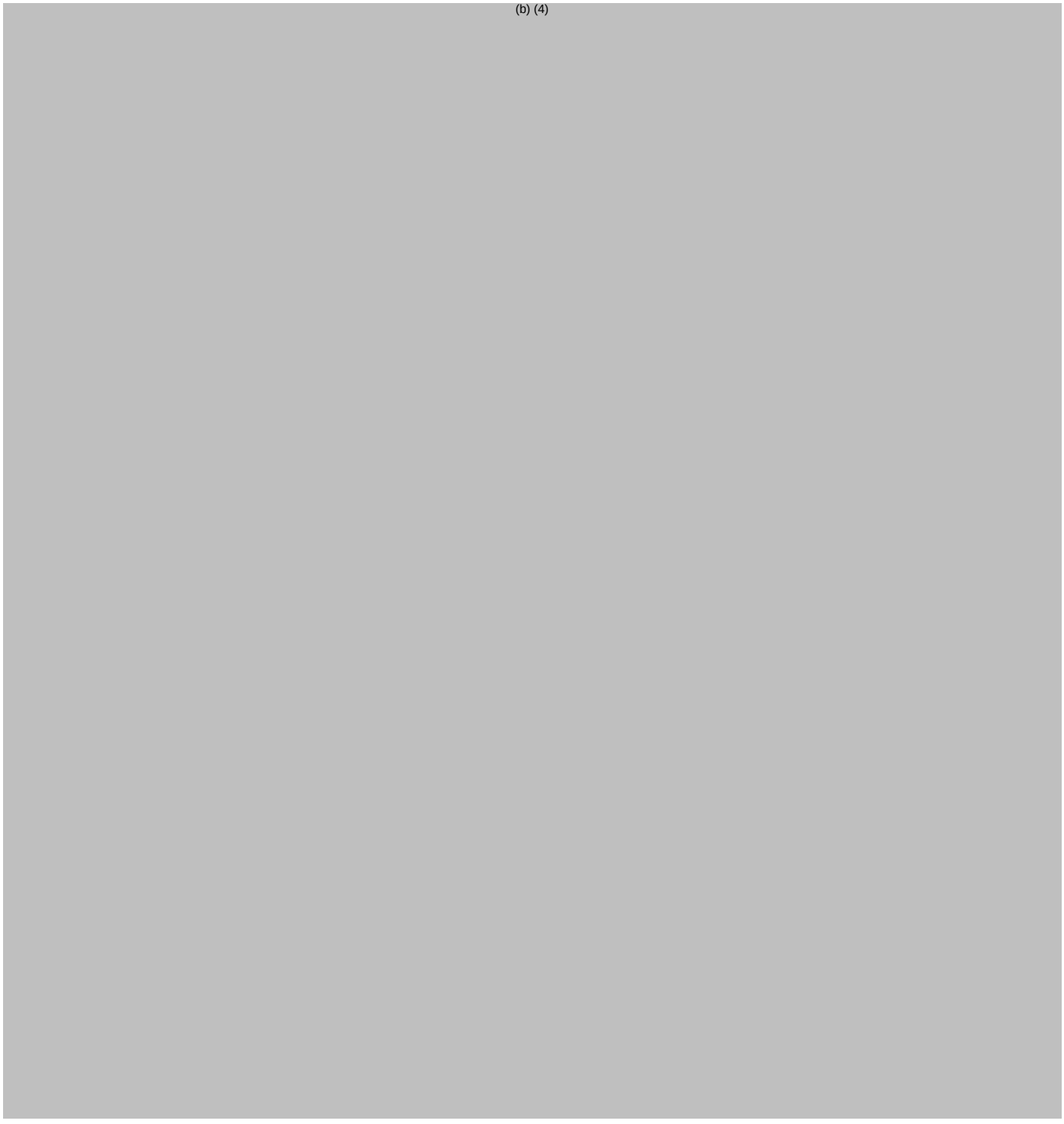
5.3 Conclusions and Recommendations

Based on my review of the Phase 3 study, I conclude that Hysingla ER was more efficacious than placebo in chronic pain reduction.

5.4 Labeling Recommendations

The applicant submitted the following wording for the clinical study section in the labeling for review:

(b) (4)



(b) (4)

I have the following general recommendation to the applicant:

- (b) (4)

Appendix

Summary of Demographics and Baseline Characteristics

Study HYD3002 (Source: Clinical Study Report Table 14.1.3.1.1)

Variable	Non-randomized (N=312)	Randomized			Total (N=905)
		Placebo[a] (N=292)	HYD (N=296)	Overall (N=588)	
Age (years)					
n	312	292	296	588	905
Mean (SD)	47.3 (13.40)	47.9 (13.23)	49.2 (13.51)	48.6 (13.38)	48.2 (13.43)
Median	47.0	49.0	50.0	50.0	49.0
Min, Max	20, 81	18, 83	18, 81	18, 83	18, 83
Age Group, n (%)					
< 65 years	275 (88)	261 (89)	260 (88)	521 (89)	798 (88)
18 - 39 years	100 (32)	78 (27)	73 (25)	151 (26)	251 (28)
40 - 64 years	175 (56)	183 (63)	187 (63)	370 (63)	547 (60)
≥ 65 years	37 (12)	31 (11)	36 (12)	67 (11)	107 (12)
65 - 74 years	29 (9)	29 (10)	29 (10)	58 (10)	89 (10)
≥ 75 years	8 (3)	2 (1)	7 (2)	9 (2)	18 (2)
Missing	0	0	0	0	0
Sex, n (%)					
Male	121 (39)	126 (43)	124 (42)	250 (43)	373 (41)
Female	191 (61)	166 (57)	172 (58)	338 (57)	532 (59)
Missing	0	0	0	0	0
Race, n (%)					
White	234 (75)	207 (71)	195 (66)	402 (68)	640 (71)
Black or African American	63 (20)	51 (17)	67 (23)	118 (20)	182 (20)
Native Hawaiian or other Pacific Islander	0	0	0	0	0
Asian	5 (2)	29 (10)	25 (8)	54 (9)	59 (7)
American Indian or Alaska Native	3 (1)	1 (< 1)	2 (1)	3 (1)	6 (1)
Other	7 (2)	4 (1)	7 (2)	11 (2)	18 (2)
Missing	0	0	0	0	0
Ethnicity, n (%)					
Hispanic or Latino	37 (12)	45 (15)	58 (20)	103 (18)	140 (15)
Not Hispanic or Latino	275 (88)	247 (85)	238 (80)	485 (82)	765 (85)
Missing	0	0	0	0	0
Height (cm)					
n	312	292	296	588	905
Mean (SD)	168.88 (9.788)	168.99 (10.337)	169.73 (10.571)	169.36 (10.453)	169.21 (10.211)
Median	167.60	169.20	168.90	168.90	168.70
Min, Max	144.8, 203.0	142.0, 205.7	147.3, 200.7	142.0, 205.7	142.0, 205.7
Baseline Weight (kg)					
n	312	292	296	588	905
Mean (SD)	87.10 (23.423)	90.12 (23.383)	89.77 (22.695)	89.94 (23.020)	88.94 (23.191)
Median	83.90	87.45	88.50	87.75	86.20
Min, Max	45.3, 162.4	41.1, 172.4	45.4, 172.5	41.1, 172.5	41.1, 172.5
Body Mass Index (kg/m^2)					
n	312	292	296	588	905
Mean (SD)	30.483 (7.6596)	31.558 (7.7681)	31.191 (7.6854)	31.373 (7.7222)	31.049 (7.7010)
Median	29.470	31.000	29.890	30.435	30.040
Min, Max	16.26, 61.88	13.72, 57.80	16.56, 64.92	13.72, 64.92	13.72, 64.92
Opioid Experienced[b], n (%)					
Experienced	169 (54)	128 (44)	131 (44)	259 (44)	431 (48)
Naïve	143 (46)	164 (56)	165 (56)	329 (56)	474 (52)
Urine Drug Screen Results[c], n (%)					
Confirmed Positive	126 (40)	77 (26)	66 (22)	143 (24)	270 (30)
Unconfirmed Positive	1 (< 1)	0	0	0	1 (< 1)
Negative	185 (59)	215 (74)	230 (78)	445 (76)	634 (70)

Variable	Non-randomized (N=312)	Randomized			Total (N=905)
		Placebo[a] (N=292)	HYD (N=296)	Overall (N=588)	
Baseline Average Pain over Last 14 Days					
n	307	290	295	585	897
Mean (SD)	7.2 (1.17)	7.1 (1.22)	7.2 (1.20)	7.2 (1.21)	7.2 (1.20)
Median	7.0	7.0	7.0	7.0	7.0
Min, Max	3, 10	2, 10	3, 10	2, 10	2, 10
Baseline Mean Average Pain over Last 24 Hours[d]					
n	310	292	296	588	903
Mean (SD)	7.34 (1.116)	7.38 (1.186)	7.39 (1.129)	7.39 (1.157)	7.37 (1.142)
Median	7.50	7.50	7.50	7.50	7.50
Min, Max	4.5, 10.0	5.0, 10.0	5.0, 10.0	5.0, 10.0	4.5, 10.0

Signature/Distribution List

Primary Statistical Reviewer: Yan Zhou, Ph.D.
Mathematical Statistician

Concurring Reviewer: Janice Derr, Ph.D.
Team Leader

Date: July 28, 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YAN ZHOU
07/28/2014

JANICE A DERR
07/28/2014

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

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	NDA 206-627
Supplement Number:	NA
Drug Name:	Hydrocodone bitartrate extended-release oral tablets
Indication(s):	Moderate to Severe Pain
Applicant:	Puedue Pharm LP
Date(s):	Date of Document: 4/28/2014 Consult received date: 4/30/2014 PDUFA date: 3/23/2014 Completion date: 6/16/2014
Review Priority:	P
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Wei Liu, Ph.D., Mathematical Statistician, Special Projects Team, DBVI/OB/OTS
Concurring Reviewers:	Qianyu Dang, Ph.D., Team Leader, DBVI/OB/OTS Yi Tsong, Ph.D., Division Director, DBVI/OB/OTS
Medical Division:	Controlled Substance Staff
The CSS Team:	James Tolliver, Ph.D., Pharmacologist, OD/CSS Martin Rusinowitz, M.D., Medical Reviewer, OD/CSS Silvia Calderon, Team Leader, Pharmacologist, OD/CSS Michael Klein, Ph.D., Director, OD/CSS
Project Manager:	Sandra Saltz, OD/CSS
Keywords: NDA review, clinical studies, Crossover design; Clinical abuse potential study; Self-reported endpoint; Multiple endpoints	

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1. EXECUTIVE SUMMARY

Purdue Pharma LP (PPLP) submitted this New Drug Application (NDA) for once-daily, abuse-deterrent, extended-release formulation of single-entity hydrocodone bitartrate tablets (HYD) for the management of moderate to severe pain when a continuous, around the-clock opioid analgesic is needed for an extended period of time. HYD is a Schedule II Controlled Substance.

Confirmation of abuse-deterrance:

The abuse deterrent properties of HYD were evaluated in 2 randomized, double-blind, placebo and active-controlled clinical studies (HYD1013 and HYD1014) in nondependent recreational opioid drug users.

The numbers of completers were 35 (87%) and 25 (78%) in studies HYD1013 and HYD1014, respectively.

This reviewer conformed that

- In study HYD1013, HYD demonstrated significantly lower subjective effects compared to hydrocodone API solution when administered by the oral route as intact or chewed. Although statistically significant decreases were observed for the two primary endpoints at level of 0.05 for all three HYD treatments, significant decrease in the milled HYD treatment was not supported by some important secondary PD endpoints. Moreover, the clinical data suggest that treatments "HYD 60 mg milled" and "hydrocodone 60 mg solution" have similar drug abuse potential. Relatively large reductions in abuse potential were observed with intact and chewed HYD while the differences in abuse potential were less with the milled HYD treatment. The results of this study suggest that HYD when administered by the oral route as intact or chewed has a lower oral abuse potential than hydrocodone 60 mg solution.
- In study HYD1014, the intranasal abuse potential of fine and coarse particle size HYD 60 mg (produced using an industrial mill and razor blade, respectively) were compared to hydrocodone API powder (60 mg) and placebo. Mean Emax values for positive PD measures were greatest for 60 mg hydrocodone powder, followed by the fine and coarse particle size of HYD 60 mg treatments and placebo. The results of the study suggest that HYD has statistically significant lower intranasal abuse potential than non-abuse-deterrent hydrocodone 60 mg.

The results of the two clinical abuse potential studies suggest that the reductions in subjective opioid-related effects observed with HYD administration (60 mg) via the intranasal and chewed oral routes have less abuse potential when compared to hydrocodone 60 mg.

Considerations that may limit the efficacy:

- The missing rates of subjects from the two studies are high, 13% for Study HYD1013 and 22% for Study HYD1014, respectively. The effects of missing data are not considered in the statistical analyses, which could change the conclusion under worst scenario in the abuse-deterrence effect of HYD.

- Although statistically significant decreases were observed for the two primary endpoints at level of 0.05 for all three HYD treatments, differencies between HYD milled and hydrocodone solution in some important secondary PD endpoints were not statistically significant.

Recommendations:
Recommendations for the proposed label are included in part 5.4.

2. INTRODUCTION

Purdue Pharma LP (PPLP) submitted a New Drug Application (NDA 206627) for once-daily, abuse-deterrent, extended-release formulation of single-entity hydrocodone bitartrate tablets (HYD) for the management of moderate to severe pain when a continuous, aroundthe-clock opioid analgesic is needed for an extended period of time. HYD is a Schedule II Controlled Substance.

Hydrocodone is an orally active semi-synthetic opioid agonist derived from two naturally occurring opiates, codeine and thebaine. Hydrocodone is a relatively selective μ-opioid receptor agonist compared to other opioids (Reising and Pasternak, 1996; Hennies et al., 1988). Hydrocodone acts as an agonist binding to and activating opioid receptors in the brain and spinal cord, which are coupled to G-protein complexes and modulate synaptic transmission through adenylate cyclase (Reising and Pasternak, 1996). The pharmacological effects of hydrocodone including analgesia, euphoria, respiratory depression and physiological dependence are believed to be primarily mediated via μ opioid receptors.

The Phase 1 clinical pharmacology studies included two abuse potential studies (studies HYD1013 and HYD1014), (Table 1).

1. Clinical Study HYD1013 entitled "A Single-Center, Randomized, Double-Blind, Crossover Study to Evaluate the Abuse Potential, Pharmacokinetcis, and Safety of Oral Milled and Intact Controlled Release Hydrocodone (HYD) Tablets in Recreational Opioid Users.

2. Clinical Study HYD1014 entitled "A Single-Center, Randomized, Double-Blind, Crossover Study to Evaluate the Abuse Potential, Pharmacokinetics, and Safety of Milled and Intranasally Administered Controlled Release Hydrocodone in Recreational Opioid Users.

The Study protocol of the HYD1013 and HYD1014, IND 059175 (submitted in IND 059175 Serial No. 0236 Protocol Amendment – Change in Protocols on 5/15/2013) were revised to address the comments in the advice letter of the Agency dated on 4/12/2013.

- Agency's comments for HYD1013 included stricter qualification entry criteria, reporting of missing data, sample size determination, and analysis populations.
- The Agency's comments on HYD1014 were to follow recommendations for HYD1013 and provide details of the complete characterization of HYD fine and coarse powders in the protocols.

These two HAP studies submitted are required by CSS for statistical consult review. The design features of studies HYD1013 and 1014 are shown in Table 1.1.

Table 1.1 Summaries of Clinical Pharmacology Studies

Study (Country)	Study Objective(s)	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID],	No. of Dosed Subjects. (M/F) Type Age: mean (range)
HYD1013 (Canada)	To evaluate oral abuse potential and pharmacodynamic effects, PK and safety of intact HYD tablets, milled HYD, and chewed HYD compared to hydrocodone API solution and placebo	Single-center, double-blind, placebo- and positive-controlled randomized crossover study	HYD 60-mg intact tablet, 60-mg milled tablet, and 60-mg chewed tablet, po [CB-2011-41] Hydrocodone bitartrate (API) 60-mg solution, po [CB-2012-063] Placebo HYD po [CB-2011-45]	40 (33M/7F) healthy nondependent recreational opioid users 36.3 y (21-54)
HYD1014 (Canada)	To evaluate intranasal abuse potential, pharmacodynamics, PK, and safety profile of intranasally administered HYD (fine and coarse particle size) compared to hydrocodone API and placebo	Single-center, double-blind, placebo- and positive-controlled randomized 4-way crossover study	HYD 60-mg fine or coarse particle size, intranasal [CB-2011-41] Hydrocodone bitartrate (API) 60-mg, intranasal [CB-2012-063] Placebo, intranasal [12080049]	31 (28M/3F) healthy nondependent recreational opioid users with a history of intranasal abuse 38.9 y (21-54)

API=active pharmaceutical ingredient; CYP=cytochrome P450; ESRD=end-stage renal disease; F=female; M=male; No.=number; PK=pharmacokinetic; po=per os (by mouth); QTc=corrected QT interval; y=years.
Source: Table 1 in m2-7-2-summary-clin-pharm-studies-final-14mar2014.pdf

2.1 Overview

The abuse-deterrent properties of HYD were evaluated in 2 randomized, double-blind, placebo and active-controlled abuse potential studies (HYD1013 and HYD1014) in nondependent recreational opioid drug users. Particularly, the abuse potential of HYD in study HYD1013 was investigated by Drug Liking and other visual analog scales and pupillometry through oral administration of HYD 60 mg, either chewed, analytically milled, or intact; and in study HYD1014, through intranasal administration of HYD 60 mg as fine (processed in an industrial mill) and coarse (processed with a razor blade) particles, for its subjective and physiologic effects compared with hydrocodone active pharmaceutical ingredient (API).

Study HYD1013 was a single-center, randomized, double-blind, 5-way crossover study conducted in male and female nondependent recreational drug users with moderate opioid experience, aged 18 to 55 years, to evaluate the oral abuse potential, pharmacodynamic (PD) effects, PK, and safety of intact HYD, milled HYD, and chewed HYD tablets compared with hydrocodone active pharmaceutical ingredient (API) oral solution and placebo (Table 2.1.1).

Study HYD1014 was a single-center, randomized, double-blind, placebo-controlled, 4-way crossover study conducted in male and female nondependent recreational opioid users with moderate opioid experience and a history of intranasal abuse, aged 18 to 55 years, to evaluate the intranasal abuse potential, PD, PK, and safety profile of intranasally administered HYD (fine and coarse particle size) compared with hydrocodone API powder and placebo (Table 2.1.1).

In study HYD1013, 37 healthy subjects who were nondependent recreational drug users with moderate opioid experience were exposed to the 60-mg dosage of HYD in oral form. In study HYD1014, 28 subjects who were nondependent recreational opioid users with moderate opioid experience and a history of intranasal use were exposed to 60-mg dosage of HYD in intranasal form.

2.2 Data Sources

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

Application:	NDA206627
Company	Puedue Pharm LP
Drug	Hydrocodone bitartrate extended-release oral tablets
CDER EDR link	\\Cdsesub1\evsprod\NDA206627\0000
Letter date	April 28, 2014

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Review the quality and integrity of the submitted data. Relevant issues include:

- Whether it is possible to reproduce the primary analysis dataset from tabulation or "raw" datasets : yes
- Whether it is possible to trace how the primary endpoint was derived from the original data source (e.g., case report form): yes.
- Whether it is possible to verify the randomized treatment assignments: yes
- Findings from the Division of Scientific Investigation or other source(s) that question the usability of the data:

  There is no problem or difficulty to process the data.

3.2 Evaluation of Efficacy

3.2.1 Study HYD 1013

3.2.1.1 Study Design and Endpoints

Study title: Abuse Potential, Pharmacokinetics, and Safety Study of Oral Milled, Chewed and Intact HYD Tablets in Recreational Opioid Users

Study Objective:

The objectives of the study were to: evaluate oral abuse potential and PD effects of intact

HYD, milled (produced using an industrial mill) HYD, and chewed HYD 60 mg tablets compared to hydrocodone API 60 mg solution and placebo, evaluate the safety and tolerability of orally administered intact, milled, and chewed HYD, and to determine the PK profile of orally administered intact, milled, and chewed HYD compared to hydrocodone API solution.

Methods:

This was a single-center, double-blind/quadruple-dummy, randomized, placebo-controlled and active-controlled, 5-period crossover study in healthy nondependent recreational drug users with moderate experience with opioids.

Forty subjects (33M/7F) with ages ranging from 21 to 54 years (mean: 36.3 years) were randomized and 35 subjects (87.5%) completed the study. One subject (2.5%) discontinued due to an adverse event, 2 subjects (5.0%) discontinued due to subject's choice, and 2 subjects (5.0%) discontinued for administrative reasons.

The study consisted of 4 phases: screening, qualification, treatment, and follow-up. The screening phase included 2 visits: a screening visit (visit 1) and a naloxone challenge visit (visit 2). All subjects completed the naloxone challenge test at least 12 hours prior to drug administration in the qualification phase, to confirm that subjects were not opioid dependent.

The qualification phase was conducted immediately following the naloxone challenge visit.

On the morning of days 1 and 2, subjects were administered single doses of hydrocodone API 60 mg solution and placebo in a randomized fashion (washout of 24 hours) to determine if they liked and tolerated the effects of hydrocodone and could discriminate these from placebo; this visit also determined if each subject was suitable for entry into the treatment phase of the study (ie, likely to comply with the study protocol).

During the treatment phase, subjects received each of the following 5 treatments according to the randomization schedule:

- HYD 60-mg tablet, intact (Lot number: CB-2011-41)
- HYD 60-mg tablet, milled (Lot number: CB-2011-41)
- HYD 60-mg tablet, chewed(Lot number: CB-2011-41)
- Hydrocodone API 60-mg solution (Lot number: CB-2012-063)
- Placebo (Lot number: CB-2011-45)

There was a 5 to 7 day washout period between study drug administrations. PD, PK, and safety assessments were conducted up to 36 hours post-dose.

Subjects were discharged from each visit after completion of the final (i.e., 36 hours) post-dose procedures. Study drug administrations were separated by 5 to 7 days (if needed, rescheduling may have occurred up to a maximum of 14 days). Subjects participated in the study for approximately 11 weeks from screening to follow-up.

The primary PD measures were "at the moment" Drug Liking visual analog scale (VAS) and High VAS.

Secondary measures included: Overall Drug Liking VAS, Take Drug Again VAS, Subjective Drug Value, Good and Bad Effects VAS, Addiction Research Center Inventory Morphine Benzedrine Group Scale, Feeling Sick VAS, Drowsiness/Alertness VAS, and Any Effects VAS. Pupillometry was included as an objective measure of opioid effects.

Determination of Sample Size

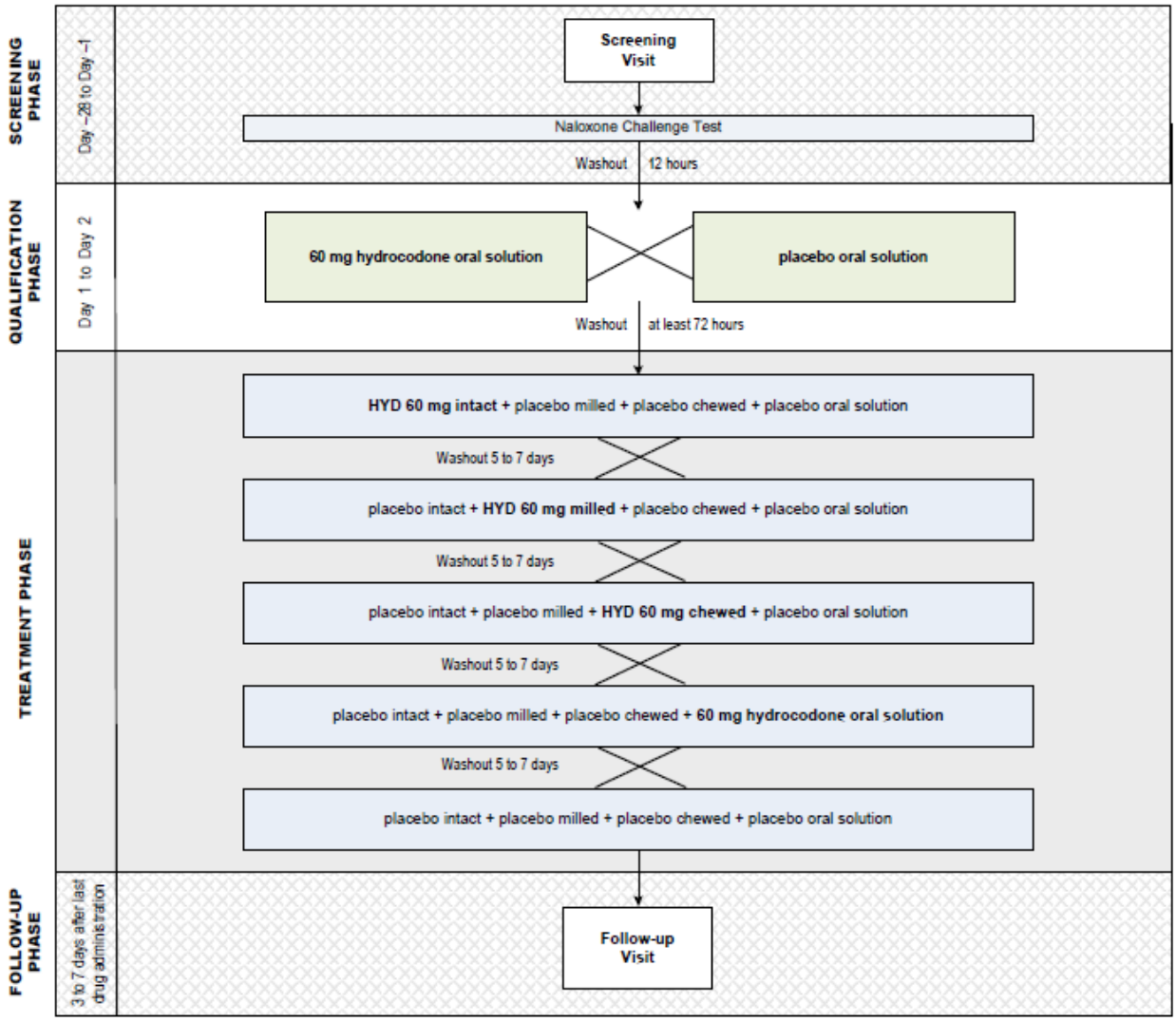
A sample size calculation was conducted based on unpublished internal placebo and oral hydrocodone 60 mg tablet data from the investigational site. As determined by a paired t-test with a 0.05 two-sided significance level and considering a mean difference of 39 points for hydrocodone oral solution 60 mg compared to placebo and a standard deviation (SD) of the differences of 20.3, a sample size of 30 completed subjects would have greater than 95% power to detect a significant difference in Drug Liking visual analogue scale (VAS) (bipolar scale) between hydrocodone oral solution and placebo (study validity).

Similarly, considering a mean difference of 74 points for hydrocodone 60 mg compared to placebo and a SD of the differences of 30.2, a sample size of 30 completed subjects would have greater than 95% power to detect a significant difference in High VAS (unipolar scale) between hydrocodone oral solution and placebo.

Therefore, approximately 40 subjects were enrolled into the Treatment Phase of the study with the intent to complete a minimum of 30 subjects (at least one subject per sequence).

The sponsor's design diagram of the study HYD1013 is shown in Figure 3.2.1.1.

Figure 3.2.1.1 Schematic of Study HYD1013 Design



Source: sponsor's hyd1013 -study-report-body.pdf Figure 1.

3.2.1.2 Statistical Methodologies

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.

Statistical methodologies used in the Sponsor's analyses:

PD endpoints for the Treatment Phase (Emax, Emin, MPC, TA_AUE, and/or TA_PAOC 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 5 days between drug administrations in the Treatment Phase was used in order to minimize the potential for carry-over effects. If the carryover effect is found to be nonsignificant at the 25% level, then the term will be dropped from the analysis model.

Baseline and carryover are included as applicable.

The residuals from the mixed-effect model will be investigated for normality using the Shapiro-Wilk W-test and for homogeneity of variance using Levene's test. Parameters will be analyzed as having a normal distribution if the probability value is >=0.05.

Parameters that do not meet this criterion will be analyzed non-parametrically. Overall treatment effect will be assessed using Friedman's test.

Pairwise treatment comparisons were assessed using the Wilcoxon sign-rank test on the within-subject differences.

The contrasts to assess the abuse potential for the HYD formulation include:

- Hydrocodone oral solution vs. placebo (reference)
- HYD (intact) vs. placebo
- HYD (intact) vs. hydrocodone oral solution
- HYD (milled) vs. placebo
- HYD (milled) vs. hydrocodone oral solution
- HYD (milled) vs. HYD (intact)
- HYD (chewed) vs. placebo
- HYD (chewed) vs. hydrocodone oral solution
- HYD (chewed) vs. HYD (intact)
- HYD (chewed) vs. HYD (milled)

ADJUSTMENT FOR TYPE I ERROR: To control for Type I errors arising from multiple comparisons of the endpoints, the Benjamini and Hochberg procedure may be used, if appropriate. The endpoints in terms of pharmacologic effect are grouped together in similar domains (balance of effects, positive effects, negative effects, other effects, and objective measures). P-values will be adjusted for multiplicity within a domain. Only the p-values from the contrasts or comparisons will be included in the Benjamini and Hochberg adjustment.

RESPONDER ANALYSIS: Percent reduction in Emax of Drug Liking VAS will be calculated as follows:

$$\% \text{ reduction} = \begin{cases} \dfrac{C - T}{C - 50} \times \left[1 - \dfrac{P - 50}{50}\right] \times 100\%, & \text{if } P > 55 \\ \dfrac{C - T}{C - 50} \times 100\%, & \text{if } P \leq 55 \end{cases}$$

Where, T=test drug; C=positive control; P= placebo

A responder is defined as a subject who demonstrates a desired % reduction in Emax of Drug Liking for T relative to C. A proportion test was used to determine the statistical significance of the responder rate within each category.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations by the sponsor is shown in Table 3.2.1.1.

Table 3.2.1.1 Patient disposition (Randomized Set)

	n (%)
Number of Subjects in the Randomized Population	40
Number (%) of Subjects who Completed Treatment Period 1 (Visit 4)	40 (100%)
Number (%) of Subjects who Completed Treatment Period 2 (Visit 5)	38 (95.0%)
Number (%) of Subjects who Completed Treatment Period 3 (Visit 6)	36 (90.0%)
Number (%) of Subjects who Completed Treatment Period 4 (Visit 7)	36 (90.0%)
Number (%) of Subjects who Completed Treatment Period 5 (Visit 8)	35 (87.5%)
Number (%) of Subjects who Completed the Study	35 (87.5%)
Number (%) of Subjects who Withdrew Early	5 (12.5%)
Number (%) of Subjects in the Safety Population	40 (100%)
Number (%) of Subjects in the Pharmacokinetic Population	40 (100%)
Number (%) of Subjects in the Pharmacodynamic Population	35 (87.5%)

Source: sponsor's hyd1013 -study-report-body.pdf Table 14.1.3

Among the 40 randomized subjects, there were 35 (87.5%) subjects completed all 4 treatment periods and were included in the PD population. Five (12.5%) subjects discontinued prior to completing all 5 treatment periods:

- Subject 01008 discontinued due to an AE following treatment period 2 dosing and received single oral doses of hydrocodone 60 mg solution and placebo.
- Subject 01058 was discontinued for administrative reasons following treatment period 2 dosing and received single oral doses of placebo and hydrocodone 60 mg solution.
- Subject 01059 discontinued for personal reasons following treatment period 4 dosing and received single oral doses of HYD 60 mg milled, HYD 60 mg chewed, HYD 60 mg intact, and hydrocodone 60 mg solution.
- Subject 01083 discontinued for personal reasons prior to dosing at treatment period 2 and received a single oral dose of HYD 60 mg milled.
- Subject 01090 was discontinued for administrative reasons following treatment period 2 dosing and received single oral doses of hydrocodone 60 mg solution and placebo.

The sponsor also provided the information of patients' demographic and baseline summary as shown in Table 3.2.1.2.

Table 3.2.1.2 Demographic and Baseline Characteristics (Randomized Set)

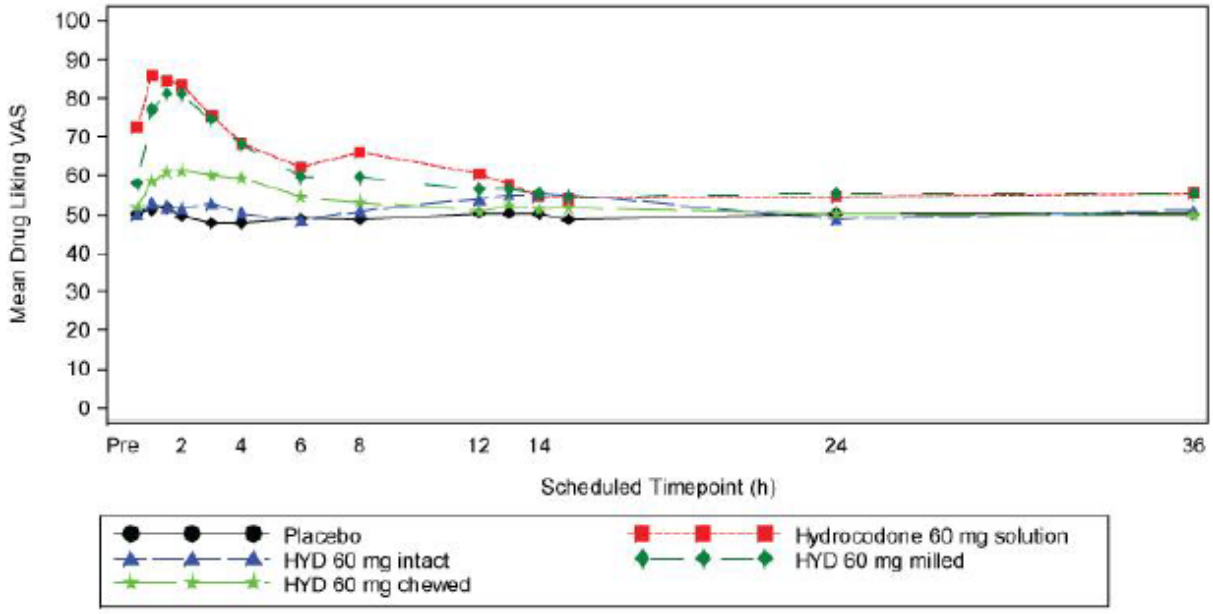
	Total N=40
Age (years)*	
n	40
Mean (SD)	36.3 (9.15)
Median	36.0
Range	21 - 54
Sex, n (%)	
n	40
Male	33 (82.5%)
Female	7 (17.5%)
Race, n (%)	
n	40
White	29 (72.5%)
Black or African American	6 (15.0%)
Asian	4 (10.0%)
American Indian or Alaska Native	1 (2.5%)
Ethnicity, n (%)	
n	40
Hispanic or Latino	1 (2.5%)
Not Hispanic or Latino	39 (97.5%)
Height (cm)	
n	40
Mean (SD)	177.19 (8.965)
Median	178.35
Range	151.2 - 197.1
Weight (kg)	
n	40
Mean (SD)	79.68 (14.442)
Median	77.45
Range	50.5 - 110.1
BMI (kg/m²)	
n	40
Mean (SD)	25.20 (3.024)
Median	25.35
Range	18.8 - 29.7

Source: sponsor's hyd1013 -study-report-body.pdf Table 14.1.

3.2.1.4 Results and Conclusions

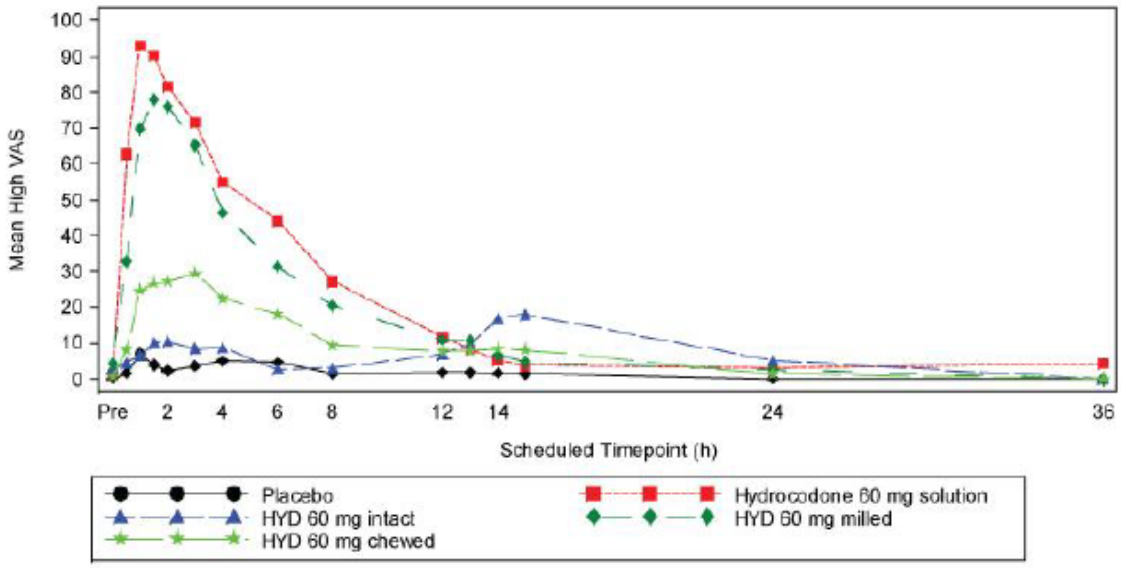
The sponsor provided the plots of mean scores over time on the primary measures of Drug Liking VAS and High VAS are presented in Figure 3.2.1.2, and Figure 3.2.1.3, respectively. It is obvious in these figures that the curves of treatments "HYD 60 mg milled" and "hydrocodone 60 mg solution" are more similar to each other as compared to other three treatments.

Figure 3.2.1.2 Mean Scores Over Time for Drug Liking VAS (Oral Administration, Chewed, Milled and Intact) in Study HYD1013 (PD Population)



Source: sponsor's hyd1013 -study-report-body.pdf Figure 2
VAS=visual analog scale. Drug Liking VAS is a bipolar scale: "At this moment, my liking for this drug is," where responses range from 0 (Strong disliking) to 100 (Strong liking), and 50 (Neither like nor dislike) is the neutral point.

Figure 3.2.1.3 Mean Scores Over Time for High VAS (Oral Administration, Chewed, Milled and Intact) in Study HYD1013 (PD Population)



Source: sponsor's hyd1013 -study-report-body.pdf Figure 5
VAS=visual analog scale. High VAS is a unipolar scale: "I am feeling high," where responses range from 0 (Definitely not) to 100 (Definitely so).

Table 3.2.1.3 from the sponsor presents a summary of Emax scores for the two primary measures and for measures of balance of effects. These results were verified by this reviewer.

Table 3.2.1.3 Summary of Maximum (Emax) Scores on Primary Endpoints and Measures of Balance of Effects Following Oral Administration of HYD (Chewed, Milled and Intact) in Recreational Opioid Users in Study HYD1013 (PD Population)

Measure	N=35	Placebo	Hydrocodone API 60 mg solution	HYD 60 mg, intact	HYD 60 mg, milled	HYD 60 mg, chewed
Drug Liking VAS	Mean (SD)	52.3 (7.14)	94.0 (10.2)	63.3 (16.0)	89.2 (14.0)	69.0 (17.5)
	Median	51.0	100	58.0	93.0	66.0
High VAS	Mean (SD)	17.5 (28.5)	97.4 (5.8)	42.0 (37.6)	85.6 (26.4)	48.3 (36.2)
	Median	0.0	100	48.0	100	50.0
Overall Drug Liking VAS	Mean (SD)	49.7 (10.0)	85.9 (17.6)	59.4 (16.2)	84.6 (17.6)	59.2 (27.9)
	Median	50.0	92.0	51.0	90.0	64.0
Take Drug Again VAS	Mean (SD)	3.9 (15.9)	89.7 (21.2)	34.3 (36.0)	84.1 (28.1)	44.3 (40.8)
	Median	0.0	100	24.0	100	55.0
Subjective Drug Value	Mean (SD)	0.521 (1.6)	26.1 (16.6)	9.24 (14.6)	26.4 (16.4)	15.0 (17.4)
	Median	0.250	26.8	3.00	26.8	9.75

Source: : sponsor's hyd1013 -study-report-body.pdf , Tables 10, 13, and 15.
Emax=maximum effect; SD=standard deviation; VAS=visual analog scale.

This reviewer noted that treatments "HYD 60 mg milled" and "hydrocodone 60 mg solution" have the same or similar values of mean and median in Table 3.2.1.3.

The pairwise comparisons of arms for drug liking VAS and high VAS are from the sponsor and are shown the Tables 3.2.1.4 and 3.2.1.5, respectively. These results were verified by this reviewer.

Table 3.2.1.4 Analysis Results for Drug Liking VAS Emax and TA_AUE (PD Population)

	E_{max}			TA_AUE		
	Median difference	IQR	*P* value	Median difference	IQR	*P* value
Overall Treatment Effect	–	–	**<0.001**	–	–	**<0.001**
Pairwise Comparisons						
Hydrocodone vs Placebo (Study Validity)						
Hydrocodone solution – Placebo	48.0	38.0, 49.0	**<0.001**	6.7	2.1, 13.0	**<0.001**
HYD vs Hydrocodone solution						
HYD intact – Hydrocodone solution	-37.0	-43.0, -22.0	**<0.001**	-4.7	-12.1, -2.0	**<0.001**
HYD milled – Hydrocodone solution	0.0	-10.0, 0.0	**0.015**	-0.9	-4.4, 2.7	0.272
HYD chewed – Hydrocodone solution	-30.0	-40.0, -9.0	**<0.001**	-4.5	-11.3, 0.4	**<0.001**
HYD vs Placebo						
HYD intact – Placebo	5.0	0.0, 19.0	**<0.001**	0.3	-0.1, 3.9	**0.035**
HYD milled – Placebo	42.0	28.0, 49.0	**<0.001**	4.1	1.2, 9.6	**<0.001**
HYD chewed – Placebo	14.0	0.0, 31.0	**<0.001**	0.9	-1.4, 6.1	0.074
HYD vs HYD						
HYD milled – HYD intact	29.0	0.0, 42.0	**<0.001**	2.9	-0.5, 8.8	**<0.001**
HYD chewed – HYD intact	4.0	0.0, 16.0	0.056	0.2	-2.0, 4.0	0.430
HYD chewed – HYD milled	-22.0	-40.0, 0.0	**<0.001**	-2.8	-11.5, 1.3	**0.015**

Source: sponsor's hyd1013 -study-report-body.pdf Table 11.

Note that the p-values for the difference of (HYD 60 mg milled – Hydrocodone 60 mg solution) are much larger than its peers, although significant at alpha level of 0.05 for Emax but not for TA_AUE (p=0.272).

Table 3.2.1.5 Analysis Results for High VAS Emax and TA_AUE (PD Population)

	E_{max}			TA_AUE		
	Median difference	IQR	*P* value	Median difference	IQR	*P* value
Overall Treatment Effect	–	–	**<0.001**	–	–	**<0.001**
Pairwise Comparisons						
Hydrocodone vs Placebo (Study Validity)						
Hydrocodone solution - Placebo	99.0	50.0, 100.0	**<0.001**	12.79	7.48, 21.30	**<0.001**
HYD vs Hydrocodone Solution						
HYD intact – Hydrocodone solution	-50.0	-97.0, -26.0	**<0.001**	-9.38	-18.41, -3.88	**<0.001**
HYD milled – Hydrocodone solution	0.0	-8.0, 0.0	**<0.001**	-3.17	-9.85, 2.39	**0.019**
HYD chewed – Hydrocodone solution	-50.0	-87.0, -13.0	**<0.001**	-6.27	-20.52, -0.33	**<0.001**
HYD vs Placebo						
HYD intact – Placebo	16.0	0.0, 62.0	**0.003**	2.08	0.00, 11.85	**<0.001**
HYD milled – Placebo	77.0	48.0, 100.0	**<0.001**	8.76	4.33, 21.17	**<0.001**
HYD chewed – Placebo	39.0	11.0, 58.0	**<0.001**	5.61	0.68, 11.82	**<0.001**
HYD vs HYD						
HYD milled – HYD intact	42.0	15.0, 77.0	**<0.001**	7.74	2.22, 10.22	**<0.001**
HYD chewed – HYD intact	1.0	-23.0, 45.0	0.483	0.96	-5.03, 5.62	0.367
HYD chewed – HYD milled	-33.0	-75.0, 0.0	**<0.001**	-4.31	-16.84, 1.92	**0.007**

Source: sponsor's hyd1013 -study-report-body.pdf Table 16.

Note that the p-value for the difference of (HYD 60 mg milled – Hydrocodone 60 mg solution) is much larger than its peers in TA_AUE (p=0.019).

Table 3.2.1.6 presents the inferential results (Emax) from the sponsor for Overall Drug Liking VAS, Take Drug Again VAS, and Subjective Drug Value, respectively.

Table 3.2.1.6 Analysis Results for Overall Drug Liking VAS, Take Drug Again, and Subjective Drug Value Emax (PD Population)

	Overall Drug Liking E_{max}			Take Drug Again E_{max}			Subjective Drug Value E_{max}		
	Median difference	IQR	*P* value	Median difference	IQR	*P* value	Median difference	IQR	*P* value
Overall Treatment Effect	–	–	**<0.001**	–	–	**<0.001**	–	–	**<0.001**
Pairwise Comparisons									
Hydrocodone vs Placebo (Study Validity)									
Hydrocodone solution – Placebo	40.0	24.0, 50.0	**<0.001**	97.0	86.0, 100.0	**<0.001**	26.5	10.5, 47.8	**<0.001**
HYD vs Hydrocodone Solution									
HYD intact – Hydrocodone solution	-30.0	-40.0, -1.0	**<0.001**	-70.0	-94.0, -3.0	**<0.001**	-13.5	-29.0. -0.500	**<0.001**
HYD milled – Hydrocodone solution	0.0	-12.0, 2.0	0.419	0.0	-14.0, 2.0	0.325	0.00	-7.75, 0.00	0.713
HYD chewed – Hydrocodone solution	-23.0	-44.0, 0.0	**<0.001**	-40.0	-92.0, 0.0	**<0.001**	-5.75	-29.0, 0.00	**0.001**
HYD vs Placebo									
HYD intact – Placebo	1.0	-1.0, 20.0	**0.004**	13.0	0.0, 50.0	**<0.001**	2.00	0.00, 9.50	**<0.001**
HYD milled – Placebo	39.0	24.0, 50.0	**<0.001**	100.0	71.0, 100.0	**<0.001**	26.5	9.50, 47.8	**<0.001**
HYD chewed – Placebo	14.0	0.0, 27.0	**0.028**	55.0	1.0, 77.0	**<0.001**	9.50	0.00, 26.5	**<0.001**
HYD vs HYD									
HYD milled – HYD intact	28.0	4.0, 40.0	**<0.001**	60.0	0.0, 93.0	**<0.001**	13.5	1.50, 26.5	**<0.001**
HYD chewed – HYD intact	1.0	-15.0, 14.0	0.763	5.0	-5.0, 41.0	0.150	0.00	-0.500, 10.8	**0.041**
HYD chewed – HYD milled	-27.0	-49.0, 0.0	**<0.001**	-32.0	-94.0, 0.0	**<0.001**	-9.50	-22.5, 1.00	**0.002**

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

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

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

Source: sponsor's hyd1013 -study-report-body.pdf Table 14.

Note that the p-values for the difference of (HYD 60 mg milled – Hydrocodone 60 mg solution) are much larger than its peers and not significant at alpha level of 0.05 for all the three endpoints.

Responder Analysis – Drug Liking VAS

Responders were categorized into those who demonstrated a 30%, 40%, or 50% reduction in Emax of Drug Liking, along with other deciles as appropriate. Table 3.2.1.7 presents the sponsor's results of the proportion test in Drug Liking VAS Emax score following administration of HYD intact, milled, or chewed in comparison to their scores following administration of hydrocodone solution. The results were verified by this reviewer.

Table 3.2.1.7 Drug Liking VAS Responder Analysis (PD Population)

	HYD 60 mg intact vs Hydrocodone 60 mg solution					
	(30,40)	(40,50)	(50,60)	(60,70)	(70,80)	(80,90)
Responder rate	0.83	0.83	0.74	0.63	0.60	0.49
Z-score	3.89	3.89	2.87	1.52	1.18	-0.17
P value	**<0.001**	**<0.001**	**0.002**	0.064	0.118	0.567
	HYD 60 mg milled vs Hydrocodone 60 mg solution					
	(30,40)	(40,50)	(50,60)	(60,70)	(70,80)	(80,90)
Responder rate	0.17	0.14	0.09	0.09	0.06	0.06
Z-score	-3.89	-4.23	-4.90	-4.90	-5.24	-5.24
P value	1.000	1.000	1.000	1.000	1.000	1.000
	HYD 60 mg chewed vs Hydrocodone 60 mg solution					
	(30,40)	(40,50)	(50,60)	(60,70)	(70,80)	(80,90)
Responder rate	0.69	0.63	0.60	0.49	0.43	0.34
Z-score	2.20	1.52	1.18	-0.17	-0.85	-1.86
P value	**0.014**	0.064	0.118	0.567	0.801	0.969

The first row denotes the percent of reduction from the positive control (hydrocodone solution) to the test drug (HYD intact, HYD milled, or HYD chewed).
Responder Rate is the proportion of subjects with reduction ≥XX%, where XX is the lower limit in the column header. *P* values shown in bold are significant ($P<0.05$).
Source: sponsor's hyd1013 -study-report-body.pdf Table 12.

Note that the p-values are not significant for HYD 60 mg milled vs. Hydrocodone 60 mg solution.

This reviewer also performed the following analyses. Table 3.2.1.8 (A, B, and C) shows the frequency distribution of subjects in terms of their responses to the positive control as well as their percent reductions for the test drug relative to the positive control. Note that there is 60% (n=21) of patients in the HYD 60 mg milled treatment with Emax VAS greater than or equal to that of the patients treated with the positive control. The percentages of patients with Emax VAS greater than or equal to that of the patients treated with the positive control were ≤20% (n≤7) in patients with other HYD treatments. The differences suggest that the Emax VAS values of patients treated with the HYD 60 mg milled are much closer to that of the patients treated with hydrocodone 60 mg solution than those treated with other HYD 60 mg forms.

With a 30% reduction cut-off, the responder rates are 68% and 83% in HYD 60 mg chewed and intact arms, respectively. Only 17% of subjects had at least 30% reduction in liking in the milled arm.

Table 3.2.1.8 Contingency Table for Emax of Drug Liking VAS of the positive control by percent reduction (Study 1013).

A. HYD 60 mg Chewed vs. Hydrocodone 60 mg Solution

Hydrocodone 60 mg solution (Emax)	Percent of Reduction (%)													
	<0	0	(0, 10)	[10, 20)	[20, 30)	[30, 40)	[40, 50)	[50, 60)	[60, 70)	[70, 80)	[80, 90)	[90, 100)	≥100	Total
≤55	1	0	0	0	0	0	0	0	0	0	0	0	0	1
(55, 60]	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(60, 65]	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(65, 70]	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(70, 75]	0	0	0	0	0	0	0	1	0	0	0	0	0	1
(75, 80]	0	0	0	0	0	1	0	0	0	0	0	0	0	1
(80, 85]	0	0	0	0	1	0	0	0	0	0	0	0	0	1
(85, 90]	1	0	0	1	0	0	0	0	0	1	0	3	0	6
(90, 95]	0	0	0	0	1	0	0	0	0	0	1	2	0	4
(95, 100]	0	5	0	0	1	1	1	3	2	2	1	4	1	21
Total	2	5	0	1	3	2	1	4	2	3	2	9	1	35
pct(%)	5.7	14.3	0	2.9	8.6	5.7	2.9	11.4	5.7	8.6	5.7	25.7	2.9	100
cpct(%)	100	94	80	80	77	68	63	60	48	43	34	28	3	

B. HYD 60 mg Milled vs. Hydrocodone 60 mg Solution

Hydrocodone 60 mg solution (Emax)	Percent of Reduction (%)													
	<0	0	(0, 10)	[10, 20)	[20, 30)	[30, 40)	[40, 50)	[50, 60)	[60, 70)	[70, 80)	[80, 90)	[90, 100)	>=100	Total
<=55	1	0	0	0	0	0	0	0	0	0	0	0	0	1
(55, 60]	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(60, 65]	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(65, 70]	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(70, 75]	0	0	0	1	0	0	0	0	0	0	0	0	0	1
(75, 80]	1	0	0	0	0	0	0	0	0	0	0	0	0	1
(80, 85]	0	0	0	0	0	0	0	0	0	0	0	0	1	1
(85, 90]	2	0	0	0	2	0	0	0	1	0	0	1	0	6
(90, 95]	2	0	1	0	1	0	0	0	0	0	0	0	0	4
(95, 100]	0	15	1	0	2	1	2	0	0	0	0	0	0	21
Total	6	15	2	1	5	1	2	0	1	0	0	1	1	35
pct(%)	17.1	42.9	5.7	2.9	14.3	2.9	5.7	0	2.9	0	0	2.9	2.9	100
cpct(%)	100	83	40	34	31	17	14	8	8	6	6	6	3	

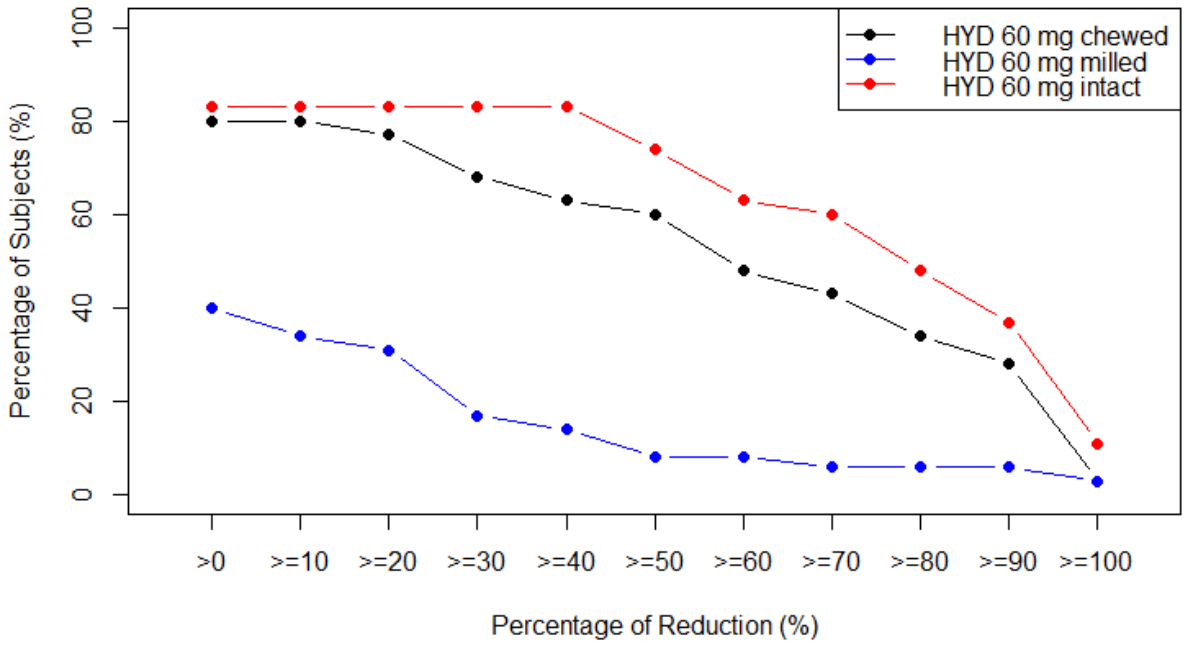
C. HYD 60 mg Intact vs. Hydrocodone 60 mg Solution

Hydrocodone 60 mg solution (Emax)	Percent of Reduction (%)													
	<0	0	(0, 10)	[10, 20)	[20, 30)	[30, 40)	[40, 50)	[50, 60)	[60, 70)	[70, 80)	[80, 90)	[90, 100)	>=100	Total
<=55	0	1	0	0	0	0	0	0	0	0	0	0	0	1
(55, 60]	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(60, 65]	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(65, 70]	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(70, 75]	1	0	0	0	0	0	0	0	0	0	0	0	0	1
(75, 80]	0	0	0	0	0	0	0	0	0	0	1	0	0	1
(80, 85]	0	0	0	0	0	0	0	0	0	1	0	0	0	1
(85, 90]	0	0	0	0	0	0	0	1	0	0	1	3	1	6
(90, 95]	0	0	0	0	0	0	0	1	1	0	0	2	0	4
(95, 100]	0	4	0	0	0	0	3	2	0	3	2	4	3	21
Total	1	5	0	0	0	0	3	4	1	4	4	9	4	35
pct(%)	2.9	14.3	0	0	0	0	8.6	11.4	2.9	11.4	11.4	25.7	11.4	100
cpct(%)	100	97	83	83	83	83	83	74	63	60	48	37	11	

Note: The pct, and cpct denote the percentage of subjects and the cumulative percentage of subjects, respectively.

Figure 3.2.1.4 shows that the degree of potential drug abuse relative to the positive control are in the order of HYD 60 mg milled (crushed) > HYD 60 mg chewed > HYD 60 mg intact.

Figure 3.2.1.4 Percent Reduction Profile for Emax of Drug Liking VAS for Study 1013.



Note that the curve for HYD 60 mg milled treatment is distinctively lower than the other two curves, suggesting its VAS scores are closer to that of the Hydrocodone 60 mg solution treatment.

Summary of Study HYD1013
HYD demonstrated significantly lower subjective effects compared to hydrocodone API solution, when administered by the oral route as intact or chewed. Although statistically significant decreases were observed for the two primary endpoints at level of 0.05 for all three HYD treatments, significant decrease in the milled HYD treatment was not supported by some important secondary PD endpoints. Moreover, the clinical data suggest that treatments "HYD 60 mg milled" and "hydrocodone 60 mg solution" have similar drug abuse potential as evidenced:

- The sponsor provided The plots of mean scores over time on the primary measures of Drug Liking VAS and High VAS (Figure 3.2.1.2, and Figure 3.2.1.3), from the sponsor showed that the curves of treatments "HYD 60 mg milled" and "hydrocodone 60 mg solution" are closer to each other than other three treatments.
- The treatments "HYD 60 mg milled" and "hydrocodone 60 mg solution" have the same or similar values of mean and median in maximum (Emax) scores on primary endpoints and measures of balance of effects as shown in Table 3.2.1.3.
- The p-values for the difference of (HYD 60 mg milled – Hydrocodone 60 mg solution) are much larger than its peers. Although it is significant at alpha level of 0.05 for Emax, it is not significant for TA_AUE (p=0.272) (Table 3.2.1.4).
- The p-value for the difference of (HYD 60 mg milled – Hydrocodone 60 mg solution) is much larger than its peers in TA_AUE (p=0.019) (Table 3.2.1.5).
- The p-values for the difference of (HYD 60 mg milled – Hydrocodone 60 mg solution) are much larger than its peers and not statistically significant at alpha level of 0.05 for all the three endpoints (Table 3.2.1.6).
- The p-values are not significant for HYD 60 mg milled vs. Hydrocodone 60 mg solution in drug liking VAS responder analysis (Table 3.2.1.7).
- Figure 3.2.1.4 shows that the curve for HYD 60 mg milled treatment is distinctively lower than the other two curves, suggesting its VAS scores are closer to that of the Hydrocodone 60 mg solution treatment.

Relatively large reductions in abuse potential were observed with intact and chewed HYD while the differences in abuse potential were less with the milled HYD treatment. The results of this study suggest that HYD when administered by the oral route as intact or chewed has a lower oral abuse potential compared to hydrocodone 60 mg solution.

3.2.2 Study HYD1014

3.2.2.1 Study Design and Endpoints

Study title: Abuse Potential, Pharmacokinetics, and Safety Study of Milled and Intranasally Administered HYD in Recreational Opioid Users with a History of Intranasal Abuse.

Study Objective:

The objectives of the study were to: evaluate intranasal abuse potential and PD effects of intranasally administered fine and coarse particle size HYD 60 mg (produced using an industrial mill and razor blade, respectively) compared to hydrocodone API 60 mg powder and placebo; evaluate the safety and tolerability of intranasally administered HYD (fine and coarse particle size); and to determine the PK of intranasally administered HYD (fine and coarse particle size) compared to hydrocodone API powder.

Methods:
This was a single-center, double-blind, randomized, placebo-controlled and active-controlled, 4-period crossover study in non-dependent recreational drug users with moderate experience with opioids with a history of intranasal abuse.

Thirty-two subjects were randomized to the treatment phase. One subject (3.1%) was withdrawn prior to receiving any study drug in the treatment phase due to AEs. Thirty-one subjects (28M/3F) with ages ranging from 21 to 54 years (mean: 38.9 years) were dosed and

25 subjects (78.1%) completed the study. After dosing, 1 subject (3.1%) discontinued due to an AE, 1 subject (3.1%) discontinued due to poor venous access, and 4 subjects (12.5%) discontinued for administrative reasons.

The study consisted of 5 phases: screening, dose selection, qualification, treatment, and follow-up. The screening phase included 2 visits: a screening visit (visit 1) and a naloxone challenge visit (visit 2). All subjects completed the naloxone challenge test at least 12 hours prior to drug administration in the dose selection or qualification phases, to confirm that subjects were not opioid dependent.

Because the nasal bioavailability of hydrocodone was not known, the dose of hydrocodone used during the qualification and treatment phases was determined during a dose selection phase (visit 3a). Once a dose had been selected, a new set of eligible subjects who did not participate in the dose selection phase at the selected dose entered the qualification phase (visit 3b). During this visit, subjects were asked to intranasally administer 40-mg hydrocodone API powder (or other selected dose) and lactose powder placebo on day 1 and day 2 in a randomized crossover manner to determine if they liked and tolerated the effects of hydrocodone and could discriminate these from placebo; this visit also determined if each subject was suitable for entry into the treatment phase of the study (ie, likely to comply with the study protocol). There was a 24-hour washout period between study drug administrations.

During the treatment phase, subjects received each of the following 4 treatments according to the randomization schedule:

- Hydrocodone API 60 mg powder (Lot number: CB-2012-063)
- HYD fine particle size 60 mg (Lot number: CB-2011-41)
- HYD coarse particle size 60 mg (Lot number: CB-2011-41)
- Placebo (Lot number: 12080049)

There was a 5 to 7 day washout period between study drug administrations.

The primary PD measures were “at the moment” Drug Liking visual analog scale (VAS) and High VAS.

Secondary measures included: Overall Drug Liking VAS, Take Drug Again VAS, Subjective Drug Value, Good and Bad Effects VAS, Addiction Research Center Inventory Morphine

Benzedrine Group Scale, Feeling Sick VAS, subject-rated assessment of intranasal irritation,

Drowsiness/Alertness VAS, and Any Effects VAS. Pupillometry was included as an objective measure of opioid effects and endoscopy with intranasal photography was included as an objective measure of nasal irritation.

Determination of Sample Size

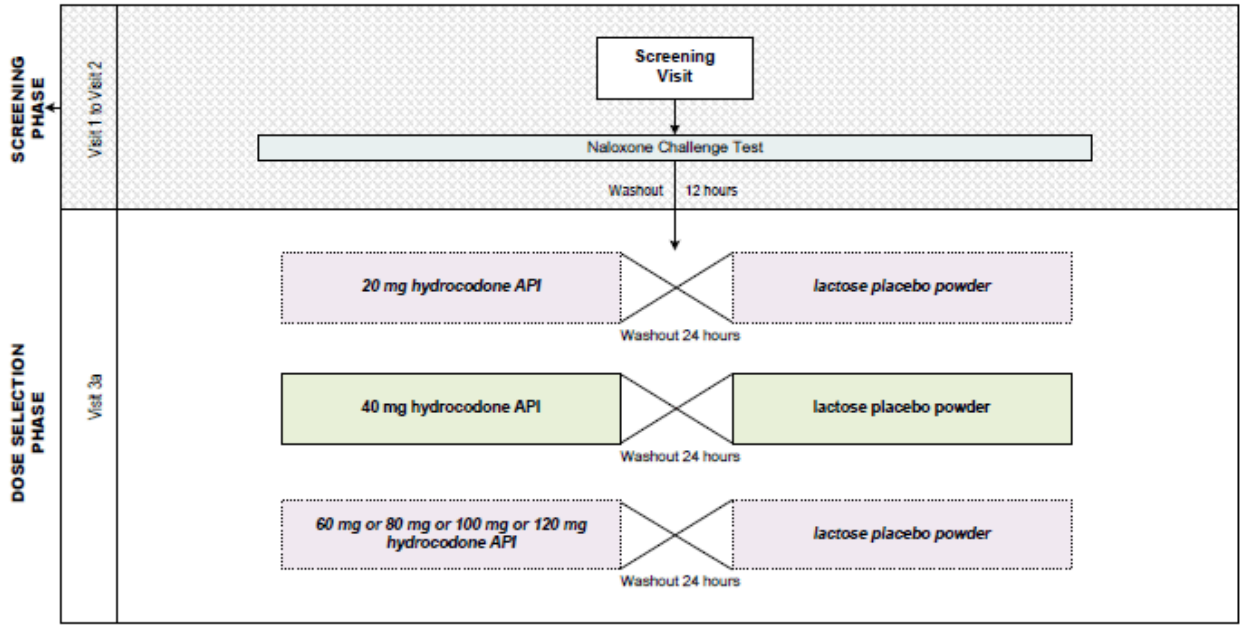
Since hydrocodone had not been administered intranasally, unpublished internal placebo and intranasal oxycodone data from the investigational site were used to estimate the sample size. As determined by a paired *t*-test with a 0.05 two-sided significance level and considering a mean difference of 41.6 points for oxycodone intranasal administration of 40 mg compared to placebo and an SD of the differences of 13.9 (based on internal placebo and oxycodone 40 mg intranasal data from the investigational site), a sample size of 24 completed subjects would have had greater than 95% power to detect a significant difference in Drug Liking VAS (bipolar scale) between hydrocodone intranasal administration and placebo (study validity).

Similarly, considering a mean difference of 88.7 points for 40 mg oxycodone compared to placebo and an SD of the differences of 25.5, a sample size of 24 completed subjects would have had greater than 95% power to detect a significant difference in High VAS (unipolar scale) between hydrocodone intranasal administration and placebo (based on internal placebo and 40 mg oxycodone intranasal data from the investigational site).

Therefore, approximately 32 subjects were planned to be enrolled into the treatment phase of the study with the intent to complete a minimum of 24 subjects (at least 1 subject per sequence).

The sponsor's design diagram of the study HYD1013 is shown in Figure 3.2.2.1.

Figure 3.2.2.1 Schematic of Study HYD1014 Design



Note: Figure shown refers to the dose selection phase. Dotted boxes indicate subsequent dose of 20 mg if the 40 mg dose was considered too high based on PD and safety data.
Similarly, the dose was to be escalated to 60 mg, 80 mg, 100 mg, and 120 mg, as needed, if the 40 mg dose was deemed insufficient.
Source: sponsor's hyd1014 -study-report-body.pdf Figure 1.

3.2.2.2 Statistical Methodologies

The statistical methods are the same as seen in 3.2.1.2 except for following.
The contrasts to assess the abuse potential for the HYD formulation are:

- Intranasal hydrocodone API vs. placebo (lactose powder) - reference contrast
- Intranasal HYD (coarse powder) vs. placebo (lactose powder)
- Intranasal HYD (fine powder) vs. placebo (lactose powder)
- Intranasal HYD (coarse powder) vs. hydrocodone API
- Intranasal HYD (fine powder) vs. hydrocodone API
- Intranasal HYD (coarse powder) vs. HYD (fine powder)

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations by the sponsor is shown in Table 3.2.2.1.

Table 3.2.2.1 Patient disposition (Randomized Set)*

	n (%)
Number of Subjects in the Randomized Population	32
Number (%) of Subjects who Completed Treatment Period 1 (Visit 4)	31 (96.9%)
Number (%) of Subjects who Completed Treatment Period 2 (Visit 5)	27 (84.4%)
Number (%) of Subjects who Completed Treatment Period 3 (Visit 6)	27 (84.4%)
Number (%) of Subjects who Completed Treatment Period 4 (Visit 7)	25 (78.1%)
Number (%) of Subjects who Completed the Study	25 (78.1%)
Number (%) of Subjects who Withdrew Early	7 (21.9%)
Number (%) of Subjects in the Safety Population	31 (96.9%)
Number (%) of Subjects in the Pharmacokinetic Population	30 (93.8%)
Number (%) of Subjects in the Pharmacodynamic Population	25 (78.1%)

Note: Percentage is calculated based on the number of subjects randomized as the denominator.
Source: sponsor's hyd1014 -study-report-body.pdf Table 14.1.4.

Among the 32 randomized subjects, there were 25 (78.1%) subjects completed all 4 treatment periods and were included in the PD population. A total of 7 (21.9%) subjects discontinued prior to completing all 4 treatment periods:

- Subject 01061 was discontinued after treatment period 1 due to an AE following a single intranasal dose of HYD coarse 60 mg.
- Subject 01095 was discontinued before receiving any study drug in the treatment phase. This subject was randomized to the treatment phase but was withdrawn from the study due to AEs before dosing on day 1 of treatment period 1.
- Subjects 01118 and 01119 were discontinued after treatment period 3 for administrative reasons, and each received single intranasal doses of HYD coarse 60 mg, placebo, and HYD fine 60 mg.
- Subjects 01122, 01127, and 01128 were discontinued after treatment period 1 for administrative reasons and received single intranasal doses of hydrocodone API 60 mg, HYD fine 60 mg, and hydrocodone API 60 mg, respectively.

The sponsor also provided the information of patients' demographic and baseline summary as shown in Table 3.2.2.2.

Table 3.2.1.2 Demographic and Baseline Characteristics (Randomized Set)*

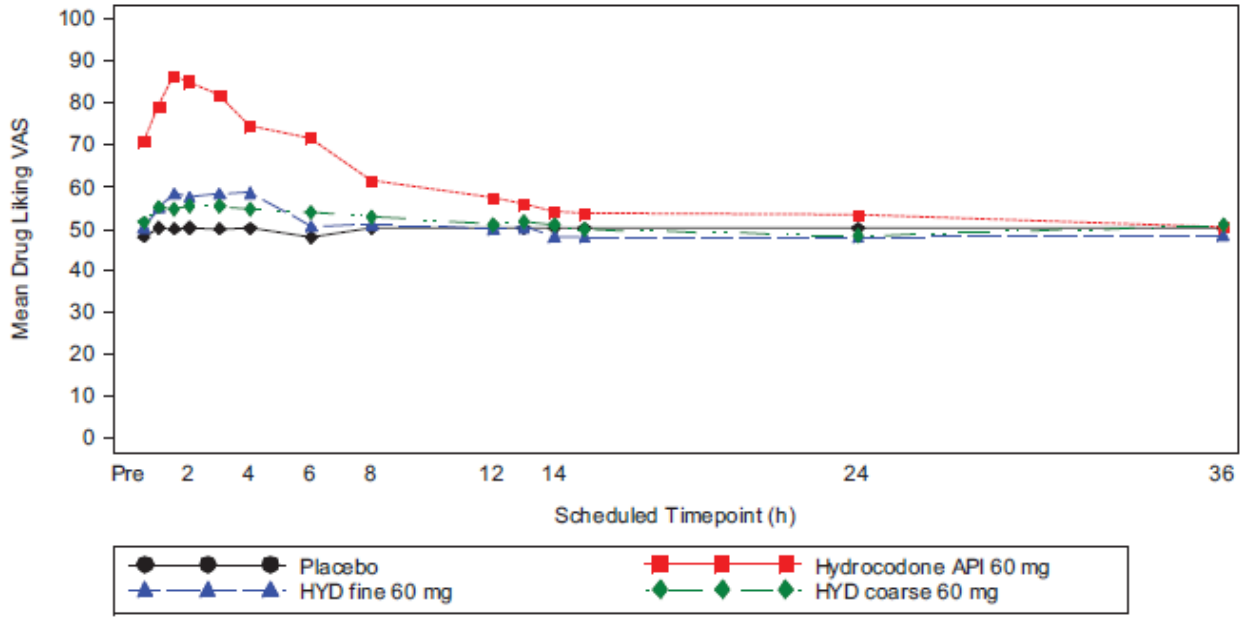
	Total (N=31)
Age (years)[a]	
Mean (SD)	38.9 (10.21)
Range	21–54
Sex, n (%)	
Male	28 (90.3)
Female	3 (9.7)
Race, n (%)	
White	20 (64.5)
Black or African American	8 (25.8)
Asian	3 (9.7)
BMI (kg/m^2)	
Mean (SD)	25.33 (2.423)
Range	20.6–29.9

BMI=body mass index; SD=standard deviation
a Age at informed consent
Source: sponsor's hyd1014 -study-report-body.pdf Table 8.

3.2.2.4 Results and Conclusions

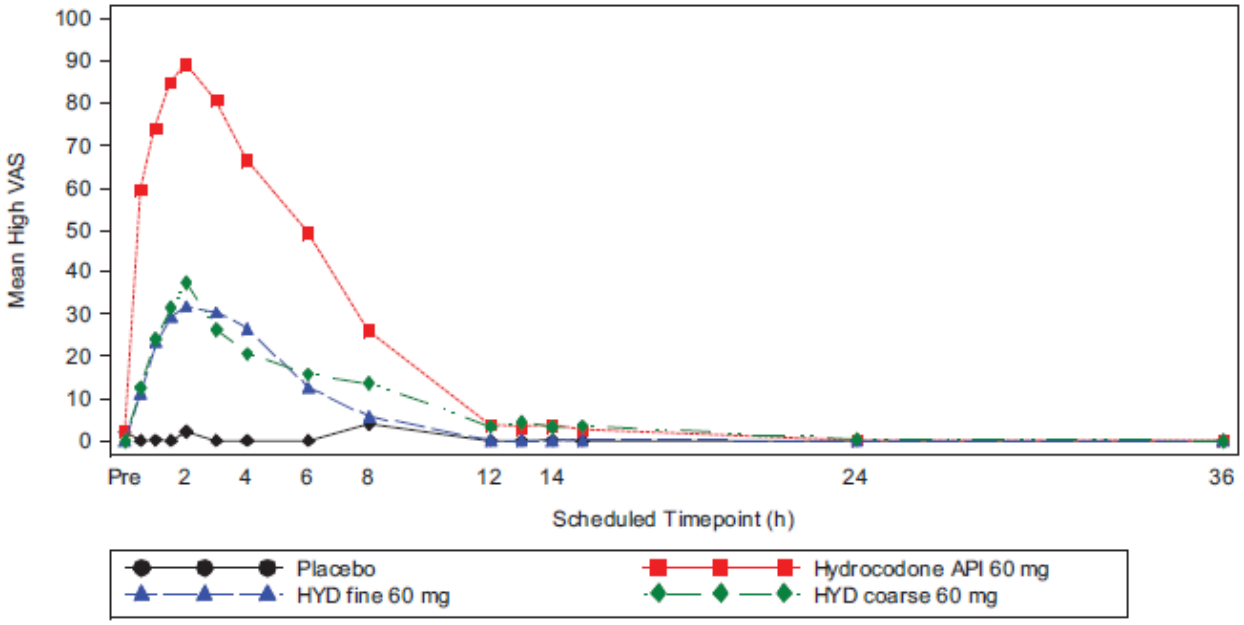
The sponsor provided the plots of mean scores over time on the primary measures of Drug Liking VAS and High VAS are presented in Figure 3.2.2.2, and Figure 3.2.2.3, respectively.

Figure 3.2.2.2 Mean Scores Over Time for Drug Liking VAS (Intranasal Administration, Fine and Coarse Particle Size) in Study HYD1014 (PD Population)



Source: sponsor's hyd1014 -study-report-body.pdf Figure 2.
API=active pharmaceutical ingredient; VAS=visual analog scale.
Drug Liking VAS is a bipolar scale: "At this moment, my liking for this drug is," where responses range from 0 (Strong disliking) to 100 (Strong liking), and 50 (Neither like nor dislike) is the neutral point.

Figure 3.2.2.3 Mean Scores Over Time for High VAS (Intranasal Administration, Fine and Coarse Particle Size) in Study HYD1014 (PD Population)



Source: sponsor's hyd1014 -study-report-body.pdf Figure 6.
API=active pharmaceutical ingredient; VAS=visual analog scale.
High VAS item: "I am feeling high," where responses range from 0 (Definitely not) to 100 (Definitely so).

Table 3.2.2.3 from the sponsor presents a summary of Emax scores for the two primary measures and for measures of balance of effects.

Table 3.2.2.3 Summary of Maximum (Emax) Scores on Primary Endpoints and Measures of Balance of Effects Following Intranasal Administration of HYD (Fine and Coarse Particle Size) in Recreational Opioid Users in Study HYD1014 (PD Population)

Measure	N=25	Placebo	Hydrocodone API 60 mg powder	HYD fine particle size 60 mg	HYD coarse particle size 60 mg
Drug Liking VAS	Mean (SD)	50.6 (0.49)	90.4 (13.2)	66.8 (18.4)	65.4 (18.4)
	Median	51.0	100	61.0	56.0
High VAS	Mean (SD)	6.3 (16.4)	93.3 (15.3)	38.8 (41.5)	44.1 (42.8)
	Median	0.0	100.0	16.0	50.0
Overall Drug Liking VAS	Mean (SD)	50.2 (0.47)	89.4 (13.6)	62.2 (21.7)	61.2 (16.4)
	Median	50.0	97.0	61.0	51.0
Take Drug Again VAS	Mean (SD)	2.0 (10.0)	85.2 (24.9)	40.7 (38.4)	36.4 (41.0)
	Median	0.0	100	50.0	14.0
Subjective Drug Value	Mean (SD)	0.25 (0.00)	29.0 (14.7)	12.4 (15.6)	8.73 (13.6)
	Median	0.25	29.3	9.0	0.25

Source: sponsor's hyd1014 -study-report-body.pdf Tables 10, 13, and 15.
Emax=maximum effect; SD=standard deviation; VAS=visual analog scale.

The pairwise comparisons of arms for drug liking VAS and high VAS are from the sponsor and are shown the Tables 3.2.2.4, 3.2.2.5, and 3.2.2.6 respectively. These results were verified by this reviewer.

Table 3.2.2.4 Analysis Results for Drug Liking VAS Emax and TA_AUE (PD Population)

	E_{max}			TA_AUE		
	Median Difference	IQR	*P* value	Median Difference	IQR	*P* value
Overall Treatment Effect	–	–	**<0.001**	–	–	**<0.001**
Pairwise Comparisons						
Hydrocodone vs Placebo (Study Validity)						
Hydrocodone API 60 mg - Placebo	49.0	32.0, 49.0	**<0.001**	3.87	2.55, 10.07	**<0.001**
HYD vs Hydrocodone API						
HYD fine 60 mg - Hydrocodone API 60 mg	-24.0	-40.0, -8.0	**<0.001**	-2.92	-9.02, -1.08	**<0.001**
HYD coarse 60 mg - Hydrocodone API 60 mg	-30.0	-42.0, -7.0	**<0.001**	-3.65	-9.19, -1.01	**<0.001**
HYD vs Placebo						
HYD fine 60 mg - Placebo	11.0	0.0, 26.0	**<0.001**	0.93	-0.00, 2.81	**0.003**
HYD coarse 60 mg - Placebo	6.0	0.0, 25.0	**<0.001**	0.34	-0.11, 1.44	0.051
HYD vs HYD						
HYD coarse 60 mg - HYD fine 60 mg	0.0	-11.0, 1.0	0.587	-0.37	-2.03, 0.08	0.238

Source: sponsor's hyd1014 -study-report-body.pdf Table 11.
API=active pharmaceutical ingredient; Emax=maximum effect; HYD=hydrocodone bitartrate q24h film coated tablet; IQR=interquartile range; PD=pharmacodynamic; TA_AUE=time-averaged area under the effect curve; VAS=visual analog scale
Overall Treatment Effect was assessed using Friedman's test. Pairwise treatment comparisons were assessed using the Wilcoxon sign-rank test on the within-subject differences. Significant *P* values appear in bold.

Table 3.2.2.5 Analysis Results for High VAS Emax and TA_AUE (PD Population)

	E_{max}			TA_AUE		
	Median Difference	IQR	*P* value	Median Difference	IQR	*P* value
Overall Treatment Effect	–	–	**<0.001**	–	–	**<0.001**
Pairwise Comparisons						
Hydrocodone vs Placebo (Study Validity)						
Hydrocodone API 60 mg - Placebo	100.0	82.0, 100.0	**<0.001**	16.43	8.24, 22.85	**<0.001**
HYD vs Hydrocodone API						
HYD fine 60 mg - Hydrocodone API 60 mg	-65.0	-99.0, -12.0	**<0.001**	-8.53	-16.43, -5.67	**<0.001**
HYD coarse 60 mg - Hydrocodone API 60 mg	-40.0	-84.0, 0.0	**<0.001**	-8.76	-11.99, -3.93	**<0.001**
HYD vs Placebo						
HYD fine 60 mg - Placebo	16.0	0.0, 70.0	**0.001**	0.76	0.00, 8.07	**0.001**
HYD coarse 60 mg - Placebo	37.0	0.0, 81.0	**<0.001**	0.59	0.00, 8.92	**0.002**
HYD vs HYD						
HYD coarse 60 mg - HYD fine 60 mg	0.0	-10.0, 19.0	0.640	0.00	-0.76, 2.91	0.672

Source: sponsor's hyd1014 -study-report-body.pdf Table 16.
API=active pharmaceutical ingredient; Emax=maximum effect; HYD=hydrocodone bitartrate q24h film coated tablet; IQR=interquartile range; PD=pharmacodynamic; TA_AUE=time-averaged area under the effect curve; VAS=visual analog scale
Overall Treatment Effect was assessed using Friedman's test. Pairwise treatment comparisons were assessed using the Wilcoxon sign-rank test on the within-subject differences. Significant *P* values appear in bold.

Table 3.2.2.6 presents the inferential results (Emax) from the sponsor for Overall Drug Liking VAS, Take Drug Again VAS, and Subjective Drug Value, respectively.

Table 3.2.2.6 Analysis Results for Overall Drug Liking VAS, Take Drug Again VAS, and Subjective Drug Value Emax (PD Population)

	Overall Drug Liking E_{max}			Take Drug Again E_{max}			Subjective Drug Value E_{max}		
	Median Difference	IQR	*P* value	Median Difference	IQR	*P* value	Median Difference	IQR	*P* value
Overall Treatment Effect	–	–	**<0.001**	–	–	**<0.001**	–	–	**<0.001**
Pairwise Comparisons									
Hydrocodone vs Placebo (Study Validity)									
Hydrocodone API 60 mg - Placebo	47.0	31.0, 50.0	**<0.001**	93.0	77.0, 100.0	**<0.001**	29.00	14.75, 40.50	**<0.001**
HYD vs Hydrocodone API									
HYD fine 60 mg - Hydrocodone API 60 mg	-25.0	-37.0, -14.0	**<0.001**	-27.0	-84.0, -15.0	**<0.001**	-14.25	-26.50, -3.00	**<0.001**
HYD coarse 60 mg - Hydrocodone API 60 mg	-28.0	-43.0, -18.0	**<0.001**	-46.0	-88.0. -10.0	**<0.001**	-15.50	-30.75, -5.25	**<0.001**
HYD vs Placebo									
HYD fine 60 mg - Placebo	11.0	0.0, 26.0	**0.003**	50.0	0.0, 71.0	**<0.001**	8.75	0.00, 14.75	**<0.001**
HYD coarse 60 mg - Placebo	1.0	0.0. 18.0	**<0.001**	14.0	0.0, 79.0	**<0.001**	0.00	0.00, 13.50	**<0.001**
HYD vs HYD									
HYD coarse 60 mg - HYD fine 60 mg	0.0	-9.0, 3.0	0.502	0.0	-10.0, 1.0	0.525	0.00	-8.00, 0.00	0.070

Source: sponsor's hyd1014 -study-report-body.pdf Table 14.
API=active pharmaceutical ingredient; Emax=maximum effect; HYD=hydrocodone bitartrate q24h film coated tablet; IQR=inter-quartile range; PD=pharmacodynamic; VAS=visual analog scale
Overall Treatment Effect was assessed using Friedman's test. Pairwise treatment comparisons were assessed using the Wilcoxon sign-rank test on the within-subject differences.
Significant *P* values appear in bold.

Responder Analysis – Drug Liking VAS

Table 3.2.2.7 presents the sponsor's results of the proportion test in Drug Liking VAS Emax score following administration of HYD fine and HYD coarse in comparison to their scores following administration of hydrocodone API. The results were verified by this reviewer.

Table 3.2.2.7 Drug Liking VAS Responder Analysis (PD Population)

	Percent Reduction					
	HYD fine 60 mg vs Hydrocodone API 60 mg					
	≥30%	≥40%	≥50%	≥60%	≥70%	≥80%
Responder rate	0.72	0.68	0.64	0.56	0.48	0.44
Z-score	2.20	1.80	1.40	0.60	-0.20	-0.60
P value	**0.014**	**0.036**	0.081	0.274	0.579	0.726
	HYD coarse 60 mg vs Hydrocodone API 60 mg					
	≥30%	≥40%	≥50%	≥60%	≥70%	≥80%
Responder rate	0.68	0.64	0.64	0.60	0.56	0.52
Z-score	1.80	1.40	1.40	1.00	0.60	0.20
P value	**0.036**	0.081	0.081	0.159	0.274	0.421

Source: sponsor's hyd1014 -study-report-body.pdf Table 12.
API=active pharmaceutical ingredient; HYD=hydrocodone bitartrate q24h film coated tablet; PD=pharmacodynamic; VAS=visual analog scale
Percent reduction is the reduction from the positive control (hydrocodone API) to the test drug (HYD fine or HYD coarse). Responder rate is the proportion of subjects with a specific percent reduction. Significant *P* values appear in bold.

This reviewer also performed the following analyses. Table 3.2.2.8 (A and B) shows the frequency distribution of subjects in terms of their responses to the positive control as well as

their percent reductions for the test drug relative to the positive control. The percentages of patients with Emax VAS greater than or equal to that of the patients treated with the positive control were 20% (n=5) in patients with HYD treatments.

Table 3.2.2.8 Contingency Table for Emax of Drug Liking VAS of the positive control by percent reduction (Study 1014).
A. HYD 60 mg Coarse vs. Hydrocodone 60 mg Solution

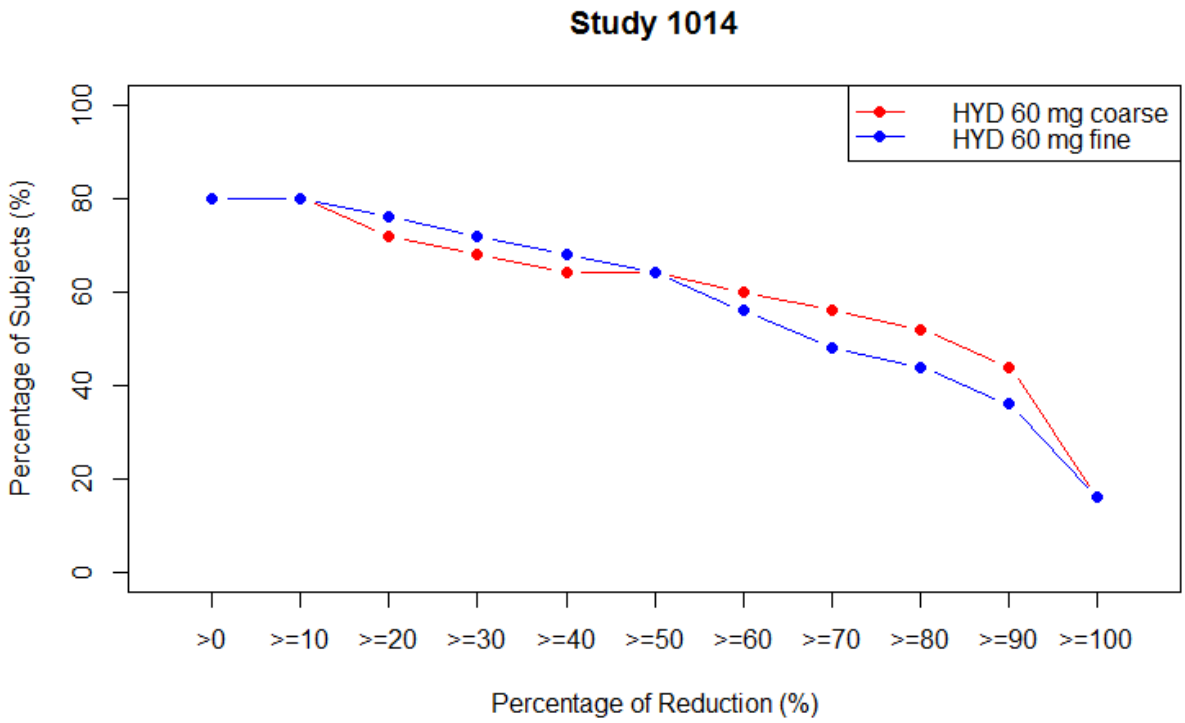
Hydrocodone 60 mg solution (Emax)	Percent of Reduction (%)													
	<0	0	(0, 10)	[10, 20)	[20, 30)	[30, 40)	[40, 50)	[50, 60)	[60, 70)	[70, 80)	[80, 90)	[90, 100)	>=100	Total
<=55	0	1	0	0	0	0	0	0	0	0	0	0	0	1
(55, 60]	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(60, 65]	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(65, 70]	0	0	0	0	0	0	0	0	0	0	0	0	1	1
(70, 75]	0	0	0	0	0	0	0	0	0	0	0	1	0	1
(75, 80]	0	1	0	0	1	0	0	0	0	0	0	0	0	2
(80, 85]	0	0	0	0	0	0	0	0	0	0	0	2	2	4
(85, 90]	1	0	0	0	0	0	0	0	0	0	0	0	0	1
(90, 95]	0	0	0	0	0	1	0	0	0	0	0	0	0	1
(95, 100]	0	2	0	2	0	0	0	1	1	1	2	4	1	14
Total	1	4	0	2	1	1	0	1	1	1	2	7	4	25
pct (%)	4	16	0	8	4	4	0	4	4	4	8	28	16	100
cpct (%)	100	96	80	80	72	68	64	64	60	56	52	44	16	

B. HYD 60 mg Fine vs. Hydrocodone 60 mg Solution

Hydrocodone 60 mg solution (Emax)	Percent of Reduction (%)													
	<0	0	(0, 10)	[10, 20)	[20, 30)	[30, 40)	[40, 50)	[50, 60)	[60, 70)	[70, 80)	[80, 90)	[90, 100)	>=100	Total
<=55	0	1	0	0	0	0	0	0	0	0	0	0	0	1
(55, 60]	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(60, 65]	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(65, 70]	0	0	0	0	0	0	0	0	0	0	0	0	1	1
(70, 75]	0	0	0	0	0	0	0	0	0	0	0	0	1	1
(75, 80]	0	0	0	0	1	0	0	0	0	0	0	1	0	2
(80, 85]	0	0	0	0	0	0	0	1	2	0	1	0	0	4
(85, 90]	1	0	0	0	0	0	0	0	0	0	0	0	0	1
(90, 95]	1	0	0	0	0	0	0	0	0	0	0	0	0	1
(95, 100]	0	2	0	1	0	1	1	1	0	1	1	4	2	14
Total	2	3	0	1	1	1	1	2	2	1	2	5	4	25
pct (%)	8	12	0	4	4	4	4	8	8	4	8	20	16	100
cpct (%)	100	92	80	80	76	72	68	64	56	48	44	36	16	

Figure 3.2.2.4 shows that the percent reduction profile of subjects in the HYD 60 mg coarse and fine arms are similar relatively to that of the positive comparator.

Figure 3.2.2.4 Percent Reduction Profile for Emax of Drug Liking VAS for Study 1014.



Note that the two curves have similar trends with the curve of HYD 60 mg fine lower in the percentage of reduction ≥60%.

Summary of Study HYD1014
The HYD formulation, when administered via the intranasal route as either fine or coarse particle size, demonstrated significantly lower subjective and physiologic effects and greater intranasal irritation compared with hydrocodone API powder administered intranasally. The results of the study indicate that HYD may have lower intranasal abuse potential compared to hydrocodone 60 mg API.

3.3 Evaluation of Safety
An evaluation of the safety of Hydrocodone bitartrate extended-release oral tablets presented in this submission is included in the clinical review by Drs. James Tolliver and Martin Rusinowitz.

3.4 Benefit:Risk Assessment (Optional)

I did not conduct a benefit:risk analysis.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

No subgroups were analyzed due to small samples sizes in each subgroup.

4.3 Other Special/Subgroup Populations
No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues
- The missing rates of subjects from the two studies are high, 13% for Study 1013 and 22% for Study 1014, respectively. The effects of missing data are not considered in the statistical analyses, which could change the conclusion under worst scenario on the abuse-deterrence effect of HYD.
- Although statistically significant decreases were observed for the two primary endpoints at level of 0.05 for all three HYD treatments, test results of HYD milled vs. hydrocodone solution in some important secondary PD endpoints were not statistically significant.

5.2 Collective Evidence
In study HYD1013, HYD demonstrated significantly lower subjective effects compared to hydrocodone API solution, when administered by the oral route as intact or chewed. Although statistically significant decreases were observed for the two primary endpoints at level of 0.05 for all three HYD treatments, significant decrease in the milled HYD treatment was not supported by some important secondary PD endpoints. Moreover, the clinical data suggest that

treatments “HYD 60 mg milled” and “hydrocodone 60 mg solution” have similar drug abuse ability as evidenced:

- The sponsor provided The plots of mean scores over time on the primary measures of Drug Liking VAS and High VAS (Figure 3.2.1.2, and Figure 3.2.1.3), from the sponsor showed that the curves of treatments “HYD 60 mg milled” and “hydrocodone 60 mg solution” are closer to each other than other three treatments.
- The treatments “HYD 60 mg milled” and “hydrocodone 60 mg solution” have the same or similar values of mean and median in maximum (Emax) scores on primary endpoints and measures of balance of effects as shown in Table 3.2.1.3.
- The p-values for the difference of (HYD 60 mg milled – Hydrocodone 60 mg solution) are much larger than its peers. Although it is significant at alpha level of 0.05 for Emax, it is not significant for TA_AUE (p=0.272) (Table 3.2.1.4).
- The p-value for the difference of (HYD 60 mg milled – Hydrocodone 60 mg solution) is much larger than its peers in TA_AUE (p=0.019) (Table 3.2.1.5).
- The p-values for the difference of (HYD 60 mg milled – Hydrocodone 60 mg solution) are much larger than its peers and not statistically significant at alpha level of 0.05 for all the three endpoints (Table 3.2.1.6).
- The p-values are not significant for HYD 60 mg milled vs. Hydrocodone 60 mg solution in drug liking VAS responder analysis (Table 3.2.1.7).
- Figure 3.2.1.4 shows that the curve for HYD 60 mg milled treatment is distinctively lower than the other two curves, suggesting its VAS scores are closer to that of the Hydrocodone 60 mg solution treatment.
- There are 60% (n=21) patients in the HYD 60 mg milled treatment with Emax VAS greater than or equal to that of the patients treated with the positive control. The percentages of patients with Emax VAS greater than or equal to that of the patients treated with the positive control were ≤20% (n≤7) in patients with other HYD treatments. The differences suggest that the Emax VAS values of patients treated with the HYD 60 mg milled are much closer to that of the patients treated with hydrocodone 60 mg solution than those treated with other HYD 60 mg forms.

In study HYD1014, the HYD formulation, when administered via the intranasal route as either fine or coarse particle size, demonstrated significantly lower subjective and physiologic effects and greater intranasal irritation compared with hydrocodone API powder administered intranasally. The results of the study indicate that HYD may have lower intranasal abuse potential compared to hydrocodone 60 mg API.

5.3 Conclusions and Recommendations

The abuse deterrent properties of HYD were evaluated in 2 randomized, double-blind, placebo and active-controlled clinical studies (HYD1013 and HYD1014) in nondependent recreational opioid drug users.

The numbers of completers were 35 (87%) and 25 (78%) in studies HYD1013 and HYD1014, respectively.

This reviewer confirmed that

- In study HYD1013, the oral abuse potential of chewed HYD 60 mg tablet and milled HYD (processed in an industrial mill) 60 mg tablet were compared to intact HYD 60 mg tablet, hydrocodone API 60 mg solution, and placebo. Mean maximum PD effect (Emax) values for positive PD measures were greatest for the hydrocodone API solution, followed in descending order by milled HYD, chewed HYD, intact HYD, and placebo. Although statistically significant decreases were observed for the two primary endpoints at level of 0.05 for all three HYD treatments, the milled HYD treatment was similar to hydrocodone 60 mg solution in some properties of important secondary PD endpoints. Relatively large reductions in abuse potential were observed with intact and chewed HYD while the differences in abuse potential were less with the milled HYD treatment. The results of this study suggest that when HYD is administered by the oral route as intact or chewed, it has lower oral abuse potential than hydrocodone 60 mg solution.
- In study HYD1014, the intranasal abuse potential of fine and coarse particle size HYD 60 mg (produced using an industrial mill and razor blade, respectively) were compared to hydrocodone API powder (60 mg) and placebo. Mean Emax values for positive PD measures were greatest for 60 mg hydrocodone powder, followed by the fine and coarse particle size of HYD 60 mg treatments and placebo. The results of the study suggest that HYD has lower intranasal abuse potential than non-abuse-deterrent hydrocodone 60 mg.

The results of the two clinical abuse potential studies suggest that the reductions in subjective opioid-related effects observed with HYD administration (60 mg) via the intranasal and chewed oral routes have less abuse potential as compared to hydrocodone 60 mg.

5.4 Labeling Recommendations (as applicable)

Labeling Recommendations:

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

1. (subsection: Clinical Abuse Potential Studies) For both Figure 1 (page 18) and Figure 2 (page 19), the last scale on the X-axis should be changed to "≥100" (currently ">100").

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/s/

WEI LIU
06/20/2014

QIANYU DANG
06/20/2014

YI TSONG
06/20/2014

Statistics Filing Checklist
Division of Biometrics II

Date: 05/29/14

NDA #: 206-627 Priority Classification: priority

Trade Name: Hydrocodone bitartrate once-daily film-coated tablets

Applicant: Purdue Pharma L.P.

Date of Submission: 04/28/14

Indication: the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

No. of Controlled Phase 3 Studies: 1

User Fee Goal Date: 10/28/14

Date of 45-Day Meeting: 05/22/14

Medical Officer: Jackie Spaulding

Project Manager: Dominic Chiapperino

Statistical Reviewer: Yan Zhou, Ph.D.

Statistical sections: Sections 2.5, 2.7 and 5.3.5

Comments:

1. It is fileable.

CHECKLIST

Item	**Check (NA if not applicable)**
Index sufficient to locate necessary reports, tables, etc.	**Yes**
Original protocols & subsequent amendments available in the NDA	**Yes**
Designs utilized appropriate for the indications requested	**Yes**
Endpoints and methods of analysis spelled out in the protocols	**Yes**
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	**Yes**
Appropriate references included for novel statistical methodology (if present)	**NA**
Data from primary studies in electronic data room	**Yes**
Sufficient data listings and intermediate analysis tables to permit statistical review	**Yes**
Intent-to-treat analysis	**Yes**
Effects of dropouts on primary analyses investigated	**Yes**
Safety and efficacy for gender, racial, and geriatric subgroups investigated	**Yes**

BRIEF SUMMARY OF CONTROLLED PHASE 3 CLINICAL TRIALS

Study Number (Dates Conducted)	Number of Sites	Sample Size	Type of Control	Design	Duration of Treatment
HYD3002 (03/2012 – 09/2013)	94 sites in US	Enrolled/screened: 1927 Run-in period: 905 Randomization: Hydrocodone: 296 Placebo: 292	Placebo	Multicenter, randomized, double-blind, placebo-controlled study with an open-label run-in period in patients with moderate to severe chronic low back pain	Open-label run-in period: up to 45 days Randomization period: 12 weeks (+ 3 days)

_____

Zhou, Yan
Mathematical Statistician

Concur: Janice Derr, Ph.D.
Team Leader

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/s/

YAN ZHOU
06/02/2014

JANICE A DERR
06/03/2014