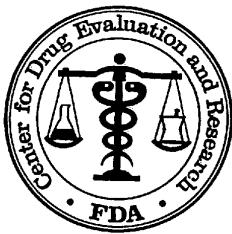


**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

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**STATISTICAL REVIEW(S)**



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

## Statistical Review and Evaluation CARCINOGENICITY STUDIES

<b>IND/NDA Number:</b>	NDA 205-777
<b>Drug Name:</b>	Naloxone HCL (Oxycodone)
<b>Indication(s):</b>	105 Week Rat and 26 Week Mouse Carcinogenicity Studies
<b>Applicant:</b>	<b>Sponsor:</b> (b) (4) 
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<b>Biometrics Division:</b>	Division of Biometrics -6
<b>Statistical Reviewer:</b>	Mohammad Atiar Rahman, Ph.D.
<b>Concurring Reviewer:</b>	Karl Lin, Ph.D.
<b>Medical Division:</b>	Division of Anesthesia, Analgesia and Addiction Products
<b>Reviewing Pharmacologist:</b>	Belinda Hayes, Ph.D.
<b>Project Manager:</b>	Lisa Basham
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## 1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in transgenic mice. These studies were intended to assess the carcinogenic potential of Naloxone HCL (Oxycodone) at appropriate dose levels, administered daily orally through dietary admixture for 2 years in rats and through gavage for 26 weeks in mice. Results of this review have been discussed with the reviewing pharmacologist Dr. Hayes.

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

## 2. Rat Study

Two separate experiments were conducted, one in male and one in female rats. In each of these two experiments there were three treated groups, one vehicle control group (Control 1), and one negative control group (Control 2). Three hundred Sprag Dawley rats of each sex were assigned randomly to the treated and control groups in equal size of 60 rats per group. The dose levels for treated groups were 4, 20, and 100 mg/kg/day. In this review these dose groups would be referred to as the low, medium, and high dose groups, respectively. The rats in vehicle control group received the vehicle (Certified rodent diet # 5002), while the rats in negative control group remained untreated.

Since the surviving number of male rats in vehicle control group reached 20, all male rats were sacrificed during Week 101. The female rats completed the study period and were sacrificed during Week 105.

During the administration period all rats were observed twice daily for morbidity and mortality. A detailed examination was performed at least once weekly for general health and clinical conditions. The rats were palpated regularly for the appearance of masses during the clinical observations. The body weights of all rats were measured once before the beginning of the study and weekly for up to Week 13 and then every fourth week.

A complete histopathological evaluation was performed on the rats in vehicle control and high dose groups. A complete histopathological evaluation was also performed on all rats that died or were necropsied prior to the scheduled termination.

### 2.1. Sponsor's analyses

#### 2.1.1. Survival analysis

The sponsor used the data from vehicle control group, low, medium, and high dose groups for survival analysis. The sponsor calculated the survival probabilities of each animal using the Kaplan-Meir method. They tested the differences in intercurrent mortalities among the study groups using the Cox's log-rank test and the generalized Wilcoxon test. The pairwise comparisons between the

vehicle control and each dose group were conducted using the Fisher exact test. In addition, Tarone's test was applied to test for a linear dose-response relationship in the probability of survival.

**Sponsor's findings:** The Sponsor's analysis showed 41, 40, 39, and 34 number of deaths in male rats and 32, 31, 34, and 35 number of deaths in female rats in vehicle control, low, medium and high dose groups, respectively. The sponsor's analysis did not show statistically significant dose response relationships or differences in mortalities among these treatment groups in either sex. The sponsor provided no information in their report regarding the mortality of rats in negative control.

### 2.1.2. Tumor data analysis

The sponsor also used the data from vehicle control group, low, medium, and high dose groups for tumor data analysis. The sponsor analyzed the tumor incidence data for positive dose response relationships and pairwise comparisons of treated groups with vehicle control using the methods outlined in the paper of Peto et al. (1980).

**Reviewer's comment:** *Since not all animals (except for animals that died during the study) in the low, and medium dose groups were histopathologically examined, the test for dose response relationship involving low and medium dose groups may not be appropriate.*

**Adjustment for multiple testing:** The sponsor did not mention of any method for multiple testing of tumor data in the submitted report.

**Sponsor's findings:** The sponsor's analyses did not show statistically significant dose response relationship across the treatment groups in any of the observed tumor types. Pairwise comparisons also did not show statistically significant increased incidence of any of the observed tumor types in the treated groups compared to the vehicle control.

## 2.2. Reviewer's analyses

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

### 2.2.1. Survival analysis

The survival distributions of rats in all five treatment groups were estimated using the Kaplan-Meier product limit method. For vehicle control, low, medium, and high dose groups, the dose response relationship was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates for all treatment groups are given in Figures 1A and 1B in the appendix for male and female rats, respectively. The intercurrent mortality data of all treatment are given in Tables 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female rats, respectively.

**Reviewer's findings:** This reviewer's analysis showed 40, 37, 38, 34, and 38 number of deaths in male rats and 32, 30, 34, 35, and 34 number of deaths in female rats in the vehicle control, low, medium, high dose, and negative control groups, respectively. The tests did not show statistically significant dose response relationship in mortality across vehicle control and treated groups in either sex. The pairwise comparisons also did not show statistically significant increased mortality in any of the treated groups compared to the vehicle control in either sex.

**Reviewer's comment:** *The sponsor's calculation showed 41, 40, 39, and 34 number of deaths in male rats and 32, 31, 34, and 35 number of deaths in female rats in vehicle control, low, medium and high dose groups, respectively, while this reviewer's analysis showed 40, 37, 38, and 34 number of deaths in male rats and 32, 30, 34, and 35 number of deaths in female rats in these groups, respectively. As seen, there are some differences between the sponsor's and this reviewer's calculation of number of deaths. These differences are due to the fact that there were 1 (#134), 3 (#315, #335, and #336), and 1 (#416) male rat in the vehicle control, low, and medium dose groups that died during the terminal sacrifice week which the sponsor counted with the naturally dead rats while this reviewer counted them with the terminally sacrificed animals. Similarly, there was 1 (#1327) female rat in the low dose groups that died during the terminal sacrifice week which the sponsor counted with the naturally dead rats while this reviewer counted them with the terminally sacrificed animals.*

## 2.2.2. Tumor data analysis

For carcinogenicity studies with a negative and a vehicle control group, the FDA guidance for the carcinogenicity study design and data analysis suggests analyzing the tumor data of treated groups along with the data of vehicle control. Following this suggestion, for this review, this reviewer used the tumor data of vehicle control, low, medium, and high dose groups for tumor data analysis.

For tumor data analysis the FDA guidance in general suggests to test for the positive dose response relationship as the primary analysis. The guidance also suggests performing the pairwise comparisons of treated groups and the controls as additional analysis. However, in special cases like the present study, where complete the data from all dose groups are not available, the dose response relationship tests may not be appropriate. In such cases pairwise comparisons of the treated groups with the control may be more meaningful. In this review, this reviewer performed both the dose response relationship tests and pairwise comparisons of treated groups with vehicle control. As mentioned above the dose response relationship test with this data may not be as meaningful. Any findings in the dose response relationship should be interpreted carefully.

Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period ( $w_{\max}$ ) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of  $s_h = 1$ . An animal that dies at week  $w_h$  without a tumor before the end of the study gets a score of  $s_h = \left(\frac{w_h}{w_{\max}}\right)^k < 1$ . The adjusted group size is defined as  $\sum s_h$ . As an interpretation, an animal with score  $s_h = 1$  can be considered as a whole animal while an animal with score  $s_h < 1$  can be considered as a partial animal. The adjusted group size  $\sum s_h$  is equal to

N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male and female rats, respectively.

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

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

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

#### Tumor Types with P-Values $\leq 0.05$ for Dose Response Relationship or Pairwise Comparisons of Treated Groups and Control in Rats

Sex	Organ Name	Tumor Name	P_Value								
			Veh	Cont	Low	Med	High	Dose Resp	C vs. L		
Male	SKIN	BASAL CELL ADENOMA, BENIG	0	0	1	3		0.0209*	.	0.5301	0.1441
Female	Brain	Malignant Pituitary adenocarcinoma,	2	0	1	5		0.0138	1.0000	0.8790	0.1908
	Adrenal gland	Benign pheochromocytoma	3	0	3	5		0.0418	1.0000	0.6615	0.3203

\*Statistically significant

Based on the criteria of adjustment for multiple testing discussed above, the incidence of benign basal cell adenoma on skin was considered to have statistically significant dose response relationship in male rats. The pairwise comparison did not show statistically significant increased incidence in any of the observed tumor types in any treated group in either sex compared to their respective vehicle

control.

**Reviewer's comment:** As mentioned earlier, not all rats in the low and medium dose groups were histopathologically examined, and hence the dose response relationship test from this data may not be meaningful. The sponsor's report showed that for skin basal cell tumor 60 (100%), 53 (88%), 48 (80%), and 60 (100%) number (percent) of male rats were histologically examined in vehicle control, low, medium, and high dose groups. This reviewer's analysis is based on all rats (60 per group) with an assumption that the unexamined rats did not develop skin basal cell tumor. Since more than 80% of male rats in each treatment group were histopathologically examined, the dose response relationship test with assumption that the unexamined rats did not develop skin basal cell tumor may be reasonable.

### 3. Mouse Study

Two separate experiments were conducted, one in male and one in female Tg.rasH2 mice. In each of these two experiments there were three treated groups (low, medium, and high), one vehicle control group, and one positive control group. The group sizes of vehicle control, positive control, low, medium, and high dose groups were 30, 15, 25, 25, and 30 in each sex. The dose levels of low, medium and high dose groups were 25, 75, and 200 mg/kg/day. The vehicle control received the vehicle (Sterile water for injection), while the positive control mice were treated by intraperitoneal injection (urethane) on study days 1, 3 and 5. The test article and vehicle were administered daily via oral gavage for up to 26 weeks.

During the administration period all mice were observed twice daily for morbidity and mortality. A detailed hands on examination was performed on study day one and weekly thereafter. The Body weights of all mice were taken once weekly beginning on study day one through Week 13, and biweekly thereafter.

#### 3.1. Sponsor's analyses

##### 3.1.1. Survival analysis

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

**Sponsor's findings:** The sponsor's analysis showed 3, 6, 2, 1, and 1 deaths of male mice, and 0, 5, 1, 0, and 0 deaths of female mice in the vehicle control, positive control, low, medium and high dose groups, respectively. The sponsor's analysis showed statistically significant increased mortality in the female mice positive dose group compared to their vehicle control group.

##### 3.1.2. Tumor data analysis

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

**Adjustment for multiple testing:** The sponsor did not mention of any method for multiple testing of tumor data in the submitted report.

**Sponsor's findings:** The sponsor's analyses did not show any statistical significant dose response relationship or increased incidence of any tumor types in the treated groups compared to the vehicle control group in either sex. The sponsor mentioned that the incidence of all pulmonary and vascular tumors in test article-treated groups fell within the historical control range established at [REDACTED]<sup>(b)(4)</sup>. The sponsor further mentioned that the incidences of all other tumors (non-vascular and non-pulmonary) involved in the isolated organs and/or fell within the historical control ranges established at [REDACTED]<sup>(b)(4)</sup>. In the positive control males and females, there was a statistically significant increase ( $p < 0.05$ ) in the incidence of pulmonary tumors and splenic hemangiosarcomas when compared to the vehicle control mice.

### 3.2. Reviewer's analyses

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

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

#### 3.2.1. Survival analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data of all treatment groups are given in Tables 4A and 4B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals for vehicle control, low, medium, and high dose groups are given in Tables 5A and 5B in the appendix for male and female mice, respectively.

**Reviewer's findings:** This reviewer's analysis showed 3, 15, 2, 1, and 1 deaths in male mice, and 0, 15, 1, 0, and 0 deaths in female mice in negative control, positive control, low, medium, and high groups, respectively. The tests did not show statistically significant dose response relationship in mortality across the negative control and treatment groups in either sex. The pairwise comparisons also did not show statistically significant increased mortality in the treated groups compared to the negative control in either sex. The pairwise comparisons showed statistically significant increased mortality in the positive control compared to the negative control in both sexes.

**Reviewer's comment:** *The sponsor's calculation showed 3, 6, 2, 1, and 1 deaths of male mice, and 0, 5, 1, 0, and 0 deaths of female mice in the vehicle control, positive control, low, medium and high dose groups, respectively, while this reviewer's analysis showed 3, 15, 2, 1, and 1 deaths in male mice, and 0, 15, 1, 0, and 0 deaths in female mice in these groups, respectively. There are some differences in the sponsor's and this reviewer's calculated in the number of deaths in positive control group in both sexes. These differences are due to the fact that there were 9 male mice (#8232, #8234, #8235, #8238, #8242, #8243, #8244, #8245, #8707) and 10 female mice (#8359, #8360, #8360, #8362, #8363, #8364, #8365, #8367, #8369, #8370) in the positive control groups that*

*were interim sacrificed at Week 18 which the sponsor counted as terminally sacrificed while this reviewer counted them as naturally dead.*

### 3.2.2. Tumor data analysis

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

**Reviewer's findings:** This reviewer's analysis did not show statistically significant dose response relationship across the negative control and treated groups in any of the observed tumor types. The pairwise comparison also did not show statistically significant increased incidence of any of the observed tumor types in the treated groups compared to the negative control in either sex.

The pairwise comparison showed statistically significant increased incidences of alveolar-bronchiolar adenoma, alveolar-bronchiolar carcinoma, hemangiosarcoma in lungs with bronchiole, and hemangiosarcoma in spleen in positive control compared to the negative control in both sexes (See Tables 7A and 7B in the appendix).

## 4. Evaluation of the validity of design of rat and mouse studies

As has been noted, other than a significant dose response relationship in the incidence of benign basal cell adenoma on skin in male rats, none of the tumor types in either rats or mice showed statistically significant dose response relationship or increased incidence in the treated groups compared to their respective vehicle controls. However, before drawing any conclusion regarding the carcinogenic or non-carcinogenic potential of the study drug in rats and mice, it is important to look into the following two issues, as have been pointed out in a 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 about fifty to sixty 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 considered as a sufficient number and adequate exposure. In addition Chu, Cueto and Ward (1981), suggested that "to be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

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

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

- (i) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."
- (ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."
- (iii) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

It should be noted that the above criteria for the evaluation of study validity are for two year studies. Since the present mouse study is a 26 week study, these evaluation criterion are not applicable to the present mouse study. Therefore, in the following we will only investigate the validity of rat study only, 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 in Rats**

	Percentage of survival		
	End of 52 weeks	End of 78 weeks	End of 91 weeks
Male	88%	68%	50%
Female	97%	78%	61%

Based on the survival criterion Haseman proposed, it may be concluded that enough female rats were exposed to the high dose for a sufficient amount of time. For male rats the number of rats survived the first 91 weeks was marginal.

The following table shows the percent differences in mean body weight gains in rats from the vehicle 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 Differences in Mean body Weight Gains from Vehicle Controls in Rats

Male			Female		
Low	Medium	High	Low	Medium	High
-7.48	8.76	31.85	-10.69	1.50	30.96

Source: Table 7 - Summary of Body Weight Gains of sponsor's report

Therefore, relative to vehicle control the male rats in high dose group had about 32% and the female rats had about 31% increments in their body weight gains.

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

### Mortality Rates at the End of the Experiment in Rats

Control	Low	Medium	High
Male	67%	63%	57%
Female	53%	57%	58%

This shows that the morality rates in the male rats high dose group is 4% lower than their control, while that in female rats is 4% higher than their control.

Thus, from the mortality and the body weight gain data it can be concluded that the used high dose level might not have reached the MTD in either sex. For a final determination of the adequacy of the doses used, 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 regular rats and one in transgenic mice. These studies were intended to assess the carcinogenic potential of Naloxone HCL (Oxycodone) at appropriate drug levels, administered orally daily through dietary admixture in for 2 years in rats and through gavage for 26 weeks in mice.

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

**Rat Study:** Two separate experiments were conducted, one in male and one in female rats. In each of these two experiments there were three treated groups, one vehicle control group (Control 1), and one negative control group (Control 2). Three hundred Sprag Dawley rats of each sex were assigned randomly to the treated and control groups in equal size of 60 rats per group. The dose levels for treated groups were 4, 20, and 100 mg/kg/day. In this review these dose groups would be referred to as the low, medium, and high dose groups, respectively. The rats in vehicle control group received the vehicle (Certified rodent diet # 5002), while the rats in negative control group remained untreated.

Since the surviving number of male rats in vehicle control group reached 20, all male rats were sacrificed during Week 101. The female rats completed the study period and were sacrificed during Week 105.

During the administration period all rats were observed twice daily for morbidity and mortality. A detailed examination was performed at least once weekly for general health and clinical conditions. The rats were palpated regularly for the appearance of masses during the clinical observations. The body weights of all rats were measured once before the beginning of the study and weekly for up to Week 13 and then every fourth week.

A complete histopathological evaluation was performed on the rats in vehicle control and high dose groups. A complete histopathological evaluation was also performed on all rats that died or were necropsied prior to the scheduled termination.

The tests did not show statistically significant dose response relationship in mortality across vehicle control and treated groups in either sex. The pairwise comparisons also did not show statistically significant increased mortality in any of the treated groups compared to the vehicle control in either sex. The test showed statistically significant dose response relationship in the incidence of benign basal cell adenoma on skin in male rats. The pairwise comparisons did not show statistically significant increased incidence in any of the observed tumor types in any treated group in either sex compared to their respective vehicle control.

From the mortality and the body weight gain data it can be concluded that the used high dose level might not have reached the MTD in either sex. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

**Mouse Study:** Two separate experiments were conducted, one in male and one in female Tg.rasH2 mice. In each of these two experiments there were three treated groups, one vehicle control group, and one positive control group. The group sizes of vehicle control, positive control, low, medium, and high dose groups were 30, 15, 25, 25, and 30 in each sex. The dose levels of low, medium and high dose groups were 25, 75, and 200 mg/kg/day. The vehicle control received the vehicle (Sterile water for injection ), while the positive control mice were treated on study days 1, 3 and 5 by intraperitoneal injection (urethane). The test article and vehicle were administered daily via oral gavage for up to 26 weeks.

During the administration period all mice were observed twice daily for morbidity and mortality. A detailed hands-on examination was performed on study day one and weekly thereafter. The Body weights of all mice were taken once weekly beginning on study day one through Week 13, and biweekly thereafter.

The tests did not show statistically significant dose response relationship in mortality across the vehicle control and treated groups in either sex. The pairwise comparison also did not show statistically significant increased mortality in the treated groups compared to the vehicle control in either sex. The pairwise comparison showed statistically significant increased mortality in the positive control compared to the vehicle control in both sexes.

The tests did not show statistically significant dose response relationship among the treated groups involving the vehicle control in the incidence of any of the observed tumor types. The pairwise comparison also did not show statistically significant increased incidence of any of the observed tumor types in the treated groups compared to the vehicle control in either sex. The pairwise comparison showed statistically significant increased incidences of alveolar-bronchiolar adenoma, alveolar-bronchiolar carcinoma, hemangiosarcoma, in lungs with bronchiole and hemangiosarcoma in spleen in the positive control compared to the vehicle control in both sexes. The findings of the positive control validate sensitivity of the study.

No evaluation of the validation of mouse study was performed.

Mohammad Atiar Rahman, Ph.D.  
Mathematical Statistician

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

cc:

Archival NDA 205-777

Dr. Hayes  
Ms. Basham

Dr. Tsong  
Dr. Lin  
Dr. Rahman  
Ms. Patrician

## 6. Appendix

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

Week	Veh Cont		4 mg/kg/day		20 mg/kg/day		100 mg/kg/day		Neg Cont	
	No. of	No. of	No. of	No. of	No. of	No. of	No. of	No. of	No. of	No. of
0 - 52	3	5.00	1	1.67	1	1.67	1	1.67	7	11.67
53 - 78	20	38.33	16	28.33	12	21.67	15	26.67	12	31.67
79 - 91	9	53.33	6	38.33	17	50.00	11	45.00	11	50.00
92 - 100	8	66.67	14	61.67	8	63.33	7	56.67	8	63.33
Ter. Sac.	20	33.33	23	38.33	22	36.67	26	43.33	22	36.67
Total	N=60		N=60		N=60		N=60		N=60	

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

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

Week	Veh Cont		4 mg/kg/day		20 mg/kg/day		100 mg/kg/day		Neg Cont	
	No. of	No. of	No. of	No. of	No. of	No. of	No. of	No. of	No. of	No. of
0 - 52	.	.	1	1.67	.	.	2	3.33	2	3.33
53 - 78	8	13.33	3	6.67	6	10.00	13	25.00	11	21.67
79 - 91	9	28.33	14	30.00	15	35.00	13	46.67	10	38.33
92 - 104	15	53.33	12	50.00	13	56.67	7	58.33	11	56.67
Ter. Sac.	28	46.67	30	50.00	26	43.33	25	41.67	26	43.33
Total	N=60		N=60		N=60		N=60		N=60	

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

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

Test*	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.4776
Homogeneity	Log-Rank	0.5513

\*Tests for dose-response and homogeneity were performed using data from Vehicle control, low, medium and high dose groups.

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

Test*	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.3324
Homogeneity	Log-Rank	0.5969

\*Tests for dose-response and homogeneity were performed using data from Vehicle control, low, medium and high dose groups.

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

Organ Name	Tumor Name	0 mg		4 mg		20 mg		100 mg		P_Value Dose Resp	P_Value Veh C vs. L	P_Value Veh C vs. M	P_Value Veh C vs. H
		Veh C N=60	N=60	Low N=60	Med N=60	High N=60	Dose vs. L	Veh C vs. M	Veh C vs. H				
BRAIN	ASTROCYTOMA, MALIGNANT	1	0	3	1	0	0.4249	1.0000	0.3539	0.7762	.	.	.
	EPENDYMOIMA, BENIGN	0	0	0	1	0	0.2632	.	.	0.5357	.	.	.
	LYMPHOMA, MALIGNANT	0	0	1	0	0	0.5118	.	0.5244	.	.	.	.
	MENINGIOMA, BENIGN	0	0	1	0	0	0.5146	.	0.5301	.	.	.	.
EAR	SQUAMOUS CELL PAPILLOMA,	0	1	1	0	0	0.6464	0.5301	0.5244	.	.	.	.
EPIDIDYMIS	PROSTATIC ADENOCARCINOMA,	0	1	0	0	0	0.7719	0.5357	.	.	.	.	.
	SCHWANNOMA, MALIGNANT	0	0	0	1	0	0.2588	.	.	0.5301	.	.	.
	TRANSITIONAL CELL CARCINO	0	1	0	0	0	0.7719	0.5357	.	.	.	.	.
EYE	FIBROSARCOMA, MALIGNANT	0	0	0	1	0	0.2588	.	.	0.5301	.	.	.
GLAND, ADRENAL	ADENOMA, CORTICAL, BENIGN	3	0	2	0	0	0.9043	1.0000	0.8555	1.0000	.	.	.
	LYMPHOMA, MALIGNANT	0	0	2	0	0	0.5146	.	0.2780	.	.	.	.
	MALIGNANT PHEOCHROMOCYTOM	1	0	0	1	0	0.4495	1.0000	1.0000	0.7762	.	.	.
	PHEOCHROMOCYTOMA, BENIGN	7	5	4	6	0	0.4773	0.8661	0.9227	0.7705	.	.	.
	PHEOCHROMOCYTOMA, BILATER	3	3	1	4	0	0.2885	0.7166	0.9526	0.5665	.	.	.
GLAND, HARDERIA	FIBROSARCOMA, MALIGNANT	0	0	0	1	0	0.2588	.	.	0.5301	.	.	.
GLAND, MAMMARY	FIBROADENOMA, BENIGN	1	1	1	0	0	0.8465	0.7874	0.7823	1.0000	.	.	.
	LIPOMA, BENIGN	2	0	0	0	0	1.0000	1.0000	1.0000	1.0000	.	.	.
GLAND, PARATHYR	ADENOMA, BENIGN	2	1	1	0	0	0.9338	0.9041	0.9005	1.0000	.	.	.
GLAND, PITUITAR	ADENOMA, PARS DISTALIS, B	29	26	28	28	0	0.5674	0.9515	0.8637	0.8637	.	.	.
	ADENOMA, PARS INTERMEDIA,	0	0	1	0	0	0.5146	.	0.5301	.	.	.	.
GLAND, PREPUTIA	SQUAMOUS CELL CARCINOMA,	0	0	1	0	0	0.5118	.	0.5244	.	.	.	.
GLAND, PROSTATE	ADENOCARCINOMA, MALIGNANT	0	2	0	0	0	0.8283	0.2840	.	.	.	.	.
	METASTATIC ADENOCARCINOMA	1	0	0	0	0	1.0000	1.0000	1.0000	1.0000	.	.	.
	SCHWANNOMA, MALIGNANT	1	0	0	0	0	1.0000	1.0000	1.0000	1.0000	.	.	.
GLAND, SALIVARY	HISTIOCYTIC SARCOMA, MALI	0	0	1	0	0	0.5118	.	0.5244	.	.	.	.
	SCHWANNOMA, MALIGNANT	1	0	0	0	0	1.0000	1.0000	1.0000	1.0000	.	.	.
GLAND, SEMINAL	MESOTHELIOMA, MALIGNANT	1	0	0	0	0	1.0000	1.0000	1.0000	1.0000	.	.	.
	METASTATIC ADENOCARCINOMA	1	0	0	0	0	1.0000	1.0000	1.0000	1.0000	.	.	.
	PROSTATIC ADENOCARCINOMA,	0	1	0	0	0	0.7719	0.5357	.	.	.	.	.
	SCHWANNOMA, MALIGNANT	1	0	0	0	0	1.0000	1.0000	1.0000	1.0000	.	.	.
	TRANSITIONAL CELL CARCINO	0	1	0	0	0	0.7719	0.5357	.	.	.	.	.
GLAND, THYROID	ADENOCARCINOMA, FOLLICULA	0	1	0	1	0	0.3323	0.5301	.	0.5301	.	.	.
	ADENOMA, C-CELL, BENIGN	1	3	2	1	0	0.7141	0.3640	0.5457	0.7823	.	.	.
	ADENOMA, C-CELL, MULTIPLE	1	1	0	0	0	0.9484	0.7823	1.0000	1.0000	.	.	.
	ADENOMA, FOLLICULAR, BENI	0	3	0	2	0	0.3160	0.1489	.	0.2780	.	.	.
	C-CELL CARCINOMA, MALIGNA	1	0	0	0	0	1.0000	1.0000	1.0000	1.0000	.	.	.
	CARCINOMA, C-CELL, MALIGN	1	0	0	0	0	1.0000	1.0000	1.0000	1.0000	.	.	.

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

Organ Name	Tumor Name	0 mg		4 mg		20 mg		100 mg		P_Value	P_Value	P_Value	P_Value
		Veh C N=60	Low N=60	Med N=60	High N=60	Dose Resp	Veh C vs. L	Veh C vs. M	Veh C vs. H				
GLAND, ZYMBAL	CARCINOMA, MALIGNANT	1	1	1	0	0.8431	0.7815	0.7762	1.0000				
GROSS LESION	HISTIOCYTIC SARCOMA, MALI	0	1	1	0	0.6448	0.5357	0.5244	.				
	LYMPHOMA, MALIGNANT	0	1	2	0	0.6573	0.5357	0.2780	.				
	MESOTHELIOMA, MALIGNANT	1	0	0	0	1.0000	1.0000	1.0000	1.0000				
HEART	LYMPHOMA, MALIGNANT	0	0	2	0	0.5146	.	0.2780	.				
	METASTATIC ADENOCARCINOMA	1	0	0	0	1.0000	1.0000	1.0000	1.0000				
	SCHWANNOMA, MALIGNANT	2	1	0	0	0.9881	0.9000	1.0000	1.0000				
JOINT	SYNOVIAL SARCOMA, MALIGNA	0	0	0	1	0.2588	.	.	0.5301				
KIDNEY	HISTIOCYTIC SARCOMA, MALI	0	0	1	0	0.5118	.	0.5244	.				
	LIPOMA, BENIGN	0	0	0	1	0.2588	.	.	0.5301				
	LIPOSARCOMA, MALIGNANT	0	1	0	0	0.7719	0.5357	.	.				
	LYMPHOMA, MALIGNANT	0	0	1	0	0.5146	.	0.5301	.				
	METASTATIC ADENOCARCINOMA	1	1	0	0	0.9470	0.7815	1.0000	1.0000				
	TRANSITIONAL CELL CARCINO	0	1	1	0	0.6463	0.5357	0.5301	.				
LARGE INTESTINE	HISTIOCYTIC SARCOMA, MALI	0	1	0	0	0.7719	0.5357	.	.				
LARYNX	SQUAMOUS CELL CARCINOMA,	0	0	0	1	0.2588	.	.	0.5301				
LIVER	CARCINOMA, HEPATOCELLULAR	0	0	0	1	0.2588	.	.	0.5301				
	CHOLANGIOMA, BENIGN	0	0	1	0	0.5146	.	0.5301	.				
	HEPATOCYTELLULAR ADENOMA, S	0	2	1	1	0.4436	0.2780	0.5301	0.5301				
	HISTIOCYTIC SARCOMA, MALI	0	1	0	0	0.7719	0.5357	.	.				
	LYMPHOMA, MALIGNANT	0	0	2	0	0.5146	.	0.2780	.				
	MESOTHELIOMA, MALIGNANT	1	0	0	0	1.0000	1.0000	1.0000	1.0000				
LUNG	METASTATIC ADENOCARCINOMA	1	0	0	0	1.0000	1.0000	1.0000	1.0000				
	BRONCHIOLAR-ALVEOLAR ADEN	1	0	0	0	1.0000	1.0000	1.0000	1.0000				
	C-CELL CARCINOMA, MALIGNA	1	0	0	0	1.0000	1.0000	1.0000	1.0000				
	HISTIOCYTIC SARCOMA, MALI	0	1	0	0	0.7719	0.5357	.	.				
	LYMPHOMA, MALIGNANT	0	0	2	0	0.5146	.	0.2780	.				
	METASTATIC CARCINOMA	1	3	0	0	0.9625	0.3628	1.0000	1.0000				
	SCHWANNOMA, MALIGNANT	2	0	0	0	1.0000	1.0000	1.0000	1.0000				
LYMPH NODE	SYNOVIAL SARCOMA, MALIGNA	0	0	0	1	0.2588	.	.	0.5301				
	TRANSITIONAL CELL CARCINO	0	1	0	0	0.7719	0.5357	.	.				
LYMPH NODE, MAN	C-CELL CARCINOMA, MALIGNA	1	0	0	0	1.0000	1.0000	1.0000	1.0000				
	TRANSITIONAL CELL CARCINO	0	1	0	0	0.7719	0.5357	.	.				
LYMPH NODE, MES	HISTIOCYTIC SARCOMA, MALI	0	0	1	0	0.5118	.	0.5244	.				
	SQUAMOUS CELL CARCINOMA,	0	0	1	0	0.5146	.	0.5301	.				
	LYMPHOMA, MALIGNANT	0	1	1	0	0.6448	0.5357	0.5244	.				
LYMPH NODE, MES	METASTATIC CARCINOMA	0	1	0	0	0.7719	0.5357	.	.				
	SYNOVIAL SARCOMA, MALIGNA	0	0	0	1	0.2588	.	.	0.5301				

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

Organ Name	Tumor Name	0 mg				P_Value	P_Value	P_Value	P_Value
		Veh C	4 mg	20 mg	100 mg				
		N=60	N=60	N=60	N=60	Dose	Veh C	Veh C	Veh C
<hr/>									
MESENTERY	MESOTHELIOMA, MALIGNANT	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	PROSTATIC ADENOCARCINOMA,	0	1	0	0	0.7719	0.5357	.	.
	SCHWANNOMA, MALIGNANT	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	TRANSITIONAL CELL CARCINO	0	1	0	0	0.7719	0.5357	.	.
MUCOSA, ORAL	SQUAMOUS CELL CARCINOMA,	0	0	1	0	0.5146	.	0.5301	.
MUSCLE, SKELETA	SCHWANNOMA, MALIGNANT	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	TRANSITIONAL CELL CARCINO	0	1	0	0	0.7719	0.5357	.	.
NASOPHARYNX	SQUAMOUS CELL CARCINOMA,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
NO	NO	60	57	54	60	0.0960	1.0000	1.0000	.
PANCREAS	ACINAR CELL ADENOMA, BENI	0	0	1	0	0.5118	.	0.5244	.
	HISTIOCYtic SARCOMA, MALI	0	0	1	0	0.5118	.	0.5244	.
	ISLET CELL ADENOMA, BENIG	0	4	2	0	0.8952	0.0772	0.2780	.
	ISLET CELL CARCINOMA, MAL	0	1	1	0	0.6463	0.5357	0.5301	.
	MESOTHELIOMA, MALIGNANT	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	PROSTATIC ADENOCARCINOMA,	0	2	0	0	0.8283	0.2840	.	.
	SCHWANNOMA, MALIGNANT	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	TRANSITIONAL CELL CARCINO	0	1	0	0	0.7719	0.5357	.	.
SKIN	BASAL CELL ADENOMA, BENIG	0	0	1	3	0.0209*	.	0.5301	0.1441
	FIBROMA, BENIGN	0	3	0	4	0.0634	0.1441	.	0.0772
	FIBROSARCOMA, MALIGNANT	1	0	1	1	0.4063	1.0000	0.7762	0.7762
	HISTIOCYtic SARCOMA, MALI	0	0	1	0	0.5118	.	0.5244	.
	KERATOACANTHOMA, BENIGN	2	6	3	5	0.3083	0.1742	0.5347	0.2578
	LIPOSARCOMA, MALIGNANT	0	0	0	1	0.2588	.	.	0.5301
	LYMPHOMA, MALIGNANT	0	0	1	0	0.5118	.	0.5244	.
	SEBACEOUS ADENOMA, BENIGN	1	1	1	2	0.2781	0.7874	0.7769	0.5457
	SQUAMOUS CELL CARCINOMA,	0	0	1	0	0.5146	.	0.5301	.
	SQUAMOUS CELL PAPILLOMA,	0	2	1	1	0.4505	0.2780	0.5244	0.5357
	TRICHOEPITHELIOMA, BENIGN	0	1	0	0	0.7706	0.5301	.	.
SMALL INTESTINE	ADENOCARCINOMA, MALIGNANT	1	0	1	0	0.7630	1.0000	0.7762	1.0000
SPLEEN	LYMPHOMA, MALIGNANT	0	0	1	0	0.5146	.	0.5301	.
	MESOTHELIOMA, MALIGNANT	1	0	0	0	1.0000	1.0000	1.0000	1.0000
STOMACH	PAPILLOMA, BENIGN	1	0	1	2	0.1767	1.0000	0.7762	0.5361
	SCHWANNOMA, MALIGNANT	1	0	0	0	1.0000	1.0000	1.0000	1.0000
TESTIS	ADENOMA, INTERSTITIAL CEL	1	0	0	2	0.1697	1.0000	1.0000	0.5541
	INTERSTITIAL CELL TUMOR,	0	0	1	0	0.5146	.	0.5301	.
THYMUS	SCHWANNOMA, MALIGNANT	1	0	0	0	1.0000	1.0000	1.0000	1.0000
TRACHEA	HISTIOCYtic SARCOMA, MALI	0	0	1	0	0.5118	.	0.5244	.
	SCHWANNOMA, MALIGNANT	1	0	0	0	1.0000	1.0000	1.0000	1.0000

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

Organ Name	Tumor Name					P_Value	P_Value	P_Value	P_Value
		0 mg Veh C N=60	4 mg Low N=60	20 mg Med N=60	100 mg High N=60				
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TRACHEA	THYROID C-CELL CARCINOMA,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
URINARY BLADDER	PROSTATIC ADENOCARCINOMA,	0	1	0	0	0.7719	0.5357	.	.

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

Organ Name	Tumor Name					P_Value	P_Value	P_Value	P_Value
		0 mg Veh C N=60	4 mg Low N=60	20 mg Med N=60	100 mg High N=60				
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BONE MARROW	HISTIOCYTIC SARCOMA, MALI	0	0	1	0	0.4811	.	0.5000	.
	LYMPHOMA, MALIGNANT	0	0	0	1	0.2312	.	.	0.4778
BONE, FEMUR	HISTIOCYTIC SARCOMA, MALI	0	0	1	0	0.4811	.	0.5000	.
BRAIN	ASTROCYTOMA, MALIGNANT	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	GRANULAR CELL TUMOR, BENI	0	1	0	0	0.7459	0.5104	.	.
	MENINGIOMA, BENIGN	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	MIXED GLIOMA, MALIGNANT	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	PITUITARY ADENOCARCINOMA,	2	0	1	5	0.0138	1.0000	0.8790	0.1908
CERVIX	GRANULAR CELL TUMOR, BENI	2	0	0	0	1.0000	1.0000	1.0000	1.0000
	HEMANGIOMA, BENIGN	0	1	0	0	0.7459	0.5104	.	.
	HISTIOCYTIC SARCOMA, MALI	0	0	1	0	0.4811	.	0.5000	.
	LEIOMYOMA, BENIGN	0	1	0	0	0.7459	0.5104	.	.
	LEIOMYOSARCOMA, MALIGNANT	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	SCHWANNOMA, MALIGNANT	1	0	2	2	0.1436	1.0000	0.5000	0.4663
	STROMAL SARCOMA, MALIGNAN	1	0	0	0	1.0000	1.0000	1.0000	1.0000
ESOPHAGUS	HISTIOCYTIC SARCOMA, MALI	0	0	1	0	0.4811	.	0.5000	.
EYE	LYMPHOMA, MALIGNANT	0	0	1	0	0.4811	.	0.5000	.
GLAND, ADRENAL	ADENOMA, CORTICAL, BENIGN	2	0	3	4	0.0510	1.0000	0.5000	0.2967
	ADENOMA, CORTICAL, MULTIP	0	1	0	0	0.7459	0.5104	.	.
	HISTIOCYTIC SARCOMA, MALI	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	LEIOMYOSARCOMA, MALIGNANT	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	LYMPHOMA, MALIGNANT	0	0	1	1	0.1700	.	0.5000	0.4778
	PHEOCHROMOCYTOMA, BENIGN	3	0	3	5	0.0418	1.0000	0.6615	0.3203
GLAND, MAMMARY	ADENOCARCINOMA, MULTIPLE,	2	4	3	1	0.8082	0.3486	0.5000	0.8576
	ADENOCARCINOMA, SINGLE, M	10	7	13	12	0.1513	0.8670	0.3374	0.3399
	ADENOLIPOMA, BENIGN	0	1	1	0	0.6023	0.5104	0.5000	.
	ADENOMA, MULTIPLE, BENIGN	3	1	5	1	0.7355	0.9463	0.3571	0.9269
	ADENOMA, SINGLE, BENIGN	4	8	5	8	0.1568	0.1986	0.5000	0.1474
	FIBROADENOMA, BENIGN	14	16	14	15	0.2944	0.4655	0.5883	0.3630
	FIBROADENOMA, MULTIPLE, B	9	10	10	3	0.9770	0.5201	0.5201	0.9780
	HISTIOCYTIC SARCOMA, MALI	0	0	0	1	0.2270	.	.	0.4719
GLAND, PITUITAR	ADENOCARCINOMA, PARS DIST	1	0	0	2	0.1341	1.0000	1.0000	0.4663
	ADENOMA, PARS DISTALIS, B	39	39	37	37	0.5218	0.6343	0.6818	0.6308
	ADENOMA, PARS INTERMEDIA,	1	0	0	0	1.0000	1.0000	1.0000	1.0000
GLAND, THYROID	ADENOMA, C-CELL, BENIGN	4	4	3	6	0.1344	0.6770	0.7826	0.3138
	ADENOMA, C-CELL, MULTIPLE	0	0	0	1	0.2312	.	.	0.4778
	GANGLIONEUROMA, BENIGN	0	0	0	1	0.2312	.	.	0.4778
GROSS LESION	HISTIOCYTIC SARCOMA, MALI	1	0	3	2	0.1598	1.0000	0.3165	0.4574
	LYMPHOMA, MALIGNANT	0	1	1	2	0.1060	0.5104	0.5000	0.2310

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

Organ Name	Tumor Name	0 mg				P_Value	P_Value	P_Value	P_Value
		Veh C N=60	4 mg N=60	20 mg N=60	100 mg N=60				
<i>ffffffffff</i>									
KIDNEY	HISTIOCYTIC SARCOMA, MALI	1	0	1	0	0.7321	1.0000	0.7527	1.0000
	LIPOMA, BENIGN	0	1	0	0	0.7459	0.5104	.	.
	LYMPHOMA, MALIGNANT	0	0	1	1	0.1700	.	0.5000	0.4778
LARGE INTESTINE	LYMPHOMA, MALIGNANT	0	0	1	0	0.4811	.	0.5000	.
LIVER	HEPATOCELLULAR ADENOMA, M	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	HEPATOCELLULAR ADENOMA, S	1	0	1	0	0.7321	1.0000	0.7527	1.0000
	HISTIOCYTIC SARCOMA, MALI	1	0	2	1	0.3289	1.0000	0.5000	0.7240
	LEIOMYOSARCOMA, METASTATIC	0	0	0	1	0.2270	.	.	0.4719
	LYMPHOMA, MALIGNANT	0	0	1	1	0.1700	.	0.5000	0.4778
LUNG	HISTIOCYTIC SARCOMA, MALI	1	0	2	0	0.6559	1.0000	0.5000	1.0000
	LYMPHOMA, MALIGNANT	0	0	1	2	0.0538	.	0.5000	0.2310
	METASTATIC CARCINOMA	3	1	2	1	0.7173	0.9438	0.8192	0.9272
LYMPH NODE, MAN	BASAL CELL CARCINOMA, MAL	0	0	1	0	0.4811	.	0.5000	.
	LYMPHOMA, MALIGNANT	0	0	1	1	0.1700	.	0.5000	0.4778
	SQUAMOUS CELL CARCINOMA,	0	0	1	0	0.4811	.	0.5000	.
LYMPH NODE, MES	HISTIOCYTIC SARCOMA, MALI	1	1	1	0	0.8134	0.7629	0.7527	1.0000
	LYMPHOMA, MALIGNANT	0	0	1	0	0.4811	.	0.5000	.
MUSCLE, SKELETA	HISTIOCYTIC SARCOMA, MALI	1	0	0	0	1.0000	1.0000	1.0000	1.0000
NERVE, SCIATIC	HISTIOCYTIC SARCOMA, MALI	1	0	1	0	0.7321	1.0000	0.7527	1.0000
NO	NO	60	55	58	60	0.0759	1.0000	1.0000	.
OVARY	ENDOMETRIAL ADENOCARCINOM	0	0	0	1	0.2312	.	.	0.4778
	GRANULOSA-THECA CELL TUMO	0	1	0	0	0.7459	0.5104	.	.
	HISTIOCYTIC SARCOMA, MALI	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	THECOMA, BENIGN	0	1	0	0	0.7459	0.5104	.	.
PANCREAS	ACINAR CELL ADENOMA, BENI	0	0	1	0	0.4811	.	0.5000	.
	HISTIOCYTIC SARCOMA, MALI	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	ISLET CELL ADENOMA, BENIG	2	0	0	0	1.0000	1.0000	1.0000	1.0000
	LYMPHOMA, MALIGNANT	0	0	1	0	0.4811	.	0.5000	.
SKIN	AMELANOTIC MELANOMA, MALI	0	0	0	1	0.2270	.	.	0.4719
	BASAL CELL CARCINOMA, MAL	0	0	1	0	0.4811	.	0.5000	.
	FIBROMA, BENIGN	2	1	0	0	0.9844	0.8865	1.0000	1.0000
	FIBROSARCOMA, MALIGNANT	0	0	0	1	0.2312	.	.	0.4778
	HIBERNOMA, BENIGN	2	0	0	0	1.0000	1.0000	1.0000	1.0000
	HISTIOCYTIC SARCOMA, MALI	1	0	2	0	0.6559	1.0000	0.5000	1.0000
	LEIOMYOSARCOMA, MALIGNANT	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	LIPOMA, BENIGN	2	0	0	0	1.0000	1.0000	1.0000	1.0000
	SCHWANNOMA, MALIGNANT	0	2	0	0	0.8012	0.2579	.	.
	SEBACEOUS ADENOMA, BENIGN	0	0	0	1	0.2270	.	.	0.4719

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

Organ Name	Tumor Name	0 mg		4 mg		20 mg		100 mg		P_Value Dose Resp	P_Value vs. L	P_Value Veh C vs. M	P_Value Veh C vs. H
		Veh C N=60	Low N=60	Med N=60	High N=60	P_Value Dose vs. L	P_Value Veh C vs. M	P_Value Veh C vs. H					
SMALL INTESTINE	LEIOMYOMA, BENIGN	0	1	0	0	0.7459	0.5104	.	.	.			
	LEIOMYOSARCOMA, MALIGNANT	0	0	0	1	0.2270	.	.	.	0.4719			
	LYMPHOMA, MALIGNANT	0	0	1	0	0.4811	.	0.5000	.				
SPLEEN	LYMPHOMA, MALIGNANT	0	0	1	1	0.1700	.	0.5000	0.4778				
STOMACH	HISTIOCYTIC SARCOMA, MALI	1	0	0	0	1.0000	1.0000	1.0000	1.0000				
	PAPILLOMA, BENIGN	0	0	2	1	0.1733	.	0.2526	0.4719				
	PAPILLOMAS, MULTIPLE, BEN	0	0	1	0	0.4811	.	0.5000	.				
THYMUS	LYMPHOMA, MALIGNANT	0	0	0	1	0.2312	.	.	0.4778				
	MALIGNANT THYMOMA	1	0	0	0	1.0000	1.0000	1.0000	1.0000				
	THYMOMA, BENIGN	0	0	0	1	0.2270	.	.	0.4719				
TRACHEA	HISTIOCYTIC SARCOMA, MALI	0	0	1	0	0.4811	.	0.5000	.				
UTERUS	ENDOMETRIAL ADENOCARCINOM	0	0	0	1	0.2312	.	.	0.4778				
	ENDOMETRIAL ADENOMA, BENI	0	0	0	1	0.2270	.	.	0.4719				
	HISTIOCYTIC SARCOMA, MALI	1	0	1	0	0.7321	1.0000	0.7527	1.0000				
VAGINA	AMELANOTIC MELANOMA, MALI	1	0	0	0	1.0000	1.0000	1.0000	1.0000				
	HISTIOCYTIC SARCOMA, MALI	0	0	1	0	0.4811	.	0.5000	.				
	SCHWANNOMA, MALIGNANT	1	0	0	2	0.1341	1.0000	1.0000	0.4663				

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

Week	Neg Cont		Pos Cont		25 mg/kg/day		75 mg/kg/day		200 mg/kg/day	
	No. of Death	Cum*. %	No. of Death	Cum*. %						
0 - 10	0	0	0	0	0	0	0	0	1	3.33
11 - 26	3	10.00	15	100.0	2	8.00	1	4.00	0	3.33
Ter. Sac.	27	90.00	0	0	23	92.00	24	96.00	29	96.67
Total	N=30		N=15		N=25		N=25		N=30	

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

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

Week	Neg Cont		Pos Cont		25 mg/kg/day		75 mg/kg/day		200 mg/kg/day	
	No. of Death	Cum*. %	No. of Death	Cum*. %						
0 - 10	0	0	2	13.33	1	4.00	0	0	0	0
11 - 26	0	0	13	100.0	0	4.00	0	0	0	0
Ter. Sac.	30	100.0	0	0	24	96.00	25	100.0	30	100.0
Total	N=30		N=15		N=25		N=25		N=30	

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

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

Test*	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.7950
Homogeneity	Log-Rank	0.6952

\*Tests for dose-response and homogeneity were performed using data from Vehicle control, low, medium and high dose groups.

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

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.9503
Homogeneity	Log-Rank	0.3340

\*Tests for dose-response and homogeneity were performed using data from Vehicle control, low, medium and high dose groups.

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

Organ Name	Tumor Name	0 mg				P_Value	P_Value	P_Value	P_Value
		Veh C N=30	25 mg N=25	75 mg N=25	200 mg N=30				
<i>oo</i>									
cranium	hemangiosarcoma	0	1	0	0	0.7358	0.4615	.	.
forelimb	papilloma	0	0	0	1	0.2736	.	.	0.5088
harderian gland	adenoma	0	0	0	1	0.2736	.	.	0.5088
liver	hepatocellular adenoma	0	0	0	1	0.2736	.	.	0.5088
lungs with bron	alveolar-bronchiolar aden	4	3	1	4	0.4886	0.7208	0.9658	0.6674
	alveolar-bronchiolar carc	0	1	1	0	0.6359	0.4615	0.4717	.
multicentric	lymphoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	mesothelioma	0	0	1	0	0.5094	.	0.4717	.
skin	papilloma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
skin, abdominal	hemangiosarcoma	0	1	0	0	0.7358	0.4615	.	.
spleen	hemangiosarcoma	1	1	1	1	0.5460	0.7149	0.7257	0.7632
stomach	papilloma	0	0	1	0	0.5094	.	0.4717	.
	squamous cell carcinoma	1	1	0	0	0.9321	0.7149	1.0000	1.0000
testes	hemangiosarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000

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

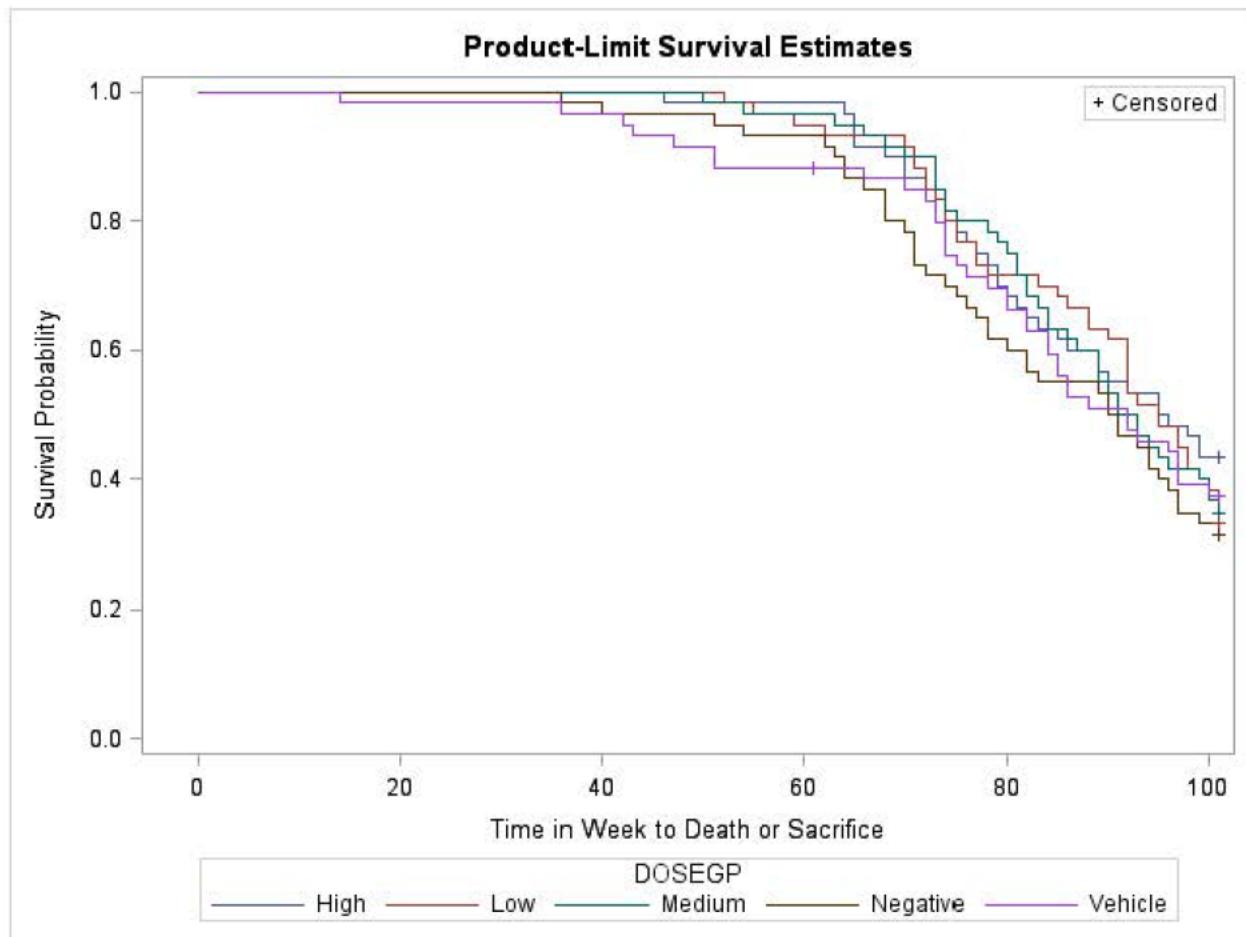
Organ Name	Tumor Name	0 mg	25 mg	75 mg	200 mg	P_Value	P_Value	P_Value	P_Value
		Veh C N=30	Low N=25	Med N=25	High N=30	Dose Resp	Veh C vs. L	Veh C vs. M	Veh C vs. H
<i>oo</i>									
cavity, nasal	carcinoma	0	1	0	0	0.7248	0.4444	.	.
harderian gland	adenoma	0	2	0	2	0.2132	0.1929	.	0.2458
	carcinoma	0	0	0	1	0.2752	.	.	0.5000
lungs with bron	alveolar-bronchiolar aden	0	2	1	1	0.4405	0.1929	0.4545	0.5000
	alveolar-bronchiolar carc	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	hemangiosarcoma	0	0	1	0	0.5046	.	0.4545	.
mediastinum	hemangioma	0	0	1	0	0.5046	.	0.4545	.
spleen	hemangiosarcoma	1	1	1	1	0.5398	0.6960	0.7071	0.7542
stomach	papilloma	0	1	0	0	0.7248	0.4444	.	.
urinary bladder	hemangioma	0	0	0	1	0.2752	.	.	0.5000
	leiomyoma	0	1	0	0	0.7248	0.4444	.	.
uterus	hemangiosarcoma	1	0	1	0	0.7569	1.0000	0.7071	1.0000
vagina	hemangiosarcoma	0	0	0	1	0.2752	.	.	0.5000

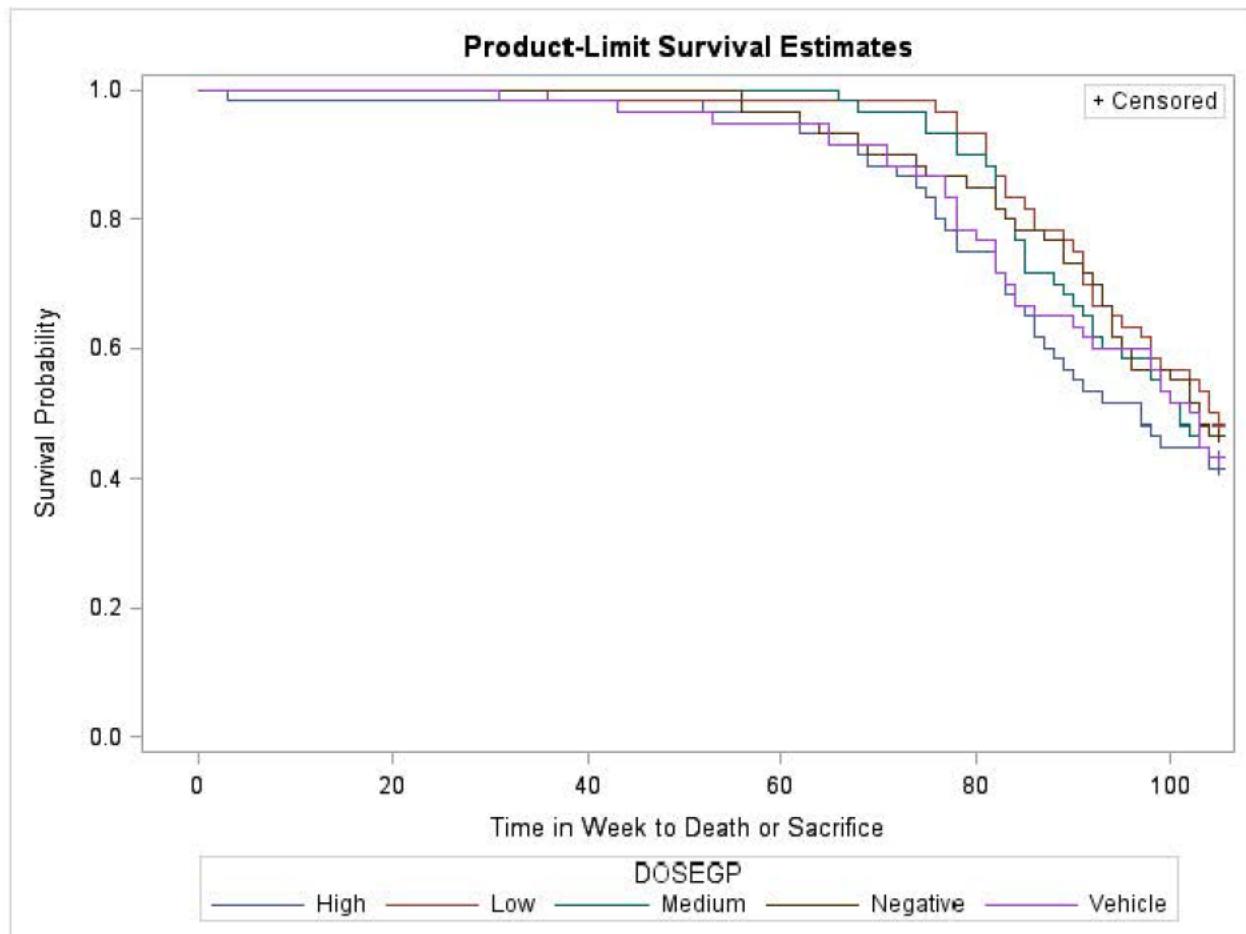
**Table 7A: Comparison of Negative and Positive Control Groups  
Male Mice**

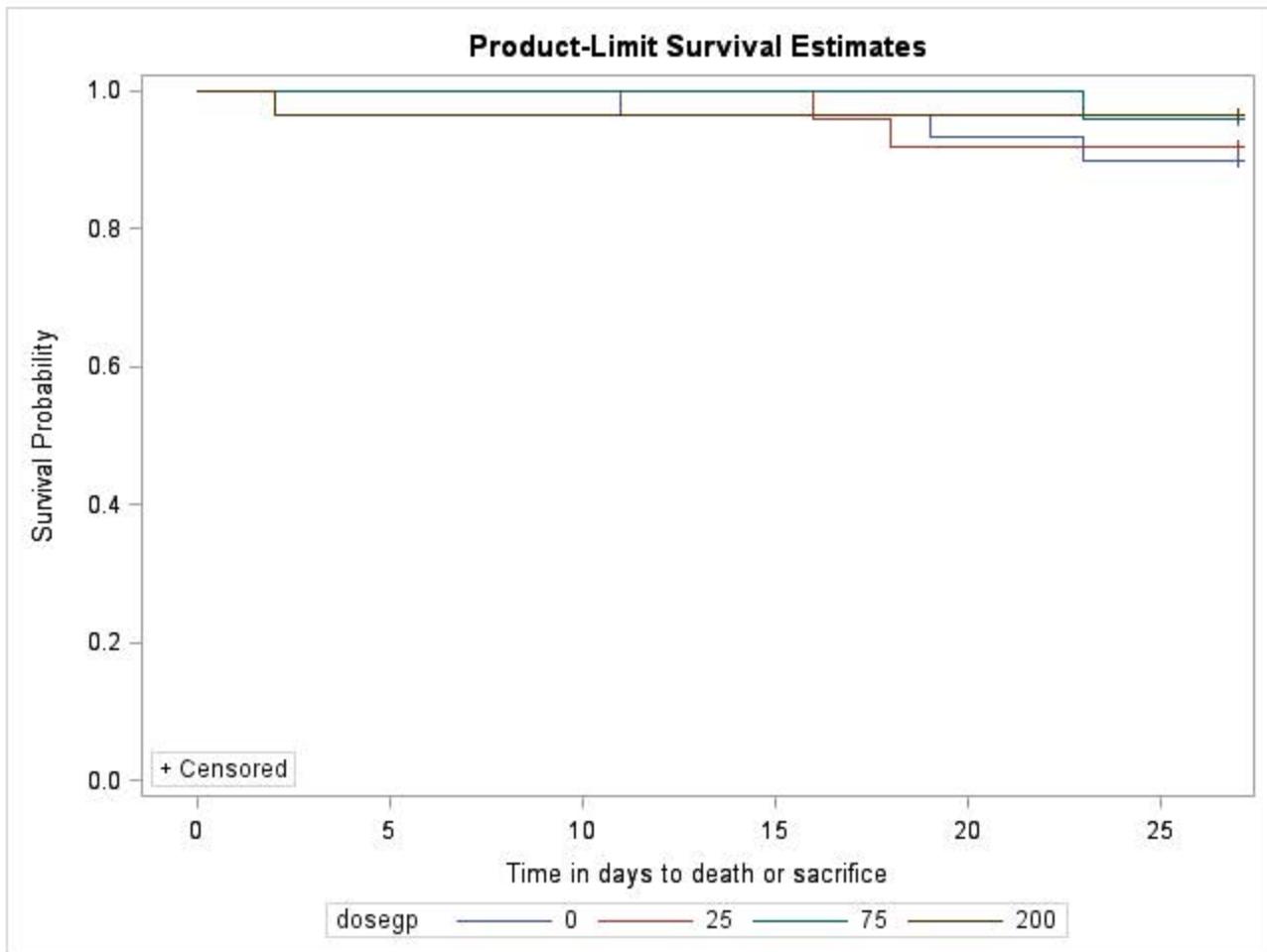
Organ Name	Tumor Name	P_Value		
		Neg C N=30	Veh C N=25	Veh C vs. Neg C
<i>oooooooooooooooooooooooooooooooooooo</i>				
lungs with bron	alveolar-bronchiolar aden	4	15	<0.001*
	alveolar-bronchiolar carc	0	6	<0.001*
	hemangiosarcoma	0	2	0.0189*
spleen	hemangiosarcoma	1	14	<0.001*

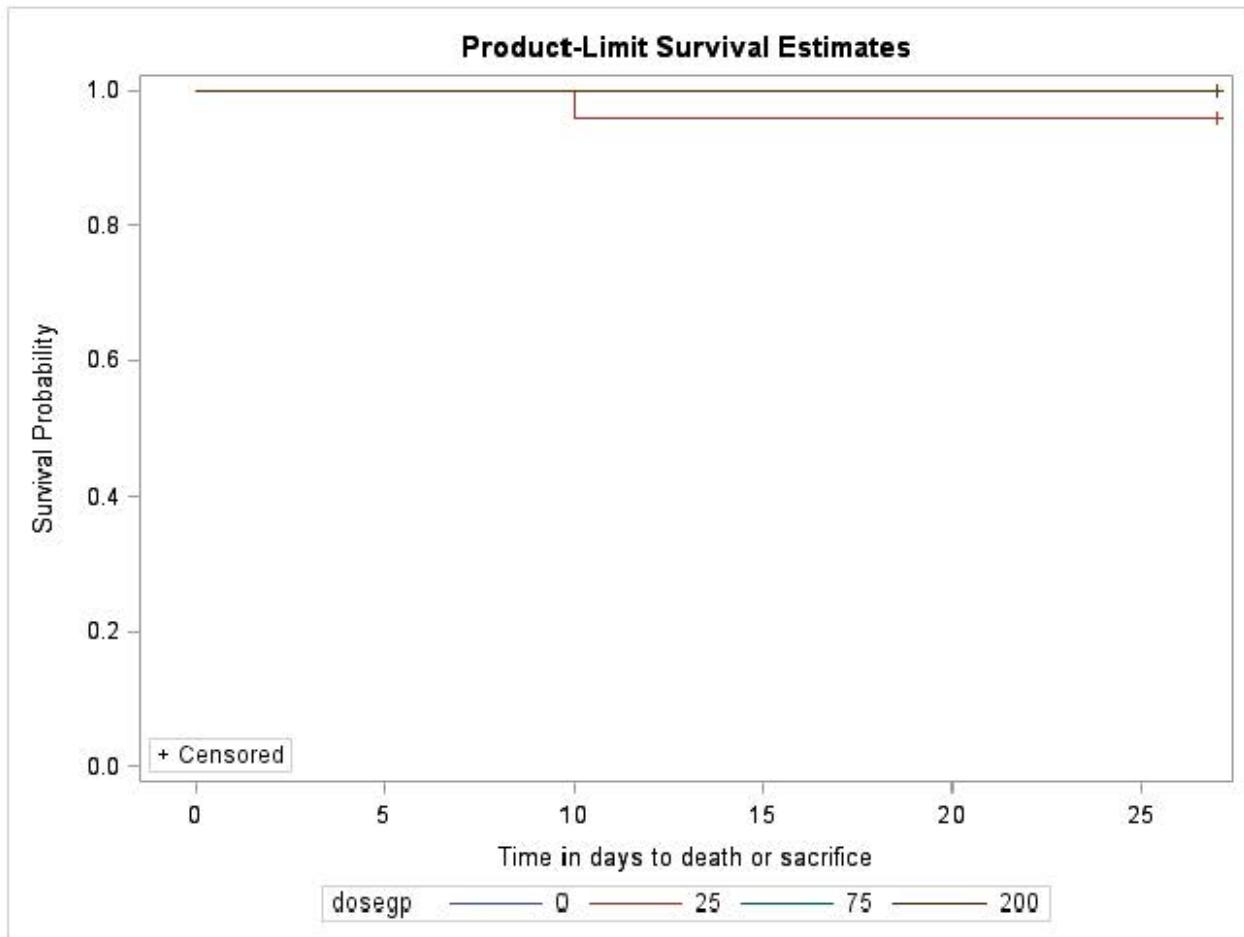
**Table 7B: Comparison of Negative and Positive Control Groups  
Female Mice**

Organ Name	Tumor Name	P_Value		
		Neg C N=30	Veh C N=25	Veh C vs. Neg C
<i>oooooooooooooooooooooooooooooooooooo</i>				
lungs with bron	alveolar-bronchiolar aden	0	15	<0.001*
	alveolar-bronchiolar carc	1	8	<0.001*
	hemangiosarcoma	0	3	0.0028*
spleen	hemangiosarcoma	1	13	<0.001*

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

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

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

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

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/s/

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MOHAMMAD A RAHMAN  
07/08/2014

KARL K LIN  
07/08/2014  
Concur with review

## **Cover Letter**

This is an amendment to the original review.

The difference of this amendment review report to the original review report is the reviewer added the 'Percentage Reduction Analysis' part and update the conclusions.

The reviewer added two more conclusions regarding the 'Percentage Reduction Analysis'.



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

# Statistical Review and Evaluation

## CLINICAL STUDIES

**NDA/Serial Number:**

205777

**Drug Name:**

Oxycodone-Naloxone tablets (ONU)

**Indication:**

(b) (4)

**Study number:**

ONU1008 (UPN 1757)

**Applicant:**

Purdue Pharma L.P.

**Date(s):**

Date of Document: Sep 23,2013

Consult received date: Nov 11, 2013

Completion date: 02/11/2014

**Review Priority:**

S

**Biometrics Division:**

DBVI

**Statistical Reviewer:**

Anna Sun, Ph.D., Mathematical Statistician, OB/DBVI

**Concurring Reviewers:**

Yi Tsong, Ph.D., Acting Division Director, OB/DBVI

**Medical Division:**

Control Substance Staff

**The CSS Team:**

James Tolliver, Ph.D., Pharmacologist, OCD/CSS

Silvia Calderon, Ph.D., Pharmacology Team Leader, OCD/CSS

**Project Manager:**

Sandra Saltz, Project Manager, CSS

**Keywords:** *Crossover design, Drug abuse potential study, Self-reported endpoint, Multiple endpoints*

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## 1. Executive Summary

Study ONU1008 (UPN 1757) was single-center, double-blind, triple-dummy, PBO-controlled, randomized, 4-way crossover study to evaluate the PD effects (subjective, physiologic and withdrawal), PK, and safety of oral ONU (chewed and intact) compared to Oxy API and PBO in methadone-maintained, opioid-dependent subjects.

The objectives of the study were to evaluate the following:

- The pharmacodynamic (PD) effects of intact and chewed ONU compared to the active pharmaceutical ingredient, oxycodone HCl (Oxy API), and PBO in methadone-maintained, opioid-dependent subjects
- The PK of oxycodone and naloxone in methadone-maintained, opioid-dependent subjects
- The safety and tolerability of intact and chewed ONU in methadone-maintained, opioid dependent Subjects

There were four treatments in the study. 33 subjects were randomized and 29 subjects were analyzed. Subjects received each of the treatments outlined below in a randomized, double-blinded, triple-dummy fashion (one per Treatment visit). Treatment A: ONU 60/30 mg intact; Treatment B: ONU 60/30 mg chewed; Treatment C: Oxy API, 60 mg oral solution; Treatment D: PBO

Primary PD outcome variable was High VAS .The reviewer analyzed the primary endpoint Drug High and the secondary endpoint Drug Liking VAS, Good Effects VAS, Bad Effects VAS, Pupil Diameter (mm), Overall Drug Liking VAS (at hour 12) and Take Drug Again VAS (at hour 12). The results from the statistical reviewer's analyses establish that:

- For the comparison of placebo and OXY, except for the Bad Effect VAS, there were statistically significant differences between these two treatments on all subjective measures. Pupil diameter was significantly lower following administration of OXY.
- For the comparison of ONU chewed and OXY, there were significant statistically differences on all subjective measures. ONU chewed was associated with greater Bad Effect VAS, higher pupil diameter and significantly lower Drug Liking, Good Effects, Bad Effects, Overall Drug Liking (at hour 12) and Take Drug Again VAS (at hour 12).
- For the comparison of ONU intact and OXY, except for the Bad Effect VAS, there were significant statistically differences on all subjective measures.
- There were few significant differences between ONU chewed and ONU intact. However, ONU chewed showed marginally higher Good Effect VAS, significantly higher score in Bad Effect VAS.
- For the comparison of ONU intact and placebo, no significant differences were observed on all subjective measures.
- Effects on the comparison of ONU chewed and placebo were minimal, no significant differences were observed, however, ONU chewed had marginally higher score on Good Effect VAS, significantly higher Bad Effect VAS

In addition, we provide the following:

- Around 83% of the subjects had some reduction in Drug Liking with ONU Intact comparing to OXY API, at least a 30% and 50% reduction in Drug Liking was 79% and 79% respectively.

- Around 76% of the subjects showed some reduction in Drug Liking with ONU Chewed comparing to OXY API, at least a 30% and 50% reduction in Drug Liking with ONU Chewed comparing to OXY API was 69% and 66% of subjects respectively.

## **2. Review Report on Study ONU1008 (UPN 1757)**

### **2.1 Overview**

Oxycodone/naloxone (ONU) tablets [REDACTED] (b) (4) 10/5 mg, 20/10 mg, and 40/20 mg oxycodone/naloxone) comprise a [REDACTED] (b) (4) combination formulation of oxycodone hydrochloride (HCl) and naloxone HCl that is [REDACTED] (b) (4) pain. Due to the inclusion of naloxone, it is expected that this combination product will be at reduced risk for abuse via the intranasal and intravenous routes of administration.

This study was designed to evaluate the abuse potential/agonist effects, withdrawal effects, PK profile, and safety of orally administered intact and chewed ONU tablets in methadone-maintained, opioid-dependent subjects.

#### **2.1.1 Objectives of the study**

The objectives of the study were to evaluate the following:

- The pharmacodynamic (PD) effects of intact and chewed ONU compared to the active pharmaceutical ingredient, oxycodone HCl (Oxy API), and PBO in methadone-maintained, opioid-dependent subjects
- The PK of oxycodone and naloxone in methadone-maintained, opioid-dependent subjects
- The safety and tolerability of intact and chewed ONU in methadone-maintained, opioid dependent Subjects

#### **2.1.2 Study design**

This was a single-center, double-blind, triple-dummy, PBO-controlled, randomized, 4-way crossover study. The study consisted of 4 phases: screening, qualification, treatment, and follow-up.

- Screening: Visit 1 for inclusion/exclusion screening was conducted within 30 days prior to admission to the qualification phase.
- Qualification: 1 visit (Visit 2) lasting 3 days (2 overnight stays). On the morning of days 1 and 2, subjects were administered single doses of Oxy API 60 mg, in oral solution and PBO in a randomized fashion (washout of 24 hours) to determine if they showed an appropriate response to PBO; this visit also determined if each subject was suitable for study entry.
- Treatment: 1 inpatient session (Visit 3) lasting 9 days (with 8 overnight stays). Subjects received each of the following treatments in a randomized, double-blind, triple-dummy fashion:
  - Treatment A: ONU 60/30 mg intact

- Treatment B: ONU 60/30 mg chewed
  - Treatment C: Oxy API 60 mg, in oral solution
  - Treatment D: PBO
- Follow-up: Visit 4 was a safety follow-up, 3 to 7 days after the last study drug administration.

### **Outcome Variables**

- Primary Pharmacodynamics outcome variable was High VAS (maximum effect [Emax], time-averaged area under the effect curve [TA\_AUE]).
- Secondary endpoints:

Subjective PD endpoints:

- Drug Liking VAS ‘at this moment’ (Emax, minimum effect [Emin], TA\_AUE)
- Overall Drug Liking VAS (end-of-session score)
- Take Drug Again VAS (end-of-session score)
- Good Effects VAS (Emax, TA\_AUE)
- Bad Effects VAS (Emax, TA\_AUE)
- Feeling Sick VAS (Emax, TA\_AUE)
- Drowsiness/Alertness VAS (Emin, TA\_AUE)
- Any Effects VAS (Emax, TA\_AUE)

Objective physiologic endpoints:

- Pupillometry (maximum pupil constriction [MPC], pupillometry area over the effect curve [PAOE] relative to baseline)

Withdrawal endpoints:

- Subjective Opioid Withdrawal Scale (SOWS) (Emax, TA\_AUE)
- Objective Opioid Withdrawal Scale (OOWS) (Emax, TA\_AUE)

#### **2.1.3 Abuse potential measure and data collection times**

Drug High VAS are the primary abuse potential variables, measured at pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 hours post-dose. The secondary variables VAS (Drug Liking, Good, Bad, Any Effects VAS) were measured at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 hours post-dose. Pupillometry was measured at pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 hours post-dose.

Overall Drug Liking, Take Drug Again VAS were measured at 4 and 12 hours post-dose. SOWS, OOWS were measured at pre-dose, 1, 2, 3, 4, 8 and 12 hours post-dose.

#### **2.1.4 Number of subjects**

A total of 118 subjects were screened for enrollment. Of these, 74 (62.7%) subjects passed screening and were eligible for the qualification phase. 33 (44.6%) subjects passed qualification criteria and were randomized to the treatment phase. Four (12.1%) subjects did not complete the study as planned. Two subjects discontinued after treatment period 1, subject 01067 was discontinued post-dose during treatment period 2 for non-compliance, and Subject 01084 was discontinued for non-compliance after completing treatment period 2. In total, 29 (87.9%) subjects completed all 4 treatment periods and were included in the PK and PD Populations.

#### **2.1.5 Statistical methodologies used in the Sponsor's analyses**

##### **Hypothesis Testing**

For each of the parameters, the null hypothesis was: there is no treatment effect, and the alternative hypothesis was: there is a treatment effect. For each of the contrasts or pairwise comparisons, the null hypothesis was: there is no treatment effect difference between the tested pair, the alternative hypothesis was: there is a treatment effect difference between the tested pair.

A 5% Type I error rate with a P value <0.05 was considered as statistically significant for all individual hypothesis tests. All statistical tests were performed using two-tailed significance criteria.

##### **Analysis of Pharmacodynamic Assessments**

PD data at each time point were summarized by descriptive statistics and presented graphically (where appropriate) for the PD Population. Derived endpoints were summarized using descriptive statistics and box-plots. Outliers were listed by measure and parameter.

PD endpoints (Emax, Emin, MPC and/or TA\_AUE or PAOE, as appropriate) were analyzed using a mixed-effect model for a crossover study. TE<sub>max</sub>/TE<sub>min</sub> was summarized descriptively; however, additional analyses may have been undertaken if appropriate. From each model, means, 95% confidence intervals and P values for treatments and treatment differences were computed. The Benjamini and Hochberg procedure was used to control for Type I error arising from the multiple comparisons. Tests for non-normality and homogeneity of variance were conducted and nonparametric methods were employed, if necessary.

The following contrasts were performed:

- Oxy API vs. PBO
- ONU (intact) vs. PBO
- ONU (intact) vs. Oxy API
- ONU (chewed) vs. PBO
- ONU (chewed) vs. Oxy API
- ONU (chewed) vs. ONU (intact)

A sensitivity analysis was also conducted for High VAS (primary endpoint), which included subjects who were considered ‘responders’ during the qualification phase, i.e., peak score (Emax) in response to Oxy API greater than that of PBO ( $\geq 15$ -point difference) for High VAS and  $< 10$  points on High VAS for PBO.

## **2.1.6 Sponsor’s Summary and Conclusions**

### **Pharmacodynamic Conclusions**

- There were statistically significant differences between PBO and Oxy API 60 mg on all subjective measures with the exception of Bad Effects VAS. Pupil diameter and subjective withdrawal (SOWS) were statistically significantly lower following administration of Oxy API 60 mg.
- No statistically significant differences were observed between ONU 60/30 mg intact and PBO on measures of subjective drug effects; however, self-reported withdrawal effects were statistically significantly lower with ONU 60/30 mg intact.
- Relative to Oxy API 60 mg, ONU 60/30 mg intact showed statistically significantly lower scores on Positive and Balance of Effects measures, less high, and less effect on pupil diameter. Drowsiness/Alertness VAS scores were statistically significantly higher (less drowsy) with ONU 60/30 mg intact relative to Oxy API 60 mg.
- Effects of ONU 60/30 mg chewed in comparison to PBO were minimal; however, ONU 60/30 mg chewed showed statistically significantly greater disliking (Drug Liking VAS Emin), statistically significantly higher Bad Effects VAS and Any Effects VAS scores, and higher Good Effects VAS scores over time (TA\_AUE). There were no statistically significant effects on pupil diameter or measures of withdrawal relative to PBO.
- Compared to Oxy API 60 mg, ONU 60/30 mg chewed was associated with statistically significantly greater disliking (Drug Liking Emin), negative effects (Bad Effects VAS), and subjective withdrawal (SOWS), and statistically significantly lower balance (Drug Liking VAS, Take Drug Again VAS, and Overall Drug Likng), positive (Good Effects VAS, High VAS), other (Any Effects VAS over time [TA\_AUE]), drowsiness/alertness (less drowsy), and pupillary effects.
- There were few statistically significant differences between ONU 60/30 mg intact and ONU 60/30 mg chewed. However, ONU 60/30 mg chewed was associated with statistically significantly greater disliking (Drug Liking VAS Emin), higher scores on

Bad Effects VAS, higher Any Effects VAS Emax, and greater self-reported withdrawal effects.

- Review of the distribution and individual subject responses on the OOWS, SOWS, and negative VAS measures suggests that most subjects experienced a mild negative effect of ONU 60/30 mg chewed, with a small subset of subjects showing mild withdrawal-like responses.

## 2.2 Data Location

The analysis datasets are located at

<\\CDSESUB1\evsprod\NDA205777\0000\m5\datasets\onu1008\analysis\adam\datasets>

## 2.3 Reviewer's Assessment

All analyses were conducted from the stand point of the pharmacodynamics analysis.

### 2.3.1 Descriptive Statistics

The descriptive statistics for the Emax endpoint for primary variable Drug High and secondary variable Drug Liking VAS are provided in Table 1 and Table 2. Mean score over time for Drug High and Drug Liking VAS are shown in Figure 1 and Figure 2. Heatmap of Emax for Drug High and Drug Liking VAS by Subject by Treatment are provided in Figure 3 and Figure 4.

Table 1 summarizes the mean, standard error, minimum, the first quartile (Q1), median, the third quartile (Q3), and maximum for four treatments in the study. Table 2 summarizes the treatment differences between ONU chewed vs. ONU intact, ONU chewed vs. Oxy, Oxy vs. ONU intact for Emax of Drug High and Drug Liking VAS.

**Table 1. E<sub>max</sub> Descriptive Statistics for Drug Liking, Drug High, PD population (N=29)**

Parameter	Planned Treatment	Mean	Std Dev	Min	Q1	Median	Q3	Max
High VAS	ONU 60/30 mg chewed	27.7	35.1	0.0	0.0	1.0	51.0	100.0
	ONU 60/30 mg intact	20.6	27.7	0.0	0.0	1.0	51.0	73.0
	Oxycodone 60 mg solution	77.9	26.8	0.0	64.0	86.0	100.0	100.0
	Placebo	21.9	27.5	0.0	0.0	1.0	50.0	82.0
Drug Liking VAS	ONU 60/30 mg chewed	54.6	17.3	0.0	50.0	51.0	51.0	100.0
	ONU 60/30 mg intact	54.7	10.6	50.0	50.0	51.0	51.0	99.0
	Oxycodone 60 mg solution	77.9	20.2	50.0	60.0	78.0	100.0	100.0
	Placebo	54.4	11.5	50.0	50.0	51.0	51.0	100.0

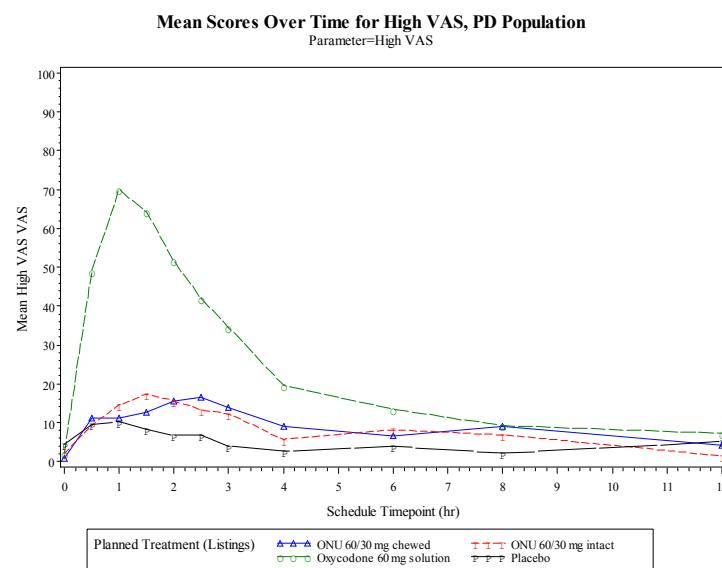
For Drug High VAS, from table 1, mean E<sub>max</sub> score for placebo and ONU intact were low, 21.9 and 20.6 respectively, mean score for ONU chewed were slightly higher with score 27.7, while mean E<sub>max</sub> for Oxy API was very high with score 77.9, around 3 times as ONU chewed, ONU intact and placebo. Figure 1 shows mean scores for High VAS over time for the four treatments. Mean E<sub>max</sub> scores of Oxy API increased rapidly to the peak of ~70 at hour one post-dose. ONU intact, ONU chewed and placebo had similar mean E<sub>max</sub> score over the first 3 to 4 hours post-

dose. Over the time, mean score of ONU intake and ONU chewed were only slight higher than the mean score of placebo.

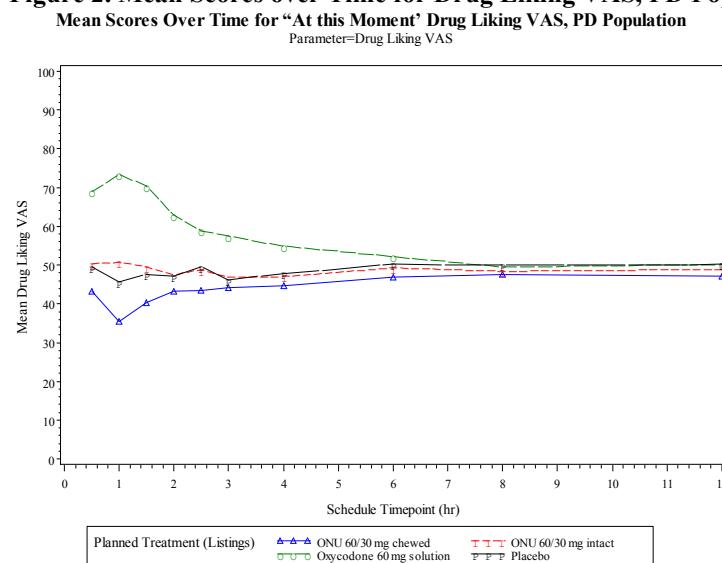
For Drug Liking VAS, as can be seen in table 1, the mean score of placebo (54.4) is slightly higher than the neutral range, first quartile, median and third quartile of placebo was within the neutral range which is ~50. Mean  $E_{max}$  for ONU chewed and ONU intact are similar as placebo, but mean score for OXY API is high, with score 77.9.

We can further explore the individual's  $E_{max}$  score for each treatment from Figure 3 and Figure 4. For example, in Figure 4 the Drug Liking VAS for each subject, one subject has the score 100 in placebo group, 4 out of 29 subjects (13.8%) had the placebo score  $>60$ , these high score explained why the mean  $E_{max}$  score of placebo is higher than the neutral range.

**Figure 1. Mean Scores over Time for High VAS, PD Population**



**Figure 2. Mean Scores over Time for Drug Liking VAS, PD Population**



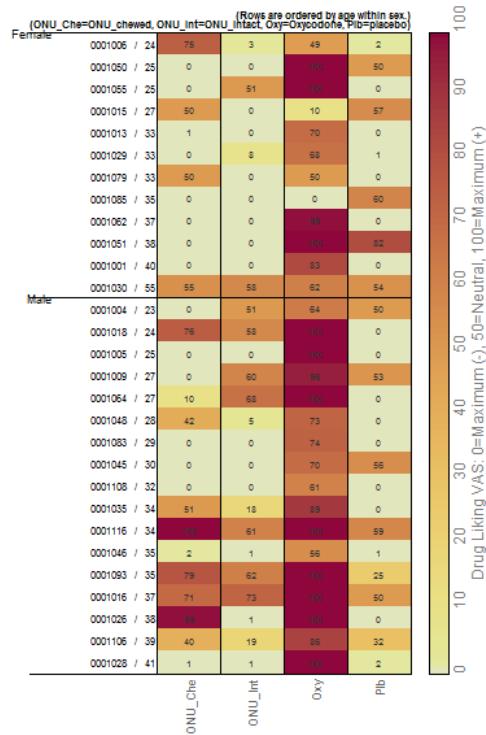
**Table 2. Treatment difference of Emax for Drug High, Drug Liking, PD population (N=29)**

Parameter	Variable	Mean	Std Dev	Min	Q1	Median	Q3	Max	t Value	Pr >  t
High VAS	ONU_chew_VS_ONU_intact	7.0	35.7	-60.0	0.0	0.0	21.0	98.0	1.06	0.2973
	ONU_chew_VS_OXY	-50.3	42.1	-100.0	-90.0	-61.0	-21.0	40.0	-6.43	<.0001
	OXY_VS_ONU_intact	57.3	30.4	0.0	38.0	60.0	74.0	100.0	10.15	<.0001
Drug Liking VAS	ONU_chew_VS_ONU_intact	-0.1	17.7	-51.0	0.0	0.0	1.0	49.0	-0.03	0.9751
	ONU_chew_VS_OXY	-23.3	24.2	-99.0	-44.0	-15.0	-1.0	5.0	-5.18	<.0001
	OXY_VS_ONU_intact	23.2	22.7	-48.0	8.0	23.0	44.0	50.0	5.50	<.0001

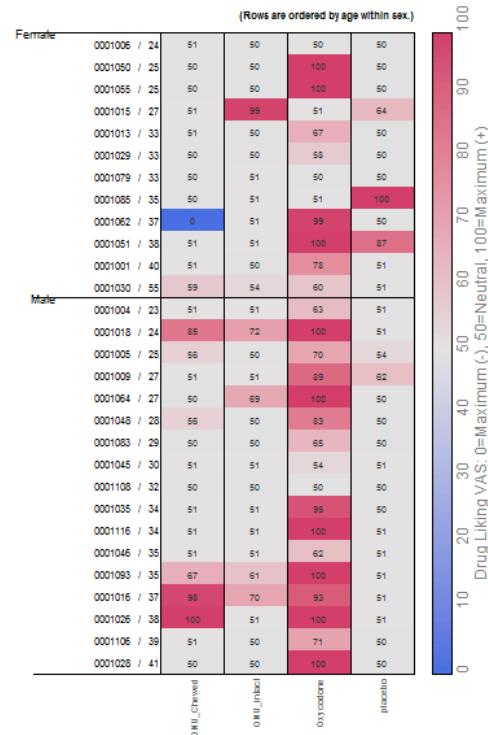
For the treatment difference comparison of high VAS, there is no significant difference between ONU chewed and ONU intact ( $p>0.05$ ), but there are significant statistically differences between the comparisons of ONU chewed and OXY ( $P<0.001$ ), ONU intact and OXY ( $P<0.001$ ). Similar results were observed for the Drug Liking VAS comparison.

Individual  $E_{max}$  scores are displayed by subject for all treatments in Figures 3-4, the rows of the table plot are ordered by age within sex. One can visually compare the  $E_{max}$  for each patient at different treatment, and the heat map also showed that more subjects had higher Drug High and Drug Liking VAS scores in OXY group comparing with ONU intact, ONU chewed and placebo.

**Figure 3. Emax for Drug High by Subject x Treat**



**Figure 4. Emax for Drug Liking by Subject x Treat**



### 2.3.2 Primary Analysis

#### Statistical model fitting

The reviewer analyzed the hypotheses of the primary objective using the mixed-effect model, the final model the reviewer used is treatment, period and sequence as fixed effects and subject

nested within sequence as a random effect. Table 3 is the analysis results for Emax of Drug High, Table 4 is the analysis results for Emax of Drug Liking VAS.

Table 3 shows that a significant treatment effect for this primary endpoint ( $p < 0.0001$ ). Placebo and ONU intact have similar least square mean (21.8 and 20.28 respectively), ONU chewed has slightly higher least square mean (27.57), while OXY has the highest least square mean (77.48), around 2-3 times as the other treatments. From treatment contrast, the least square mean difference of ONU chewed, ONU intact and placebo are significant different from OXY ( $P < 0.0001$ ). Similar results are observed from table 4.

Note: Sponsor didn't do the type I error rate adjustment in this study. Holm's procedure is recommended for the type I error rate adjustment for the multiple comparisons.

**Table 3. Analysis Results for High VAS Emax , PD Population.**

	LS Means	StdE	Pr >  t	Lower	Upper
<b>Treatments</b>					
ONU 60/30 mg chewed	27.57	4.82	<.0001	17.99	37.16
ONU 60/30 mg intact	20.28	4.82	<.0001	10.69	29.87
Oxycodone 60 mg solution	77.48	4.82	<.0001	67.90	87.07
Placebo	21.80	4.82	<.0001	12.21	31.38
<b>Contrasts (difference)</b>					
ONU 60/30 mg chewed - ONU 60/30 mg intact	7.30	6.70	0.2795	-6.04	20.63
ONU 60/30 mg chewed - Oxy 60 mg solution	-49.91	6.69	<.0001	-63.23	-36.59
ONU 60/30 mg chewed - Placebo	5.78	6.69	0.3906	-7.54	19.09
ONU 60/30 mg intact - Oxy 60 mg solution	-57.20	6.69	<.0001	-70.52	-43.89
ONU 60/30 mg intact - Placebo	-1.52	6.69	0.8211	-14.84	11.80
Oxy 60 mg solution - Placebo	55.69	6.70	<.0001	42.35	69.02

**Table 4. Analysis Results for Drug Liking VAS Emax , PD Population.**

	LS Mean	StdE	Pr >  t	Lower	Upper
<b>Treatments</b>					
ONU 60/30 mg chewed	54.09	2.59	<.0001	48.94	59.24
ONU 60/30 mg intact	54.16	2.59	<.0001	49.01	59.31
Oxycodone 60 mg solution	77.47	2.59	<.0001	72.32	82.62
Placebo	53.89	2.59	<.0001	48.74	59.04
<b>Contrasts (difference)</b>					
ONU 60/30 mg chewed - ONU 60/30 mg intact	-0.07	3.60	0.9841	-7.23	7.09
ONU 60/30 mg chewed - Oxy 60 mg solution	-23.38	3.60	<.0001	-30.53	-16.22
ONU 60/30 mg chewed - Placebo	0.20	3.60	0.9547	-6.95	7.36
ONU 60/30 mg intact - Oxy 60 mg solution	-23.30	3.60	<.0001	-30.46	-16.15
ONU 60/30 mg intact - Placebo	0.28	3.60	0.9389	-6.88	7.43
Oxy 60 mg solution - Placebo	23.58	3.60	<.0001	16.42	30.74

### 2.3.3 Secondary Analysis

Besides the analysis of the secondary endpoint Drug Liking VAS, the reviewer also analyzed the other secondary endpoints, they are: Good Effects VAS, Bad Effects VAS, Pupil Diameter (mm), Overall Drug Liking VAS and Take Drug Again VAS. The final mixture-effect model the reviewer used is treatment, period and sequence as fixed effects and subject nested within sequence as a random effect.

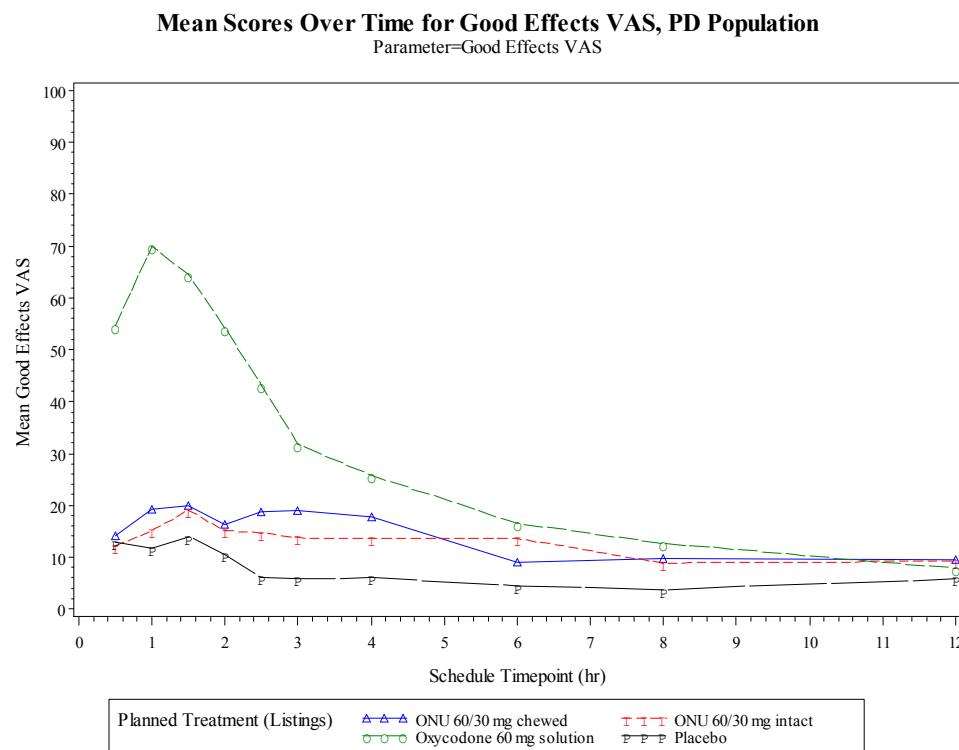
### Descriptive Statistics

The descriptive statistics of Emax for secondary endpoint variables: Good Effects VAS, Bad Effects VAS and Pupil Diameter, Overall Drug Liking VAS (at hour 12) and Take Drug Again VAS (at hour 12) are provided in Table 5. Mean score over time for Bad Effects VAS, Good Effects VAS and Pupil Diameter are shown in Figure 5, Figure 6 and Figure 7.

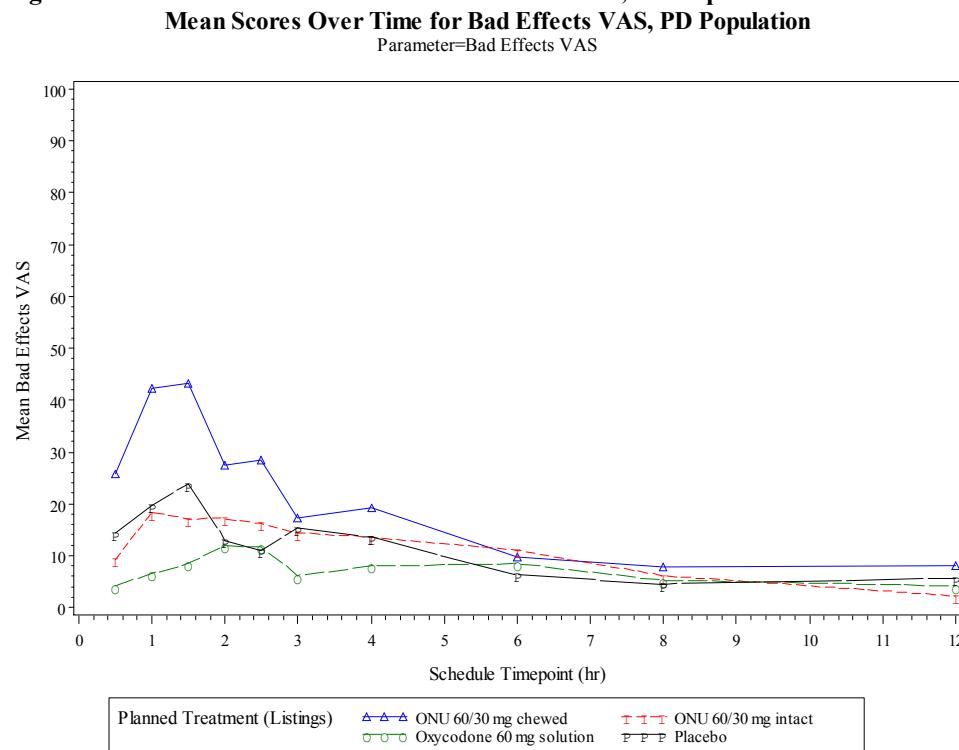
**Table 5. Emax Descriptive Statistics for Good Effects VAS, Bad Effects VAS, Pupil Diameter, Overall Drug Liking VAS (at hour 12) and Take Drug Again VAS (at hour 12), PD population (N=29)**

Parameter	Treatment	Mean	Std Dev	Min	Q1	Median	Q3	Max
Good Effects VAS	ONU 60/30 mg chewed	37	33.6	0	0	50	58	100
	ONU 60/30 mg intact	24.3	29.5	0	0	2	51	85
	OXY 60 mg solution	77.8	28.4	0	63	90	100	100
	Placebo	23.8	30.5	0	0	2	51	100
Bad Effects VAS	ONU 60/30 mg chewed	60.1	37.2	0	50	57	100	100
	ONU 60/30 mg intact	29.2	36.1	0	0	1	51	100
	OXY 60 mg solution	27.2	28.3	0	1	15	50	100
	Placebo	30.8	37	0	0	4	56	100
Pupil Diameter (mm)	ONU 60/30 mg chewed	5.9	1.1	3.3	5.1	6.4	6.6	7.4
	ONU 60/30 mg intact	5.9	0.9	4.0	5.4	6.2	6.6	7.1
	OXY 60 mg solution	5.5	1.1	3.5	4.6	6.0	6.4	6.9
	Placebo	6.0	0.9	3.9	5.5	6.2	6.6	7.2
Overall Drug Liking VAS (hour 12)	ONU 60/30 mg chewed	44.8	19	0	50	50	51	77
	ONU 60/30 mg intact	48.1	14.9	0	50	50	50	90
	OXY 60 mg solution	60.3	15.4	50	50	50	69	100
	Placebo	48.1	8.3	7	50	50	50	52
Take Drug Again VAS (hour 12)	ONU 60/30 mg chewed	32.6	31.7	0	0	50	51	100
	ONU 60/30 mg intact	38.5	30.7	0	0	50	51	100
	OXY 60 mg solution	61.4	31.6	0	50	50	100	100
	Placebo	41.5	27.1	0	33	50	50	100

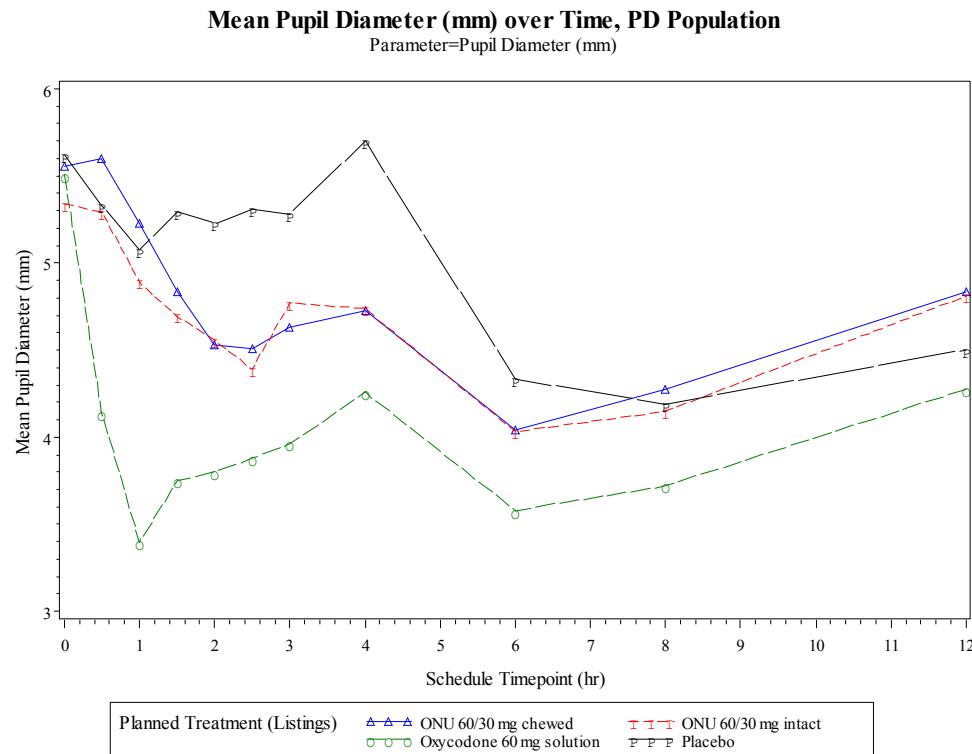
**Figure 5. Mean Scores over Time for Good Effects VAS, PD Population**



**Figure 6. Mean Scores over Time for Bad Effects VAS, PD Population**



**Figure 7. Mean Pupil Diameter (mm) over Time, PD Population**



From table 5 we can see for the Good Effect VAS, Mean Emax score for OXY is significant higher than the other three treatments. For the Bad Effect VAS, there is no big difference among these four treatments after hour 3. The mean Pupil Diameter (mm) in OXY group is lower than the other three treatments over time. OXY mean score at hour 12 for Overall Drug Liking VAS is higher than the other three treatments, while there is no significant difference among these three treatments. Similar results are observed from Take Drug Again VAS at hour 12.

Figure 5 shows that for the mean scores over time for Good Effect VAS, OXY were much higher than the other three treatments from hour 1 to hour 3. For the Bad Effect VAS, Figure 6 shows there is no significant mean scores difference among ONU intact, OXY and placebo, however, ONU chewed had higher mean score for the first three hours. Figure 7 is the mean pupil diameter over time, OXY decreased rapidly in pupil diameter that peaked at 1 hour post-dose and remained lower than the other three treatments until approximately 8 hours post-dose.

### Statistical model fitting

The reviewer analyzed the hypotheses of the secondary objective using the mixed-effect model, the final model the reviewer used is treatment, period and sequence as fixed effects and subject nested within sequence as a random effect. Table 6 to Table 8 are the analysis results for  $E_{\max}$  of Good Effect VAS, Bad Effect VAS and Pupil Diameter (mm) respectively. Table 9 and Table 10 are the analysis result for Overall Drug Liking VAS and Take Drug Again VAS at hour 10 respectively.

Table 6 to Table 10 showed that all treatments are significant ( $P < 0.0001$ ). Except for Bad Effect VAS, the analysis results for Good Effect VAS, Pupil Diameter, Overall Drug Liking VAS

and Take Drug Again VAS are similar, the OXY scores were significantly higher than the scores for the other three treatments. There were few significant differences between ONU chewed and ONU intact. For the comparison of ONU intact and placebo, no significant differences were observed. For the Bad Effect VAS, table 7 shows no significant difference between OXY and placebo ( $P$  value=0.5785), but there is significant different for the comparison of ONU chewed with the other three treatments.

**Table 6. Analysis Results for Good Effect VAS Emax , PD Population.**

	LS Mean	StdE	Pr >  t	Lower	Upper
Treatments					
ONU 60/30 mg chewed	35.63	4.97	<.0001	25.74	45.51
ONU 60/30 mg intact	23.04	4.97	<.0001	13.16	32.93
Oxycodone 60 mg solution	76.47	4.97	<.0001	66.58	86.35
Placebo	22.13	4.97	<.0001	12.25	32.02
Contrasts (difference)					
ONU 60/30 mg chewed - ONU 60/30 mg intact	12.58	6.91	0.0723	-1.17	26.33
ONU 60/30 mg chewed - Oxy 60 mg solution	-40.84	6.90	<.0001	-54.57	-27.11
ONU 60/30 mg chewed - Placebo	13.49	6.90	0.054	-0.24	27.23
ONU 60/30 mg intact - Oxy 60 mg solution	-53.42	6.90	<.0001	-67.15	-39.69
ONU 60/30 mg intact - Placebo	0.91	6.90	0.8951	-12.82	14.65
Oxy 60 mg solution - Placebo	54.33	6.91	<.0001	40.59	68.08

**Table 7. Analysis Results for Bad Effect VAS Emax , PD Population.**

	LS Mean	StdE	Pr >  t	Lower	Upper
Treatments					
ONU 60/30 mg chewed	58.23	5.31	<.0001	47.67	68.80
ONU 60/30 mg intact	26.05	5.31	<.0001	15.49	36.61
Oxycodone 60 mg solution	24.37	5.31	<.0001	13.80	34.93
Placebo	28.48	5.31	<.0001	17.92	39.05
Contrasts (difference)					
ONU 60/30 mg chewed - ONU 60/30 mg intact	32.19	7.38	<.0001	17.50	46.87
ONU 60/30 mg chewed - Oxy 60 mg solution	33.87	7.37	<.0001	19.20	48.54
ONU 60/30 mg chewed - Placebo	29.75	7.37	0.0001	15.08	44.42
ONU 60/30 mg intact - Oxy 60 mg solution	1.68	7.37	0.8201	-12.99	16.35
ONU 60/30 mg intact - Placebo	-2.44	7.37	0.7419	-17.11	12.24
Oxy 60 mg solution - Placebo	-4.12	7.38	0.5785	-18.81	10.57

**Table 8. Analysis Results for Pupil Diameter Emax , PD Population.**

	<b>LS Mean</b>	<b>StdE</b>	<b>Pr &gt;  t </b>	<b>Lower</b>	<b>Upper</b>
Treatments					
ONU 60/30 mg chewed	5.98	0.15	<.0001	5.68	6.27
ONU 60/30 mg intact	5.95	0.15	<.0001	5.66	6.25
Oxycodone 60 mg solution	5.61	0.15	<.0001	5.32	5.90
Placebo	6.14	0.15	<.0001	5.85	6.43
Contrasts (difference)					
ONU 60/30 mg chewed - ONU 60/30 mg intact	0.02	0.11	0.845	-0.20	0.25
ONU 60/30 mg chewed - Oxy 60 mg solution	0.37	0.11	0.0018	0.14	0.59
ONU 60/30 mg chewed - Placebo	-0.16	0.11	0.1592	-0.39	0.06
ONU 60/30 mg intact - Oxy 60 mg solution	0.34	0.11	0.0033	0.12	0.57
ONU 60/30 mg intact - Placebo	-0.18	0.11	0.1097	-0.41	0.04
Oxy 60 mg solution - Placebo	-0.53	0.11	<.0001	-0.76	-0.30

**Table 9. Analysis Results for Overall Drug Liking VAS Emax at hour 12 , PD Population.**

	<b>LS Mean</b>	<b>StdE</b>	<b>Pr &gt;  t </b>	<b>Lower</b>	<b>Upper</b>
Treatments					
ONU 60/30 mg chewed	44.72	2.58	<.0001	39.58	49.87
ONU 60/30 mg intact	48.67	2.58	<.0001	43.52	53.81
Oxycodone 60 mg solution	60.48	2.58	<.0001	55.34	65.62
Placebo	48.24	2.58	<.0001	43.09	53.38
Contrasts (difference)					
ONU 60/30 mg chewed - ONU 60/30 mg intact	-3.94	3.59	0.276	-11.09	3.21
ONU 60/30 mg chewed - Oxy 60 mg solution	-15.76	3.59	<.0001	-22.90	-8.61
ONU 60/30 mg chewed - Placebo	-3.51	3.59	0.331	-10.65	3.63
ONU 60/30 mg intact - Oxy 60 mg solution	-11.81	3.59	0.0015	-18.96	-4.67
ONU 60/30 mg intact - Placebo	0.43	3.59	0.9047	-6.71	7.58
Oxy 60 mg solution - Placebo	12.24	3.59	0.001	5.09	19.40

**Table 10. Analysis Results for Take Drug Again VAS Emax at hour 12 , PD Population**

	LS Mean	StdE	Pr >  t	Lower	Upper
Treatments					
ONU 60/30 mg chewed	29.65	4.46	<.0001	20.78	38.52
ONU 60/30 mg intact	37.13	4.46	<.0001	28.25	46.00
Oxycodone 60 mg solution	58.92	4.46	<.0001	50.05	67.79
Placebo	39.18	4.46	<.0001	30.31	48.06
Contrasts (difference)					
ONU 60/30 mg chewed - ONU 60/30 mg intact	-7.47	6.10	0.224	-19.61	4.66
ONU 60/30 mg chewed - Oxy 60 mg solution	-29.27	6.09	<.0001	-41.39	-17.15
ONU 60/30 mg chewed - Placebo	-9.53	6.09	0.1216	-21.65	2.59
ONU 60/30 mg intact - Oxy 60 mg solution	-21.79	6.09	0.0006	-33.92	-9.67
ONU 60/30 mg intact - Placebo	-2.06	6.09	0.7366	-14.18	10.07
Oxy 60 mg solution - Placebo	19.74	6.10	0.0018	7.60	31.88

### Percentage Reduction Analysis

Percent reduction analysis is an important abuse potential measure, and it is recommended for the clinical abuse potential studies. Generally the percent reduction formula is defined as:

$$\% \text{ reduction} = \frac{C_i - t_i}{C_i - 50}, \quad i = 1, 2 \dots n \quad (1)$$

This formula does not include an adjustment factor for placebo responses.

Chen, Klein and Calderon [3] gave an example for the definition of the percentage reduction for the test drug relative to the active control for Drug Liking VAS in their poster presentation at the 74th College on Problems of Drug Dependence (CPDD) annual scientific meeting held in Palm Spring in June of 2012 as follows:

$$\% \text{ reduction} = \begin{cases} \frac{C-T}{C-50} \times \left(1 - \frac{P-50}{50}\right) \times 100\%, & \text{if } P > 55; \\ \frac{C-T}{C-50} \times 100\%, & \text{if } P \leq 55. \end{cases} \quad (2)$$

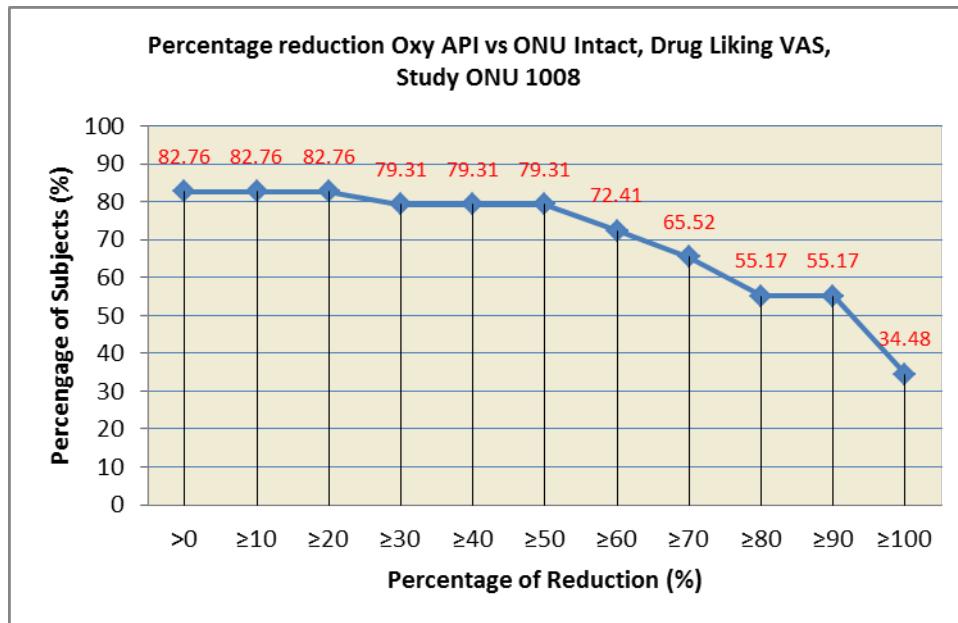
where T, C, and P denote  $E_{\max}$  of the test drug, the active control drug and placebo, respectively.

The reviewer use formula (2) to calculate the percent reduction between treatments.

From Table 11 and Figure 8, 24 out of the 29 subjects who completed the study (~83%) had some reduction in Drug Liking with ONU Intact comparing to OXY API while 17% subjects had no reduction or negative reduction. 23 subjects (~79%) had at least 30% reduction in Drug Liking with ONU Intact and 23 subjects (~79%) had at least 50% reduction. 10 subjects (~34.5%) had greater or equal than 100% reduction. Table 12 and Figure 9 showed approximately 76% of

subjects showed some reduction in Drug Liking with ONU Chewed comparing to OXY API, and around 24% of subjects had no reduction or negative reduction in Drug Liking. At least a 30% and 50% reduction in Drug Liking with ONU Chewed comparing to OXY API was 69% and 66% of subjects respectively.

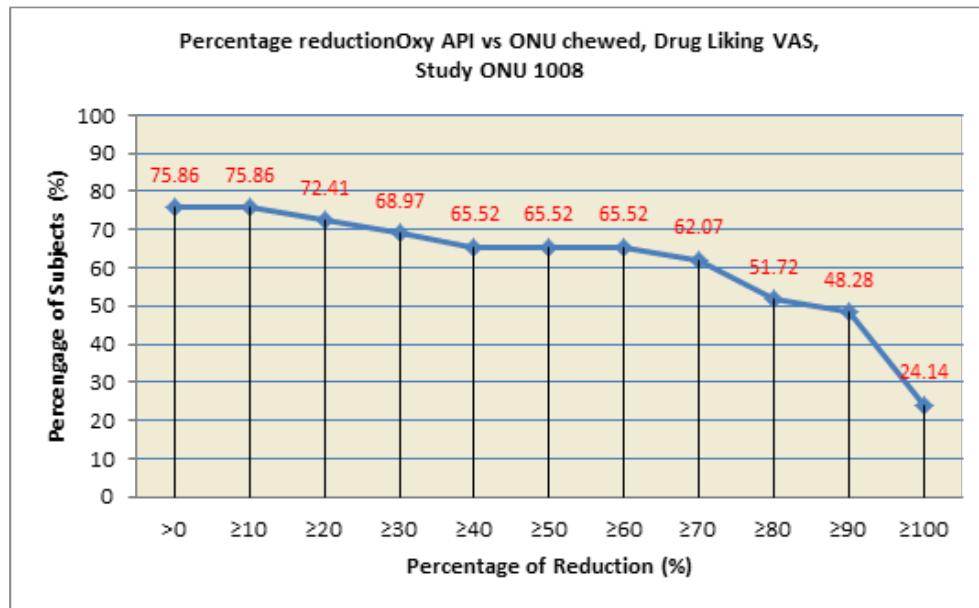
**Figure 8 . OXY API vs ONU Intact, Drug Liking VAS, percentage reduction**



**Table 11. OXY API vs ONU Intact, Drug Liking VAS, percentage reduction**

Percentage of Reduction (%)	Frequency	Percentage of subjects (%)
>0	24	82.76
≥10	24	82.76
≥20	24	82.76
≥30	23	79.31
≥40	23	79.31
≥50	23	79.31
≥60	21	72.41
≥70	19	65.52
≥80	16	55.17
≥90	16	55.17
≥100	10	34.48

**Figure 9. OXY API vs ONU Chewed, Drug Liking VAS, percentage reduction**



**Table 12 OXY API vs ONU Chewed, Drug Liking VAS, percentage reduction**

Percentage of Reduction (%)	Frequency	Percentage of subjects (%)
>0	22	75.86
≥10	22	75.86
≥20	21	72.41
≥30	20	68.97
≥40	19	65.52
≥50	19	65.52
≥60	19	65.52
≥70	18	62.07
≥80	15	51.72
≥90	14	48.28
≥100	7	24.14

### 3. Conclusion

The study was validated using mean statistical differences between the medicated products and the placebo. As to the primary and secondary analysis, the reviewer analyzed the primary endpoint Drug High and the secondary endpoint Drug Liking VAS, Good Effects VAS, Bad Effects VAS, Pupil Diameter (mm), Overall Drug Liking VAS (at hour 12) and Take Drug Again VAS (at hour 12). The results from the statistical reviewer's analyses establish that:

- For the comparison of placebo and OXY, except for the Bad Effect VAS, there were statistically significant differences between these two treatments on all subjective measures. Pupil diameter was significantly lower following administration of OXY.
- For the comparison of ONU chewed and OXY, there were significant statistically differences on all subjective measures. ONU chewed was associated with greater Bad Effect VAS, higher pupil diameter and significantly lower Drug Liking, Good Effects, Bad Effects, Overall Drug Liking (at hour 12) and Take Drug Again VAS (at hour 12).
- For the comparison of ONU intact and OXY, except for the Bad Effect VAS, there were significant statistically differences on all subjective measures.
- There were few significant differences between ONU chewed and ONU intact. However, ONU chewed showed marginally higher Good Effect VAS, significantly higher score in Bad Effect VAS.
- For the comparison of ONU intact and placebo, no significant differences were observed on all subjective measures.
- Effects on the comparison of ONU chewed and placebo were minimal, no significant differences were observed, however, ONU chewed had marginally higher score on Good Effect VAS, significantly higher Bad Effect VAS

In addition, we provide the following:

- Around 83% of the subjects had some reduction in Drug Liking with ONU Intact comparing to OXY API, at least a 30% and 50% reduction in Drug Liking was 79% and 79% respectively.
- Around 76% of the subjects showed some reduction in Drug Liking with ONU Chewed comparing to OXY API, at least a 30% and 50% reduction in Drug Liking with ONU Chewed comparing to OXY API was 69% and 66% of subjects respectively.

#### 4. References

- Guidance for Industry: Assessment of Abuse Potential for Drugs (January 2010)  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>
- Guidance for Industry: Abuse Deterrent Opioids – Evaluation and Labeling (January 2013)  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf>
- Holm, S. (1979). "A simple sequentially rejective multiple test procedure". Scandinavian Journal of Statistics 6 (2): 65–70

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ANNA SUN  
07/01/2014

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07/01/2014

## **Cover Letter**

This is an amendment to the original review.

The difference of this amendment review report to the original review report is the 'Percentage Reduction Analysis' part and the conclusions.

The reviewer updated the original 'Percentage Reduction Analysis' part and added two more conclusions regarding the 'Percentage Reduction Analysis'.



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

# Statistical Review and Evaluation

## CLINICAL STUDIES

<b>NDA/Serial Number:</b>	205777
<b>Drug Name:</b>	Oxycodone-Naloxone tablets (ONU)
<b>Indication:</b>	(b) (4)
<b>Study number:</b>	ONU1007 (UPN 1608)
<b>Applicant:</b>	Purdue Pharma L.P.
<b>Date(s):</b>	Date of Document: Sep 23,2013 Consult received date: Nov 11, 2013 PDUFA date: Completion date: 01/10/2014
<b>Review Priority:</b>	P
<b>Biometrics Division:</b>	DBVI
<b>Statistical Reviewer:</b>	Anna Sun, Ph.D., Mathematical Statistician, OB/DBVI
<b>Concurring Reviewers:</b>	Yi Tsong, Ph.D., Acting Division Director, OB/DBVI
<b>Medical Division:</b>	Control Substance Staff
<b>The CSS Team:</b>	James Tolliver, Ph.D., Pharmacologist, OCD/CSS Silvia Calderon, Ph.D., Pharmacology Team Leader, OCD/CSS
<b>Project Manager:</b>	Sandra Saltz, Project Manager, CSS

**Keywords:** *Crossover design, Drug abuse potential study, Self-reported endpoint, Multiple endpoints*

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## 1. Executive Summary

Study ONU1007 (UPN 1608) was a Single-Center, Randomized, Double-Blind Study in Recreational Opioid Users to Evaluate the Abuse Potential, Pharmacokinetics, and Safety of Oxycodone/Naloxone (ONU) Tablets when Chewed or Administered Intact via the Oral Route.

The objectives of the study were to evaluate the following:

- The oral abuse potential and pharmacodynamic (PD) effects of chewed ONU and intact ONU compared to oxycodone oral solution and placebo (PBO) in healthy, adult, non-physically dependent recreational opioid users with a history of oral chewing abuse/misuse.
- The safety and tolerability of orally administered chewed and intact ONU in healthy, adult, non-physically dependent recreational opioid users with a history of oral chewing abuse/misuse.
- The comparative PK profile of orally administered chewed and intact ONU compared to oxycodone oral solution

There were four treatments in the study. 37 subjects were randomized (including 1 replacement subject for an early withdrawal) and 36 subjects were analyzed. Subjects received each of the treatments outlined below in a randomized, double-blinded, triple-dummy fashion (one per Treatment visit):

Treatment A: ONU 40/20 mg tablet, intact + ONU PBO tablet, chewed + PBO oral solution

Treatment B: ONU PBO tablet, intact + ONU 40/20 mg tablet, chewed + PBO oral solution

Treatment C: ONU PBO tablet, intact + ONU PBO tablet, chewed + oxycodone oral solution

Treatment D: ONU PBO tablet, intact + ONU PBO tablet, chewed + PBO oral solution

Pharmacodynamic Conclusions:

- The study was validated using mean statistical differences between the medicated products and the placebo for the primary endpoint  $E_{max}$  of the two primary measures of relative abuse potential, Drug Liking VAS and Drug High VAS.
- $E_{max}$  values of Drug liking VAS for Oxy API and ONU chewed were both significantly higher than for ONU intact. In contrast, there is no significant difference between Oxy API and ONU chewed.  $E_{max}$  values of Drug high VAS for Oxy API and ONU chewed were both significantly higher than for ONU intact, but there is no significant differences between Oxy API and ONU chewed were observed.
- Mean peak scores of Drug liking VAS and Drug high VAS for ONU Intact were generally delayed compared to Oxy API and ONU chewed.

In addition, we provide the following:

- Around 67% had some reduction in Drug Liking with ONU Intact comparing to OXY API, at least a 30% and 50% reduction in Drug Liking was 58% and 47% respectively. No significant percentage reduction was observed in Drug Liking with ONU Chewed comparing to OXY API.
- Around 72% had some reduction in Drug High with ONU Intact comparing to OXY API, at least a 30% and 50% reduction in Drug High was 50% and 25% respectively. No significant percentage reduction was observed in Drug High with ONU Chewed comparing to OXY API.

## **2. Review Report on Study ONU1007 (UPN 1608)**

### **2.1 Overview**

ONU ( [REDACTED] <sup>(b) (4)</sup> 10/5 mg, 20/10 mg, and 40/20 mg oxycodone/naloxone) is a [REDACTED] <sup>(b) (4)</sup> combination formulation of oxycodone hydrochloride and naloxone hydrochloride [REDACTED] <sup>(b) (4)</sup> pain.

This study was designed to evaluate the abuse potential, PK profile, and safety of orally-administered ONU tablets when chewed or intact in subjects with a history of recreational opioid use who are not physically dependent on opioids.

#### **2.1.1 Objectives of the study**

The objectives of the study were to evaluate the following:

- The oral abuse potential and pharmacodynamic (PD) effects of chewed ONU and intact ONU compared to oxycodone oral solution and placebo (PBO) in healthy, adult, non-physically dependent recreational opioid users with a history of oral chewing abuse/misuse.
- The safety and tolerability of orally administered chewed and intact ONU in healthy, adult, non-physically dependent recreational opioid users with a history of oral chewing abuse/misuse.
- The comparative PK profile of orally administered chewed and intact ONU compared to oxycodone oral solution.

#### **2.1.2 Study design**

This was a single-center, double-blind, randomized, crossover study. The study consisted of 4 phases:

- Screening: Visit 1 for inclusion/exclusion screening and Visit 2 for a naloxone challenge test to screen for symptoms of opioid withdrawal.
- Qualification: Visit 3 for a randomized, crossover pharmacologic qualification (oxycodone and PBO) to ensure tolerability, appropriate reporting of positive subjective effects, and to demonstrate that subjects were able to complete the study procedures (including the chewing procedures).
- Treatment: Visit 4 to Visit 7 where each of the following single-dose treatments were administered (1 per visit): ONU 40/20 mg tablet, intact + ONU PBO tablet, chewed + PBO oral solution; ONU PBO tablet, intact + ONU 40/20 mg tablet, chewed + PBO oral solution; ONU PBO tablet, intact + ONU PBO tablet, chewed + oxycodone oral solution; ONU PBO tablet, intact + ONU PBO tablet, chewed + PBO oral solution
- Follow-up: Visit 8 for a safety follow-up, 3 to 7 days after the last Treatment Phase drug administration

#### **Outcome Variables**

Primary Pharmacodynamics outcome variables were 'at this moment' Drug Liking visual analog scale (VAS) and High VAS ( $E_{max}$ , TA\_AUE). However, conclusions regarding the abuse

potential of ONU when administered via the oral route will consider responses on all measures, which can be categorized as follows:

Balance of effects:

- ‘At the moment’ Drug Liking VAS (maximum effect [ $E_{max}$ ], minimum effect [ $E_{min}$ ], time averaged area under the effect curve [TA\_AUE])
- Overall Drug Liking (ODL) VAS ( $E_{max}$ ,  $E_{min}$ , end-of-day [12 hours] and next day [24 hours] mean scores)
- Take Drug Again (TDA) VAS ( $E_{max}$ , end-of-day and next day mean scores)
- Subjective Drug Value (SDV) ( $E_{max}$  end-of-day and next day mean scores)

Positive/euphoric effects:

- High VAS ( $E_{max}$ , TA\_AUE)
- Good Effects VAS ( $E_{max}$ , TA\_AUE)
- ARCI MBG scale ( $E_{max}$ , TA\_AUE)

Negative effects:

- Bad Effects VAS ( $E_{max}$ , TA\_AUE)
- Feeling Sick VAS ( $E_{max}$ , TA\_AUE)

Sedative effects:

- Drowsiness/Alertness VAS ( $E_{min}$ , TA\_AUE)

Other effects:

Any Effects VAS ( $E_{max}$ , TA\_AUE)

Objective measure:

- Pupillometry (maximum pupil constriction [MPC], time-averaged pupillometry area over the curve [TA\_PAOC] relative to baseline)

Time to peak effect ( $TE_{max}$ ,  $TE_{min}$  and/or  $T_{MPC}$ , as applicable) will also be calculated for ARCI, VAS (excluding ODL and TDA), and pupillometry measures.

### **2.1.3 Abuse potential measure and data collection times**

Drug Liking VAS and Drug High VAS are the primary abuse potential variables, measured predose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hours post-dose. The secondary variable VAS (Overall Drug Liking, Take Drug Again) and Subjective Drug Value were measured at 12 and 24 hours post-dose, ARCI MBG was measured at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hours post-dose and pupillometry was measured at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hours post-dose.

### **2.1.4 Number of subjects**

A total of 114 subjects were screened of whom 65 subjects were eligible to proceed to the Qualification Phase. Of the 65 subjects who were dosed during the Qualification Phase, 28 (43.1%) subjects did not pass the Qualification Phase and 37 (56.9%) subjects were randomized to the Treatment Phase and received at least 1 dose of the study drug. One (2.7%) subject discontinued after Treatment Period 1 for administrative reasons. In total, 36 subjects completed all 4 Treatment Periods including all protocol-specified procedures and assessments. All 36 subjects were included in the PK and PD populations.

## **2.1.5 Statistical methodologies used in the Sponsor's analyses**

### **Hypothesis Testing**

For each of the parameters, the null hypothesis was: there is no treatment effect, and the alternative hypothesis was: there is a treatment effect. For each of the contrasts or pairwise comparisons, the null hypothesis was: there is no treatment effect difference between the tested pair, and the alternative hypothesis was: there is a treatment effect difference between the tested pair.

A 5% Type I error rate with a P value less than 0.05 was considered as statistically significant for all individual hypothesis tests. All statistical tests were performed using two-tailed significance criteria.

### **Analysis of Pharmacodynamic Assessments**

Pharmacodynamic data at each time point were summarized by descriptive statistics and presented graphically (where appropriate) for the Qualification Phase and for the Treatment Phase. Derived endpoints were summarized using descriptive statistics and box-plots. Outliers were listed by measure and parameter.

Pharmacodynamic endpoints for the Treatment Phase (maximum effect [ $E_{max}$ ], minimum effect [ $E_{min}$ ], maximum pupil constriction [MPC] and/or time-averaged area under the effect curve [TA\_AUE]/ time-averaged pupillometry area over the curve [TA\_PAOC], as appropriate) were analyzed using a mixed-effect model for a crossover study. Time to maximum effect and time to minimum effect ( $TE_{max}$  and  $TE_{min}$ ) were summarized descriptively; however, additional analyses could have been undertaken, if appropriate. From each model, means, 95% confidence intervals, and P values for treatments and treatment differences were computed. The Benjamini and Hochberg procedure was used to control for Type I error arising from the multiple comparisons, as necessary. Tests for non-normality and homogeneity of variance were conducted for the primary measures. Nonparametric sensitivity analyses were employed, as necessary.

The contrasts to assess the abuse potential for the ONU formulation included:

- Oxycodone oral solution vs. PBO (reference)
- ONU (intact) vs. PBO
- ONU (intact) vs. oxycodone oral solution
- ONU (chewed) vs. PBO
- ONU (chewed) vs. oxycodone oral solution
- ONU (chewed) vs. ONU (intact)

## **2.1.6 Sponsor's Summary and Conclusions**

### **Pharmacodynamic Conclusions**

This study demonstrated that Oxy API showed significantly greater effects compared to PBO on the majority of endpoints, thereby confirming the validity of the study. ONU administered via the intended route (oral ONU intact) showed greater effects than PBO but significantly lower effects compared to Oxy API and ONU chewed. In addition, effects of ONU were generally delayed compared to Oxy API and ONU chewed. However, chewed ONU tablets showed significantly

greater effects than ONU intact and were not significantly different from Oxy API. Brief summary conclusions are provided below for each type of measure:

#### Balance of Effects

- ‘At this moment’ Drug Liking  $E_{max}$  values (primary) for Oxy API and ONU tablets (both intact and chewed) were significantly higher compared to PBO.  $E_{max}$  values for Oxy API and ONU chewed were both significantly higher than that for ONU intact, and no significant differences between Oxy API and ONU chewed were observed.
- For secondary global measures (Overall Drug Liking VAS, Take Drug Again VAS, and SDV), administration of Oxy API and ONU (intact and chewed) resulted in a significantly higher  $E_{max}$  compared to PBO on all measures.  $E_{max}$  values for intact ONU were significantly lower than those for Oxy API and ONU chewed, which were not significantly different from each other.

#### Positive Effects

- $E_{max}$  on the High VAS (primary) was significantly higher than PBO for Oxy API and ONU (intact and chewed).  $E_{max}$  values for Oxy API and ONU chewed were also significantly higher than that for ONU intact and not significantly different from each other.
- For ARCI MBG and Good Effects VAS, the secondary measures of positive effects, the same pattern of results was observed as for High VAS.

#### Negative Effects

- Negative effects were modest in this study. For both measures of negative effects (Bad Effects and Feeling Sick VAS),  $E_{max}$  for Oxy API and ONU chewed did not differ from each other and each was significantly higher than that for PBO. For ONU intact,  $E_{max}$  was not significantly different from PBO for either measure. For Bad Effects,  $E_{max}$  for ONU intact was significantly lower than that for ONU chewed but not significantly different from that for Oxy API. For Feeling Sick,  $E_{max}$  for ONU intact was significantly different than those for Oxy API and ONU chewed.

#### Sedative and Other Effects

- For sedative and any effects, all active treatments (Oxy API and ONU intact and chewed) had significantly greater effects compared to PBO. As with other measures, administration of Oxy API and ONU chewed resulted in peak effects ( $E_{min}$  for Drowsiness/Alertness and  $E_{max}$  for Any Effects) that were significantly greater than those for ONU intact but not significantly different from each other.

#### Objective Effects

- For the objective measure of pupillometry, MPC was observed to be significantly higher for Oxy API and ONU (intact and chewed) compared to PBO. Consistent with results from most subjective effects, MPC measurements for Oxy API and ONU chewed were significantly greater than those for ONU intact and not significantly different from each other.

## 2.2 Data Location

The analysis datasets are located at  
<\\CDSESUB1\evsprod\NDA20577\0000\m5\datasets\onu1007\analysis\adam\datasets>

## 2.3 Reviewer's Assessment

All analyses were conducted from the stand point of the pharmacodynamics analysis.

### 2.3.1 Descriptive Statistics

The descriptive statistics for the Emax endpoint for primary variables Drug Liking and Drug High are provided in Table 1 and Table 2.  $E_{max}$  is calculated as the maximum effect in the first 8 hours in the review's analysis.

Table 1 summarizes the mean, standard error, minimum, the first quartile (Q1), median, the third quartile (Q3), and maximum for four treatments in the study. Table 2 summarizes the treatment differences between ONU chewed vs. ONU intact, ONU chewed vs. Oxy API, Oxy API vs. ONU intact for  $E_{max}$  of Drug Liking VAS and Drug High.

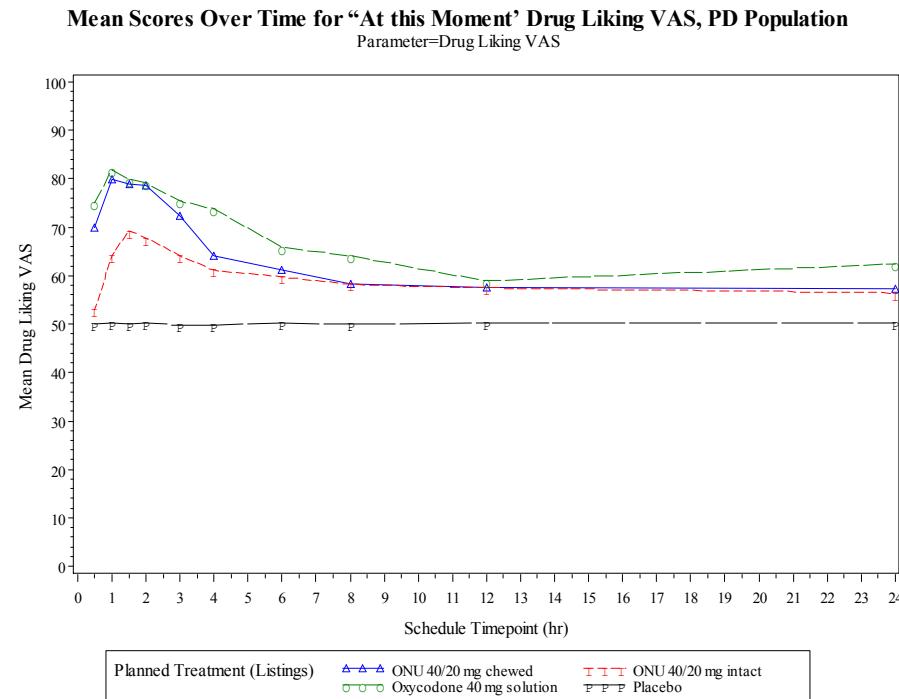
**Table 1.  $E_{max}$  Descriptive Statistics for Drug Liking, Drug High, PD population (N=36)**

Parameter	Planned Treatment	Mean	Std Dev	Min	Q1	Median	Q3	Max
Drug Liking VAS	ONU 40/20 mg chewed	86.3	16.0	51.0	72.5	96.0	100.0	100.0
	ONU 40/20 mg intact	72.5	19.0	50.0	53.5	73.5	86.0	100.0
	Oxy API 40 mg	88.5	16.9	50.0	79.0	100.0	100.0	100.0
	Placebo	50.8	0.6	50.0	50.0	51.0	51.0	52.0
High VAS	ONU 40/20 mg chewed	87.2	17.8	22.0	76.5	100.0	100.0	100.0
	ONU 40/20 mg intact	59.2	37.4	0.0	28.5	66.5	94.0	100.0
	Oxy API 40 mg	90.5	18.4	15.0	91.5	100.0	100.0	100.0
	Placebo	13.4	24.5	0.0	0.0	0.5	6.0	91.0

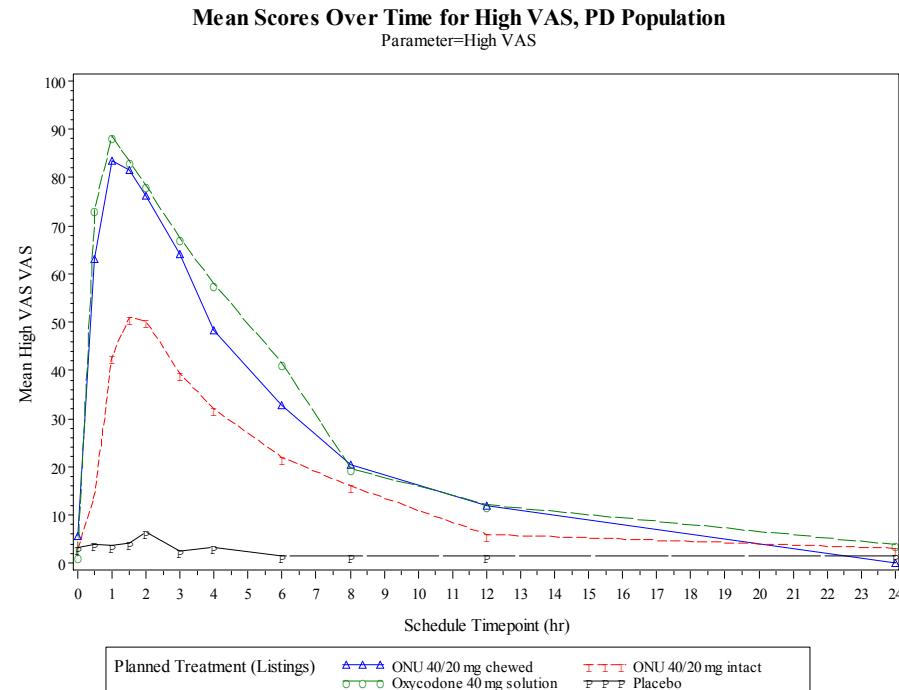
For Drug Liking VAS, as can be seen in table 1, the mean, first quartile, median and third quartile of placebo was within the neutral range (~50). Mean  $E_{max}$  for ONU chewed and Oxycodone 40 mg oral solution (Oxy API) are close with values 86.3 and 88.5 respectively. Mean  $E_{max}$  for ONU intact is 72.5, which is relatively lower than ONU chewed and Oxy API. From Figure 1, it can be seen that, the  $E_{max}$  of ONU is occurred at around 1.5 hours post-dose, slightly later than ONU chewed and Oxy API.

For Drug High VAS, from table 1, mean  $E_{max}$  for placebo was low (~13), while mean  $E_{max}$  for ONU chewed and Oxy API were high, 87.2 and 90.5 respectively. The median scores for both ONU chewed and Oxy API are 100. Figure 2 shows mean scores for placebo remained less than 10. Mean scores of ONU chewed and Oxy API increased rapidly to the peak of ~89 and ~83. Mean peak scores of ONU intact (~50) also increased to high scores compared with placebo but lower than ONU chewed and Oxy API, and occurred with slower onset, around 1.5 to 2 hours post-dose.

**Figure 1. Mean Scores over Time for Drug Liking VAS, PD Population**



**Figure 2. Mean Scores over Time for High VAS, PD Population**



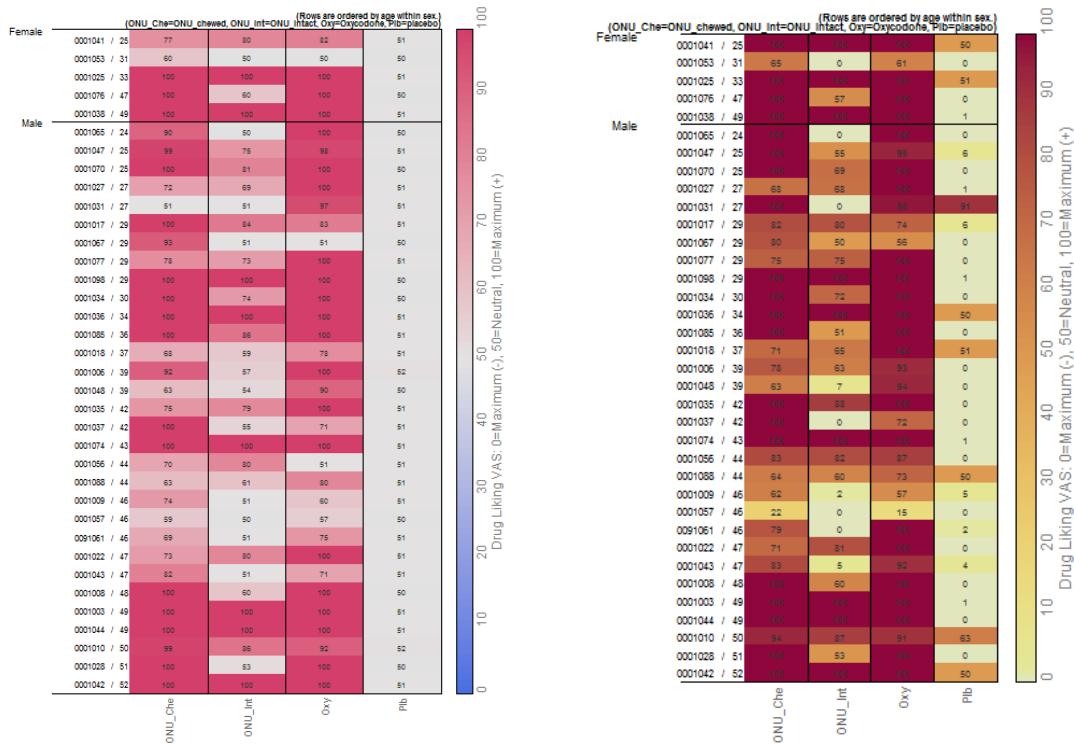
**Table 2. Treatment difference of E<sub>max</sub> for Drug Liking, Drug High, PD population (N=36)**

Parameter	Treatment difference	Mean	Std Dev	Min	Q1	Median	Q3	Max	t Value	Pr >  t
Drug Liking VAS	ONU_chew_VS_ONU_intact	13.8	16.7	-10.0	0.0	9.0	25.0	47.0	4.94	<.0001
	ONU_chew_VS_OXY	-2.2	16.6	-46.0	-9.0	0.0	1.5	42.0	-0.79	0.4328
	OXY_VS_ONU_intact	16.0	17.9	-29.0	0.0	17.5	26.5	50.0	5.35	<.0001
High VAS	ONU_chew_VS_ONU_intact	28.1	33.3	-10.0	0.0	13.5	48.0	100.0	5.06	<.0001
	ONU_chew_VS_OXY	-3.3	13.4	-32.0	-6.5	0.0	1.0	28.0	-1.47	0.1517
	OXY_VS_ONU_intact	31.3	32.7	-6.0	0.0	26.5	48.0	100.0	5.74	<.0001

For the Drug Liking VAS and high VAS difference, ONU intact showed a significantly lower E<sub>max</sub> value compared to both ONU chewed and Oxy API (P-value <0.0001), indicating less liking of ONU intact.

Individual E<sub>max</sub> scores are displayed by subject for all treatments in Figures 3-4, the rows of the table plot are ordered by age within sex. One may see the E<sub>max</sub> for each patient at different treatment, and the heat map also show that less liking of ONU intact.

**Figure 3. Emax for Drug Liking by Subject x Treatment      Figure 4. Emax for Drug High by Subject x Treatment**



### 2.3.2 Statistical Analysis

#### Statistical model fitting

The reviewer analyzed the hypotheses of the primary objective using the mixed-effect model, the final model the reviewer used is treatment as fixed effects and subject nested within sequence as a random effect. Table 3 is the analysis results for E<sub>max</sub> of Drug Liking VAS, Table 4 is the analysis results for E<sub>max</sub> of Drug high.

Table 3 shows that a significant treatment effect for this primary endpoint ( $p<0.0001$ ). From treatment contrast, ONU 40/20 mg chewed and ONU 40/20 mg intact are significant different, but there is no significant difference between ONU 40/20 mg chewed and Oxy 40 mg solution ( $P=0.4383$ ). Similar results are seen from table 4.

Note: In the proposal page 59 table 12, sponsor adjusted the p values using the Benjamini and Hochberg procedure. A more appropriate type I error rate adjusting procedure is Holm's procedure.

**Table 3. Analysis Results for Drug Liking VAS Emax , PD Population.**

	LS Mean	StdE	Pr >  t	Lower	Upper
Treatments					
ONU 40/20 mg chewed	86.31	2.46	<.0001	81.42	91.19
ONU 40/20 mg intact	72.53	2.46	<.0001	67.64	77.41
Oxy 40 mg solution	88.50	2.46	<.0001	83.61	93.39
Placebo	50.75	2.46	<.0001	45.86	55.64
Contrasts (difference)					
ONU 40/20 mg chewed - ONU 40/20 mg intact	13.78	2.82	<.0001	8.19	19.37
ONU 40/20 mg chewed - Oxy 40 mg solution	-2.19	2.82	0.4383	-7.79	3.40
ONU 40/20 mg chewed - Placebo	35.56	2.82	<.0001	29.96	41.15
ONU 40/20 mg intact - Oxy 40 mg solution	-15.97	2.82	<.0001	-21.56	-10.38
ONU 40/20 mg intact - Placebo	21.78	2.82	<.0001	16.19	27.37
Oxy 40 mg solution - Placebo	37.75	2.82	<.0001	32.16	43.34

**Table 4. Analysis Results for High VAS Emax ,PD Population**

	LS Mean	StdE	Pr >  t	Lower	Upper
Treatments					
ONU 40/20 mg chewed	87.22	4.23	<.0001	78.83	95.62
ONU 40/20 mg intact	59.17	4.23	<.0001	50.77	67.56
Oxy 40 mg solution	90.50	4.23	<.0001	82.11	98.89
Placebo	13.44	4.23	0.002	5.05	21.84
Contrasts (difference)					
ONU 40/20 mg chewed - ONU 40/20 mg intact	28.06	5.07	<.0001	18.00	38.12
ONU 40/20 mg chewed - Oxy 40 mg solution	-3.28	5.07	0.5197	-13.34	6.78
ONU 40/20 mg chewed - Placebo	73.78	5.07	<.0001	63.72	83.84
ONU 40/20 mg intact - Oxy 40 mg solution	-31.33	5.07	<.0001	-41.39	-21.27
ONU 40/20 mg intact - Placebo	45.72	5.07	<.0001	35.66	55.78
Oxy 40 mg solution - Placebo	77.06	5.07	<.0001	67.00	87.12

## Percentage Reduction Analysis

Percent reduction analysis is an important abuse potential measure, and it is recommended for the clinical abuse potential studies. Generally the percent reduction formula is defined as:

$$\% \text{ reduction} = \frac{c_i - t_i}{c_i - 50}, \quad i = 1, 2 \dots n \quad (1)$$

This formula does not include an adjustment factor for placebo responses.

Chen, Klein and Calderon [3] gave an example for the definition of the percentage reduction for the test drug relative to the active control for Drug Liking VAS in their poster presentation at the 74th College on Problems of Drug Dependence (CPDD) annual scientific meeting held in Palm Spring in June of 2012 as follows:

$$\% \text{ reduction} = \begin{cases} \frac{C - T}{C - 50} \times \left(1 - \frac{P - 50}{50}\right) \times 100\%, & \text{if } P > 55; \\ \frac{C - T}{C - 50} \times 100\%, & \text{if } P \leq 55. \end{cases} \quad (2)$$

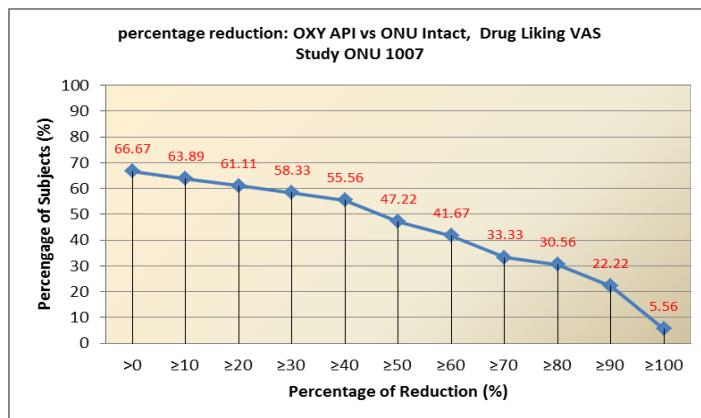
where T, C, and P denote  $E_{max}$  of the test drug, the active control drug and placebo, respectively.

The reviewer use formula (2) to calculate the percent reduction between treatments.

From Table 5 and Figure 5, 24 out of the 36 subjects who completed the study (~67%) had some reduction in Drug Liking with ONU Intact comparing to OXY API while 33% subjects had no reduction or negative reduction. 21 subjects (~58%) had at least 30% reduction in Drug Liking with ONU Intact and 17 subjects (~47%) had at least 50% reduction. 2 subjects (~5.6%) had greater or equal than 100% reduction. Table 6 and Figure 6 showed approximately 33% of subjects showed some reduction in Drug Liking with ONU Intact comparing to OXY API, and around 67% of subjects had no reduction or negative reduction in Drug Liking. At least a 30% and 50% reduction in Drug Liking with ONU Intact comparing to OXY API was 22% and 17% of subjects respectively.

From Table 7 and Figure 7, 26 out of the 36 subjects who completed the study (~72%) had some reduction in Drug High with ONU Intact comparing to OXY API while 28% subjects had no reduction or negative reduction. 18 subjects (50%) had at least 30% reduction in Drug High with ONU Intact and 9 subjects (25%) had at least 50% reduction. 6 subjects (~16.7%) had greater or equal than 100% reduction. Table 8 and Figure 8 showed approximately 28% of subjects showed some reduction in Drug High with ONU Chewed comparing to OXY API, and around 72% of subjects had no reduction or negative reduction in Drug High. At least a 30% and 50% reduction in Drug high with ONU Chewed comparing to OXY API was 5.6% and 5.6% of subjects respectively.

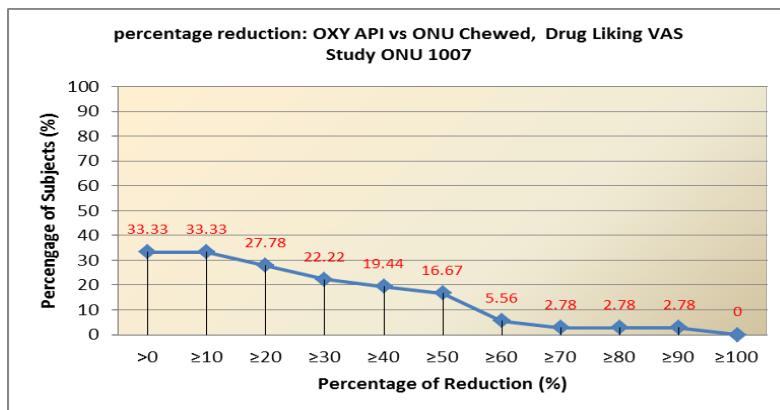
**Figure 5. OXY API vs ONU Intact, Drug Liking VAS, percentage reduction**



**Table 5. OXY API vs ONU Intact, Drug Liking VAS, percentage reduction**

Percentage of Reduction (%)	Frequency	Percentage of subjects (%)
>0	24	66.67
≥10	23	63.89
≥20	22	61.11
≥30	21	58.33
≥40	20	55.56
≥50	17	47.22
≥60	15	41.67
≥70	12	33.33
≥80	11	30.56
≥90	8	22.22
≥100	2	5.56

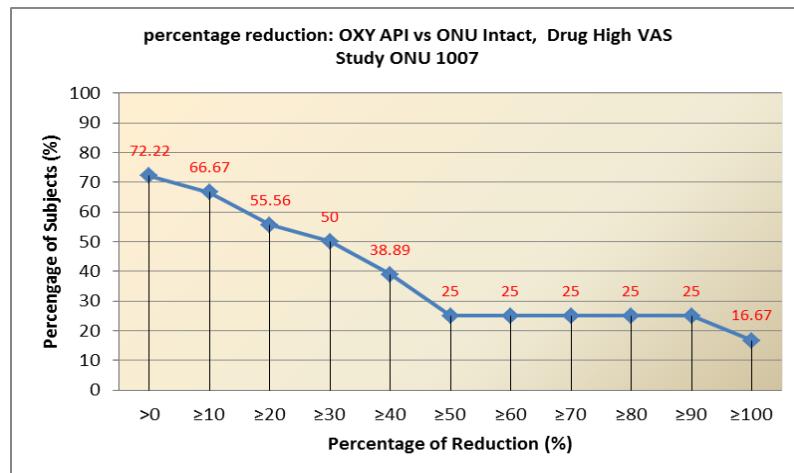
**Figure 6. OXY API vs ONU chewed, Drug Liking VAS, percentage reduction**



**Table 6. OXY API vs ONU chewed, Drug Liking VAS, percentage reduction**

Percentage of Reduction (%)	Frequency	Percentage of subjects (%)
>0	12	33.33
$\geq 10$	12	33.33
$\geq 20$	10	27.78
$\geq 30$	8	22.22
$\geq 40$	7	19.44
$\geq 50$	6	16.67
$\geq 60$	2	5.56
$\geq 70$	1	2.78
$\geq 80$	1	2.78
$\geq 90$	1	2.78
$\geq 100$	0	0

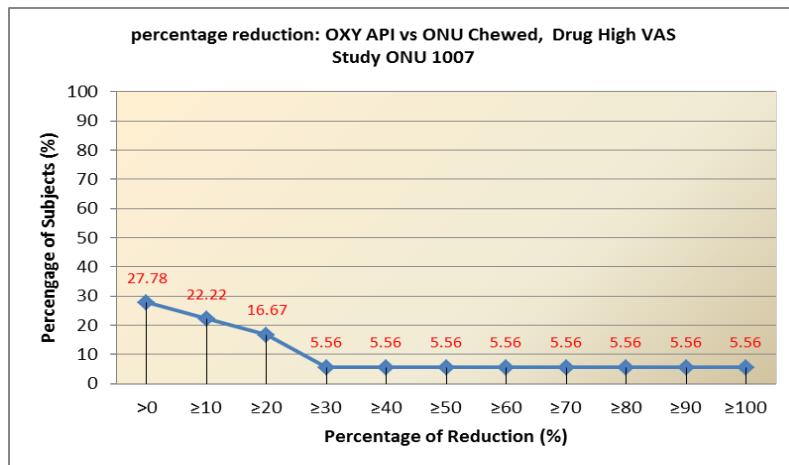
**Figure 7. OXY API vs ONU Intact, Drug High VAS, percentage reduction**



**Table 7. OXY API vs ONU Intact, Drug High VAS, percentage reduction**

Percentage of Reduction (%)	Frequency	Percentage of subjects (%)
>0	26	72.22
$\geq 10$	24	66.67
$\geq 20$	20	55.56
$\geq 30$	18	50
$\geq 40$	14	38.89
$\geq 50$	9	25
$\geq 60$	9	25
$\geq 70$	9	25
$\geq 80$	9	25
$\geq 90$	9	25
$\geq 100$	6	16.67

**Figure 8 . OXY API vs ONU Chewed, Drug High VAS, percentage reduction**



**Table 8. OXY API vs ONU Chewed, Drug High VAS, percentage reduction**

Percentage of Reduction (%)	Frequency	Percentage of subjects (%)
>0	10	27.78
≥10	8	22.22
≥20	6	16.67
≥30	2	5.56
≥40	2	5.56
≥50	2	5.56
≥60	2	5.56
≥70	2	5.56
≥80	2	5.56
≥90	2	5.56
≥100	2	5.56

### 3. Conclusion

The primary objective of the study is to evaluate oral abuse potential and pharmacodynamic (PD) effects of chewed ONU and intact ONU compared to Oxy API oral solution 40 mg and placebo. The results from the statistical reviewer's analyses establish that:

- The study was validated using mean statistical differences between the medicated products and the placebo for the primary endpoint  $E_{max}$  of the two primary measures of relative abuse potential, Drug Liking VAS and Drug High VAS.
- $E_{max}$  values of Drug liking VAS for Oxy API and ONU chewed were both significantly higher than for ONU intact. In contrast, there is no significant difference between Oxy API and ONU chewed.
- $E_{max}$  values of Drug high VAS for Oxy API and ONU chewed were both significantly higher than for ONU intact, but there is no significant differences between Oxy API and ONU chewed were observed.
- Mean peak scores of Drug liking VAS and Drug high VAS for ONU Intact were generally delayed compared to Oxy API and ONU chewed.

In addition, we provide the following:

- Around 67% had some reduction in Drug Liking with ONU Intact comparing to OXY API, at least a 30% and 50% reduction in Drug Liking was 58% and 47% respectively. No significant percentage reduction was observed in Drug Liking with ONU Chewed comparing to OXY API.

- Around 72% had some reduction in Drug High with ONU Intact comparing to OXY API, at least a 30% and 50% reduction in Drug High was 50% and 25% respectively. No significant percentage reduction was observed in Drug High with ONU Chewed comparing to OXY API.

#### 4. References

- 1) Guidance for Industry: Assessment of Abuse Potential for Drugs (January 2010)  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>
- 2) Guidance for Industry: Abuse Deterrent Opioids – Evaluation and Labeling (January 2013)  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf>
- 3) Chen, Klein and Calderon (2012) poster presentation at the 74th College on Problems of Drug Dependence (CPDD) annual scientific meeting held in Palm Springs.
- 4) Holm, S. (1979). "A simple sequentially rejective multiple test procedure". *Scandinavian Journal of Statistics* 6 (2): 65–70

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

## STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

**NDA/BLA #:**

NDA 205-777

**Drug Name:**

Oxycodone hydrochloride/naloxone hydrochloride

**Indication(s):**

Management of (b) (4) pain (b) (4),  
around-the-clock (b) (4)

**Applicant:**

Purdue Pharma L.P.

**Date(s):**

Letter date: September 23, 2013, PDUFA date: July 23, 2014

**Review Priority:**

Standard

**Biometrics Division:** II

**Statistical Reviewer:** Feng Li, Ph.D.

**Concurring Reviewers:** Janice Derr, Ph.D.

**Medical Division:** Division of Anesthesia, Analgesia, and Addiction Products

**Clinical Team:** Elizabeth Kilgore, M.D.

**Project Manager:** Lisa Basham, M.S.

**Keywords:** NDA review, Clinical Studies

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## **1. EXECUTIVE SUMMARY**

Purdue Pharma L.P. submitted a New Drug Application for a fixed-dose combination product of oxycodone hydrochloride and naloxone hydrochloride (OXN) with potential abuse-deterring features, seeking an indication for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. A confirmatory Phase 3 efficacy study (Study ONU3701) in opioid-experienced subjects with chronic low back pain was submitted to support the efficacy of OXN administered twice daily in comparison to placebo. Based on my review, the study provided evidence that OXN has an analgesic effect in comparison to placebo.

The clinical development program of OXN was discussed at several occasions. At the meeting in February 2009, the division advised the applicant that an analysis of pain response at Week 12 is necessary to support an indication in chronic pain. In the advice letter dated May 18, 2010, the division informed the applicant that a single, adequate and well-controlled efficacy study would be acceptable for demonstrating analgesic efficacy. In the advice letter dated August 19, 2011, the division stated that the design and primary efficacy analysis of Study ONU3701 appeared acceptable.

Study ONU3701 was a double-blind, placebo-controlled, parallel group, and randomized withdrawal study of OXN in subjects with moderate to severe chronic low back pain. The study consisted of three phases: the pre-randomization phase including a screening period and an open-label titration period (up to 28 days), the 12-week double-blind phase, and the safety follow-up phase. Subjects who demonstrated analgesic benefit and acceptable tolerability with OXN treatment during the open-label titration period were eligible for entering the double-blind phase. A total of 601 subjects were randomized to receive either OXN or matching placebo, based on their OXN dose at the end of the open-label titration period. Supplemental pain medication (immediate-release oxycodone) for breakthrough low back pain was allowed except during the 30 hours preceding study visits. The study report stated that subjects who discontinued double-blind study drug early were expected to complete the remaining visits and procedures unless they discontinued from the study.

The primary efficacy outcome was the “average pain over the last 24 hours” at Week 12. The protocol stated that the causal estimand was the difference in the primary efficacy outcome between the placebo and OXN treatment groups at Week 12 for all randomized subjects regardless of study drug compliance. The primary analysis was based on a mixed-model repeated measures analysis (MMRM) and an adaption of a hybrid imputation approach for handling missing data due to dropouts, which assigns high pain scores to discontinuations due to adverse events. The primary efficacy population included the subjects who were randomized and received study drug. The primary analysis only included data while subjects were taking study drug.

Based on my review, the study demonstrated the superiority of OXN over placebo in pain reduction over 12 weeks. There was a statistically significant difference in the Week 12 pain between the two treatment groups based on the pre-specified analysis. Sensitivity analyses employing several different methods for handling subjects who discontinued the study drug early produced similar results. About 40% (121/302) of the subjects randomized to placebo and 27% (80/299) of the subjects randomized to OXN discontinued the double-blinded treatment early, primarily due to lack of efficacy or adverse events. Among these subjects, approximately 40% (49/121) from the placebo and 31% (25/80) from the OXN groups continued to stay in the study until completion. Results from the analyses including the pain measurements collected after stopping study drug were also similar to those from the primary analysis. Secondary efficacy endpoints including Patient's Global Impression of Change and Sleep Disturbance subscale were also consistently in favor of OXN.

In my review, I addressed an issue concerning some ambiguity in the definition of the estimand. The ambiguity concerned the handling of pain scores in subjects who discontinued the study drug but remained in the study and continued to record their pain intensity (“retrieved dropouts”). I conducted additional sensitivity analyses that encompassed several ways of handling the post-discontinuation pain scores from retrieved dropouts. I found that the study conclusions were not affected by this issue.

In my opinion, Study ONU3701 has provided evidence of analgesic efficacy for OXN. The review team will need to consider the totality of evidence including safety analyses and findings from abuse studies to decide whether the benefit-risk profile justifies the approval of this combination product.

## 2. INTRODUCTION

### 2.1 Overview

Purdue Pharma L.P. is developing OXN as a fixed-dose combination opioid product with potential abuse-deterring features for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The formulation is approved in Europe as Targin and indicated for “The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. The naloxone component in a fixed combination with oxycodone is indicated for the therapy and/or prophylaxis of opioid induced constipation.” OXN is a controlled-release oral tablet formulation of oxycodone and naloxone in a fixed 2:1 ratio (such as 10/5 mg, 20/10 mg, 40/20 mg). Oxycodone is an opioid agonist readily bioavailable when administered orally. Naloxone is an antagonist of the opioid receptors activated by oxycodone and has been used intravenously to reverse the effects of opioid overdose. It has limited bioavailability following oral administration because of first-pass metabolism. The applicant believes that the naloxone component of OXN could serve as a potential deterrent to abuse because of high bioavailability in typical and popular abuse-related modes of administration. (b) (4)

(b) (4)

The development program of OXN has been discussed with the agency under IND 70,851. Issues relevant to this statistical review are summarized as below:

- At the meeting in February 2009, the division informed the applicant to perform a landmark analysis assessing the change in pain intensity from baseline to Week 12 using a conservative imputation method rather than an analysis on time to recurrent pain events to support analgesic efficacy.
- (b) (4)
- In the advice letter dated May 18, 2010, the division informed the applicant that the European Phase 3 trials will not support the analgesic efficacy of OXN or the impact of naloxone on the efficacy of OXN as the efficacy endpoints were not acceptable. The division confirmed that a single Phase 3 adequate and well-controlled study would be acceptable to demonstrate the analgesic efficacy. The applicant was advised to use a hybrid imputation method which accounts for opioid withdrawal in the primary efficacy analysis.
- (b) (4)  
The primary concern was the proposed hybrid single imputation method. The division suggested the applicant to propose methods that are consistent with the report on missing data published in 2010 by the National Academy of Science (NAS).
- In the advice letter dated August 19, 2011, the division stated that one adequate and well-controlled trial is sufficient for the proposed analgesic indication. The design and the primary efficacy analysis of Study ONU3701 appeared acceptable.
- In the advice letter dated October 25, 2012, the division expressed some concerns on the possibility that good pain scores would be assigned to discontinued patients who experienced both adverse events and opioid withdrawal symptoms.

In this statistical evaluation, I focused on Study ONU3701 and looked how the statistical comparisons were affected by the approach to handling early discontinuation.

## 2.2 Data Sources

The efficacy data submitted for Study ONU3701 can be found at  
<\\cdsesub1\\evsprod\\nda205777\\0000\\m5\\datasets\\onu3701\\tabulations\\sdtm> and

### **3. STATISTICAL EVALUATION**

#### **3.1 Data and Analysis Quality**

The applicant submitted study tabulation datasets and analysis datasets in CDISC format. The submitted datasets and define documents are of acceptable quality.

According to the applicant, one investigational site ( [REDACTED]<sup>(b) (4)</sup>) was placed on hold after routine monitoring uncovered a number of inconsistencies, including drug dispensation anomalies and other violations. This site was subsequently removed from the study following allegations that the investigator was involved in writing prescriptions to illegally provide drugs for abuse. Data from this site was excluded from the analyses.

The applicant reported that six subject numbers were found to potentially represent three unique subjects, based on birth dates and other factors in the database. Sensitivity analyses excluding the six subject numbers were conducted and produced similar results to the primary analysis.

Additionally, I found that for some subjects the actual treatment received in the double-blind period was different from the randomized (planned) treatment. For example, some subjects were randomized to the 30/15 mg dose but actually received 10/5 mg dose. The randomization error occurred only at the dose level. It did not affect the overall comparison between OXN and placebo. In response to the agency's information request, the applicant explained that dose level during the double-blind period was determined according to subject's diary data, which was incorrectly entered by some subjects.

#### **3.2 Evaluation of Efficacy**

##### **3.2.1 Study Design and Endpoints**

Study ONU3701 was a double-blind, placebo-controlled, parallel group, and randomized withdrawal study of OXN in subjects with moderate to severe pain due to chronic low back pain. The study consisted of three phases: the pre-randomization phase including a screening period and an open-label titration period (up to 28 days), the 12-week double-blind phase, and the safety follow-up phase.

Each subject entering the 12-week double-blind phase was required to have demonstrated analgesic benefit and acceptable tolerability with OXN treatment during the open-label titration period. Eligible subjects were randomized equally to receive either OXN (on 1 of 4 regimens: OXN 10/5 mg, OXN 20/10 mg, OXN 30/15 mg, and OXN 40/20 mg, every 12 hours) or matching placebo, based on their OXN dose at the end of the open-label titration period.

To be considered as having achieved a stable and effective OXN dose, the subject was required to meet the following double-blind period entry criteria for 7 consecutive days:

- remained on the same dose of OXN during the 7 consecutive days;
- had an “average pain over the last 24 hours” score on an 11-point numeric rating scale (NRS) of  $\leq 4$  and at least 2 points lower than their screening mean pain score;
- had not taken more than two immediate-release oxycodone 5-mg capsules on any day during these 7 days.

The double-blind phase comprised six visits: visit 3 (randomization), visit 4 (Week  $1 \pm 2$  days), visit 5 (Week  $2 \pm 2$  days), visit 6 (Week  $4 \pm 3$  days), visit 7 (Week  $8 \pm 3$  days), and visit 8 (Week  $12 \pm 3$  days). The starting dose of OXN (or matching placebo) was the stable, effective, and tolerable dose achieved at the end of the open-label titration period. At any time during the double-blind period, a subject could discontinue study drug for any reason. Subjects who discontinued double-blind study drug early were expected to complete the remaining visits and procedures unless they discontinued from the study.

All subjects underwent a blinded taper during the first 2 to 10 days of the double-blind phase. During this time, subjects randomized to placebo were tapered off OXN. Subjects randomized to placebo received OXN taper tablets in addition to the placebo tablets, and subjects randomized to OXN received dummy taper tablets in addition to the active tablets. This process was intended to minimize the effects of OXN withdrawal for subjects randomized to the placebo group.

Supplemental pain medication (immediate-release oxycodone) for breakthrough low back pain was allowed except during the 30 hours preceding study visits. Other medications with analgesic effects but taken for reasons other than chronic pain were to be avoided if possible during these 30-hour windows.

At scheduled study visits, efficacy assessments included “average pain over the last 24 hours” using an 11-point NRS, Brief Pain Inventory-Short Form (BPI-SF), the Clinical Opioid Withdrawal Scale (COWS), the modified Subjective Opioid Withdrawal Scale (SOWS), and Medical Outcomes Study (MOS) sleep scale.

The primary efficacy outcome was the “average pain over the last 24 hours” at Week 12. The secondary efficacy outcomes included Patient’s Global Impression of Chang (PGIC) and MOS Sleep Disturbance Subscale score at Week 12.

### **3.2.2 Statistical Methodologies**

The protocol stated that the causal estimand was the difference in the primary efficacy outcome between the placebo and OXN treatment groups at Week 12 for all randomized subjects regardless of study drug compliance. The primary efficacy population included all subjects who were randomized and received at least one dose of double-blind study drug. The study report further stated that the primary analysis only included pain scores collected while subjects were taking study drug. The primary analysis was based on a mixed-model repeated measures analysis

(MMRM) and an adaption of a hybrid single imputation approach for handling missing data due to dropouts. The MMRM model included the treatment and visit as fixed effects. The estimated means and variances from the MMRM model were then utilized to obtain the Week 12 estimate. The formula for calculating the estimate of the mean at Week 12 was as follows:

$$\beta_{12,trt} = \pi_{trt,complete} \hat{\mu}_{W12,trt} + \pi_{trt,AE} \hat{\mu}_{screen,trt} + \pi_{trt,OW} \hat{\mu}_{prerand,trt} + \pi_{trt,other} \frac{1}{2} (\hat{\mu}_{WK2,trt} + \hat{\mu}_{WK4,trt}),$$

where  $trt$  denotes placebo or OXN. The terms  $\pi_{trt,complete}$ ,  $\pi_{trt,AE}$ ,  $\pi_{trt,OW}$  and  $\pi_{trt,other}$  were defined as follows:

- $\pi_{trt,complete}$ : proportion of subjects who completed the study while taking study drug and were randomized to treatment  $trt$
- $\pi_{trt,AE}$ : proportion of subjects who discontinued study drug due to adverse events (AE) and had no evidence of opioid withdrawal in treatment  $trt$
- $\pi_{trt,OW}$ : proportion of subjects who discontinued study drug with evidence of opioid withdrawal in treatment  $trt$
- $\pi_{trt,other}$ : proportion of subjects who discontinued study drug due to reasons other than AE and had no evidence of opioid withdrawal in treatment  $trt$

The terms  $\hat{\mu}_{W12,trt}$ ,  $\hat{\mu}_{screen,trt}$ ,  $\hat{\mu}_{prerand,trt}$ ,  $\hat{\mu}_{WK2,trt}$  and  $\hat{\mu}_{WK4,trt}$  denote the estimates of the mean pain scores at Week 12, screening, pre-randomization, Week 2 and Week 4 for respective treatment, obtained from the MMRM analysis.

Thus, the mean of the primary efficacy outcome at Week 12 for each treatment arm was estimated as a weighted average of the mean pain score at Week 12, the mean at screening, the mean score before randomization, and the average of the means at Week 2 and Week 4. The weights were determined by the proportions of subjects within different disposition categories. The primary comparison was based on the above weighted average with corresponding variances calculated using a delta method.

I note that the proposed analysis approach is conceptually analogous to the hybrid imputation method historically accepted by the division: baseline scores carried forward for subjects who discontinued due to AE and last observations carried forward for subjects who dropped out for other reasons.

I also note that there was some ambiguity in the proposed estimand, which might lead to different interpretations and judgments of the primary analysis approach. Specifically, it is in my opinion that if the estimand was the treatment difference regardless of study drug compliance the pain scores collected after discontinuation of the study drug should be relevant and included in the primary analysis. However, the primary analysis approach did not include the pain scores collected off study drug. Thus, to the applicant, the estimand might only mean to include all randomized subjects rather than all data collected regardless of drug compliance. The proposed

approach seems to me was to estimate a utility based estimand: assigning high pain scores to discontinuations due to low utility of the drug.

The applicant performed the following analyses to investigate the robustness of the conclusion from the primary analysis:

1. NMAR – all observed data: this analysis used the same method as the primary efficacy analysis except that it included the pain data collected after a subject discontinued the study drug while remained in the study.
2. MAR – observed data on study drug: the analysis applied the standard MMRM approach to the data collected while a subject was taking the study drug.
3. NMAR – partial AE penalty: this analysis was the same as the primary analysis except that the average of the pre-randomization and screening means was used for the subjects who discontinued due to AE.
4. NMAR – differential handling of opioid withdrawal in the two treatment groups: subjects in the OXN arm who discontinued drug due to opioid withdrawal were assigned the screening mean pain score; in contrast, subjects in the placebo arm were assigned the pre-randomization mean score
5. NMAR – observed data on study drug, excluding potential repeat subjects: the primary analysis excluding the six subjects seemingly randomized twice.

Excepted for sensitivity analysis 2, all the other sensitivity analyses employed similar methods for handling dropouts as in the primary approach. Sensitivity analysis 4 was a more conservative method than the primary approach.

The analysis methods for the secondary efficacy variables were as follows. The Sleep Disturbance Subscale score was analyzed using a MMRM model. The PGIC score was analyzed using Fisher's exact test for very much improved/much improved versus all other categories. The Bonferroni-Holm procedure was applied for testing the two secondary endpoints.

Responder analyses were included as additional exploratory analyses. Subjects who discontinued the study drug prior to Week 12 were considered as non-responders. The proportion of subjects with a pain reduction from screening greater than 30% was compared between treatments using a Cochran-Mantel-Haenszel (CMH) test.

### **3.2.3 Patient Disposition, Demographic and Baseline Characteristics**

A total of 601 subjects were randomized to the double-blind phase of the study, 302 to placebo and 299 to OXN. One subject randomized to OXN did not receive the double-blind study drug. At the time of randomization, 31% of the subjects were on the 40/20 mg dose, 23% on the 30/15 mg dose, 26% on the 20/10 mg dose and 20% on the 10/5 mg dose respectively. Overall, approximately 34% of the subjects discontinued the study drug early (Table 1). The dropout rates of the placebo and OXN groups were 40% and 27% respectively. The most common reasons for early discontinuation were lack of efficacy and adverse events. About 24% of the subjects in the

placebo group and 10% of the subjects in the OXN group discontinued the study drug because of lack of efficacy. For both treatment groups, about 8% of the subjects discontinued because of adverse events. Four subjects from placebo and six subjects from OXN groups discontinued study drug with evidence of opioid withdrawal.

Subjects who discontinued the study drug were encouraged to stay in the study to complete the assessments through Week 12. Among the 121 subjects who discontinued the double-blind study treatment in the placebo group, there were 59 (49%) subjects who stayed in the study and 49 (40%) subjects who further completed the study. Among the 80 subjects who discontinued the study drug in the OXN group, there were 32 (40%) subjects who stayed in the study and 25 (31%) subjects who subsequently completed the study.

The demographic and baseline characteristics were similar between the two treatment groups (Table 2). The mean age was 53 years and 44% of the subjects were male. Overall, 77% and 19% of the subjects were white and black respectively. The average pain scores before randomization were 3 for both groups.

**Table 1: Subject Disposition – Number (%) of Patients**

	<b>Placebo</b>	<b>OXN</b>	<b>Total</b>
<b>Randomized</b>	<b>302</b>	<b>299</b>	<b>601</b>
<b>Randomized and treated (full analysis population)</b>	<b>302</b>	<b>298</b>	<b>600</b>
<b>Completed period on study drug</b>	181 (60%)	218 (73%)	399 (67%)
<b>Discontinued study drug during double-blind period</b>	121 (40%)	80 (27%)	201 (34%)
Adverse event	23 (8%)	24 (8%)	47 (8%)
Subject's choice	8 (3%)	10 (3%)	18 (3%)
Lost to follow-up	1	4 (1%)	5 (1%)
Lack of therapeutic effect	73 (24%)	31 (10%)	104 (17%)
Confirmed or suspected diversion	6 (2%)	5 (2%)	11 (2%)
Administrative	10 (3%)	6 (2%)	16 (3%)
<b>Discontinued study drug and study simultaneously</b>	62 (21%)	48 (16%)	110 (18%)
Adverse event	14 (5%)	15 (5%)	29 (5%)
Subject's choice	8 (3%)	8 (3%)	16 (3%)
Lost to follow-up	1	4 (1%)	5 (1%)
Lack of therapeutic effect	23 (8%)	10 (3%)	33 (6%)
Confirmed or suspected diversion	6 (2%)	5 (2%)	11 (2%)
Administrative	10 (3%)	6 (2%)	16 (3%)
<b>Discontinued study drug and stayed in study</b>	59 (20%)	32 (11%)	91 (15%)
Completed Week 12	49 (16%)	25 (8%)	74 (12%)
Discontinued study prior to Week 12	10 (3%)	7 (2%)	17 (3%)
Adverse event	0	7 (2%)	7 (1%)
Subject's choice	8 (3%)	0	8 (1%)
Lost to follow-up	2 (1%)	0	2

Source: Clinical Study Report, Table 14.1.1.4 and Table 14.1.1.5

**Table 2: Summary of Demographics and Baseline Characteristics**

	Placebo (N=302)	OXN (N=298)	All Subjects (N=600)
Mean age (SD)	53 ( 11)	54 ( 12)	53 (11)
Gender, n (%)			
Male	126 (42%)	136 (46%)	262 (44%)
Female	176 (58%)	162 (54%)	338 (56%)
Ethnicity, n (%)			
Hispanic or Latino	37 (25%)	40 (26%)	77 (25%)
Not Hispanic or Latino	113 (75%)	113 (74%)	226 (75%)
Race, n(%)			
White	233 (77%)	229 (77%)	462 (77%)
Black or African American	61 (20%)	53 (18%)	114 (19%)
Asia	3 (1%)	8 (3%)	11 (2%)
American Indian or Alaska Native	3 (1%)	1 (0.3%)	4 (1%)
Other	2 (1%)	7 (2%)	9 (2%)
Body Mass Index (kg/m <sup>2</sup> )			
Mean (SD)	31 (7)	31 (8)	31 (8)
Screening pain intensity			
Mean (SD)	7 (1)	7 (1)	7(1)
(Min, Max)	(4, 10)	(5, 10)	(4, 10)
Pre-randomization pain intensity			
Mean (SD)	3 (1)	3 (1)	3 (1)
(Min, Max)	(0, 6)	(0, 5)	(0, 6)

Source: Clinical Study Report, Table 14.1.2.2; SD: standard deviation

### 3.2.4 Results and Conclusions

I replicated the applicant's results from the primary efficacy analysis (Table 3). The difference between OXN and placebo in pain at Week 12 was statistically significant. The results from different sensitivities analyses (Table 4) were similar to those from the primary efficacy analysis.

**Table 3: Primary Efficacy Analysis Results**

Visit	Statistics	Placebo (N=302)	OXN (N=298)	95% CI	P-value
Screening	Mean (SE)	7.1 (0.06)	7.0 (0.06)		
Pre-randomization	Mean (SE)	3.1 (0.06)	3.1 (0.06)		
Week 12	Mean (SE)	4.2 (0.1)	3.7 (0.1)		
Overall Week 12 Difference	Difference	0.5 (0.2)		(0.1,0.8)	0.006

Source: Clinical Study Report, Table 14.2.1; SE: standard error; CI: confidence interval

**Table 4: Sensitivity Analysis Results**

Type of Analysis	Difference from Placebo (SE)	95% CI	P-value
<b>Analyses reported by the applicant</b>			
1. NMAR - all observed data	0.46 (0.16)	(0.14, 0.77)	0.004
2. MAR – observed data on study drug	0.50 (0.18)	(0.14, 0.86)	0.006
3. NMAR – partial AE penalty	0.45 (0.16)	(0.14, 0.77)	0.005
4. NMAR – differential handling of opioid withdrawal in the two treatment groups	0.37 (0.17)	(0.05, 0.7)	0.02
5. NMAR – observed data on study drug, excluding potential repeat subjects	0.44 (0.16)	(0.12, 0.76)	0.008
<b>Additional analysis by reviewer</b>			
MAR: all observed data	0.50 (0.17)	(0.17, 0.84)	0.003

Source: Clinical Study Report, Table 14.2.1; SE: standard error; CI: confidence interval

I conducted one additional sensitivity analysis using all observed data including those collected after discontinuation of the study drug (Table 4), which I think is consistent with the intention-to-treat principle or the applicant's pre-specified estimand. In the MMRM model, I included an indicator for subjects who completed the study on study drug assuming they were different from those discontinued. The results from this sensitivity analysis were close to those from the primary approach. The results from an analysis without the indicator in the model were also similar.

Overall, the similarities among the estimated treatment differences and the standard errors from these sensitivity analyses increased my confidence that there was statistically significant difference between groups due to treatments.

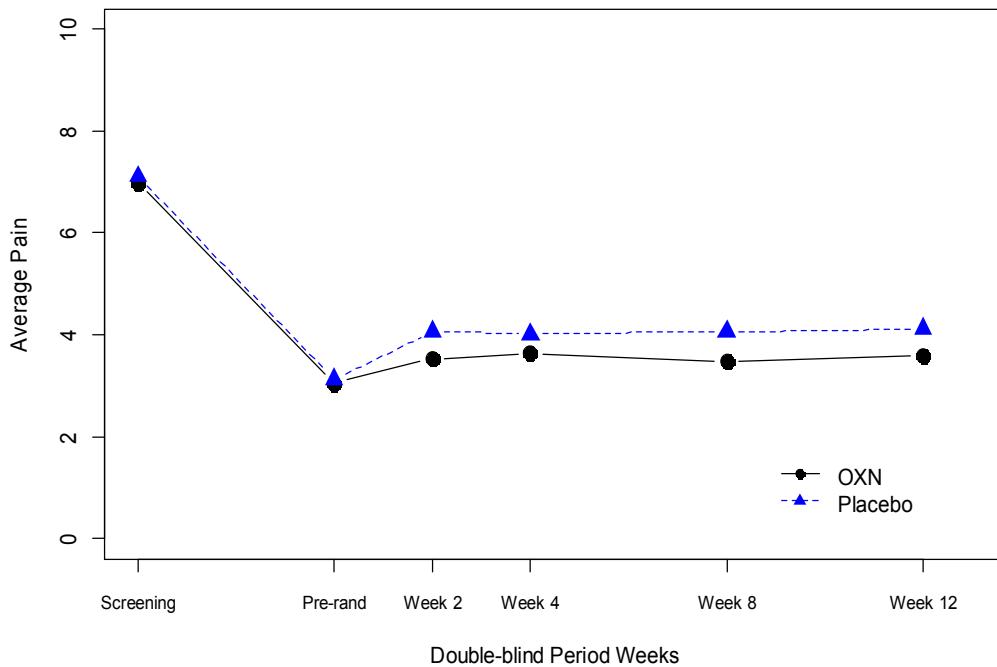
To compare the pain reduction effect over time, the average pain intensity over time of each treatment group while on study drug was depicted through Week 12 (Figure 1). It appears that the drug effect was roughly maintained from Week 2 to Week 12. Including data collected off study drug produced very similar curves.

The OXN group also had a better continuous responder curve than the placebo group (Figure 2). For example, about 55% of the subjects in the OXN group had at least 30% improvement from screening. In contrast, approximately 41% of placebo group had at least 30% improvement from screening. Subjects who discontinued study drug were considered as non-responders in the calculations. There was no notable difference between the two treatment groups in the percentages of subjects who achieved more than 80% improvement.

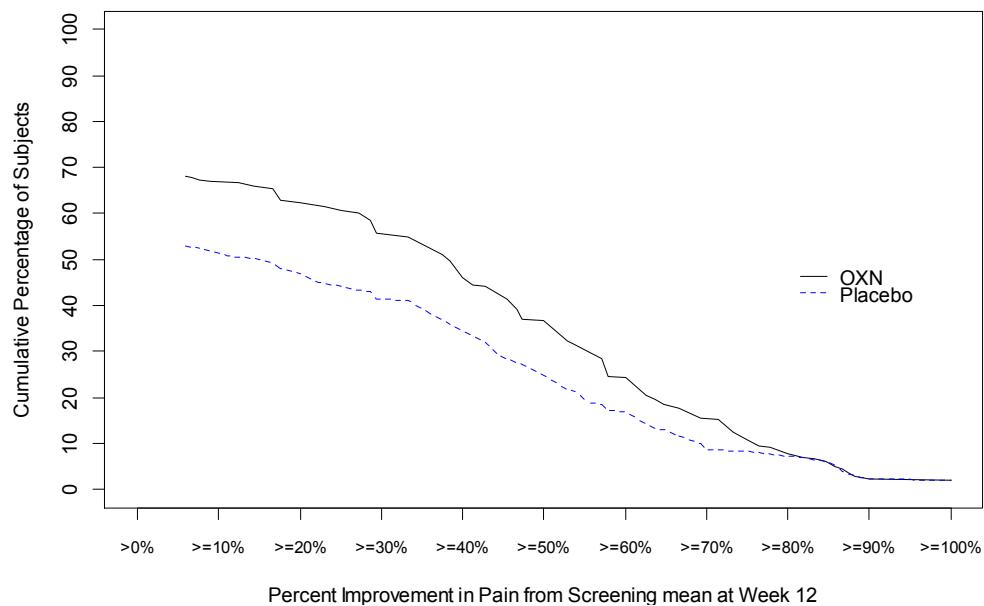
The observed mean pains of the four doses of OXN were all numerically better than those of the matching placebos at Week 12. The treatment effects of the two higher doses (30/15 mg, 40/20 mg) seemed better than those of the two low doses (Appendix, Figure 3). It should be noted that the study was not powered to show efficacy of each dose level.

The study also demonstrated superiority of OXN compared with placebo with respect to the two pre-specified secondary efficacy endpoints, PGIC and Sleep Disturbance Subscale (Appendix, Tables 7 and 8). The conclusion didn't appear sensitive to the methods for handling dropouts. These secondary endpoints supported the primary results.

**Figure 1: Average Pain Intensity on Study Drug Over Time**



**Figure 2: Continuous Responder Curve**



### **3.3 Evaluation of Safety**

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

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

The applicant investigated the subgroup effects on the primary endpoint for age, gender, and race by adding an indicator for a subgroup in the MMRM model and presented the results in the Integrated Summary of Efficacy. None of the subgroups investigated were found to be significant factors affecting the primary efficacy endpoint. I conducted subgroup summaries by age, gender, and race. Findings from the subgroup summaries of the primary efficacy endpoints were generally consistent with those observed in the overall population.

### **4.1 Gender, Age and Race**

My subgroup summaries included only data collected while subjects were on study drug (Table 5). For age, subjects were classified as < 65 or ≥65 years old. For race, subjects were classified as White or non-White. The findings from the subgroups summaries of the pain scores at Week 12 were consistent with those observed in the overall population. Subjects treated with OXN reported numerically better pain than subjects treated with placebo in all the subpopulations. Similar findings were obtained from summaries with data collected after discontinuation of study drug included.

I note that the percentage of subjects who achieved 30% or 50% improvement from baseline was higher in the non-White subjects treated with placebo than that of non-White treated with OXN. I was not overly concerned about it as the difference was not significant and likely due to differences in baseline pain and dropout rates.

**Table 5: Reviewer's Subgroup Summaries I**

<b>Subgroups</b>	<b>Statistics</b>	<b>Placebo (N=302)</b>	<b>OXN (N=298)</b>
Sex			
Female	n (%)	176 (58%)	162 (54%)
	Mean (SD)	4.2 (2.1)	3.7 (1.8)
Male	n (%)	126 (42%)	136 (46%)
	Mean (SD)	4.0 (2.0)	3.5 (1.6)
Race			
White	n (%)	233 (77%)	229 (77%)
	Mean (SD)	4.3 (2.1)	3.6 (1.7)
Non-white	n (%)	69 (23%)	69 (23%)
	Mean (SD)	3.6 (1.9)	3.5 (1.7)
Age			
<65	n (%)	258 (85%)	249 (84%)
	Mean (SD)	4.2 (2.1)	3.6 (1.7)
≥65	n (%)	44 (15%)	49 (16%)
	Mean (SD)	3.7 (1.6)	3.5 (1.8)

SD: Standard deviation

## 4.2 Other Special/Subgroup Populations

The applicant conducted a subgroup analysis for subjects using allowed antidepressants and antiepileptics. There were 33 subjects receiving placebo and 34 subjects receiving OXN who used antidepressants and antiepileptics at baseline. The use of antidepressants and antiepileptics did not appear to affect the efficacy conclusion. I summarized the primary efficacy endpoint for each treatment group based on whether antidepressants and antiepileptics were used at baseline (Table 6). OXN was better than placebo regardless of the usage of antidepressants and antiepileptics.

**Table 6: Reviewer's Subgroup Summaries II**

<b>Subgroups</b>	<b>Statistics</b>	<b>Placebo (N=302)</b>	<b>OXN (N=298)</b>
Antidepressant and Antiepileptic drugs ?			
Yes	n (%)	33 (11%)	34 (11%)
	Mean (SD)	5.2 (2.0)	3.9 (1.6)
No	n (%)	269 (89%)	264 (89%)
	Mean (SD)	4.0 (2.0)	3.5 (1.7)

SD: Standard deviation

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues

No major statistical issues were identified for Study ONU3701. There were some minor issues that did not affect the statistical conclusions from the study.

At first, it appears that six randomized subjects might actually represented three unique subjects, based on birth dates and other factors in the database. Sensitivity analyses excluding the six subject numbers were conducted and produced similar results to the primary analysis.

Second, the dose entries at the end of the open-label titration period were found to have been incorrectly entered by 57 subjects in the electronic diaries, which subsequently led to the mismatch between the randomized dose level and the actual dose level administered. I am not concerned about this issue as it did not affect the overall comparison between OXN and placebo.

Third, it seems to me that there was some ambiguity in the proposed estimand, which might lead to different interpretations and judgments of the primary analysis approach. The proposed estimand was the treatment difference at Week 12 of all randomized subjects regardless of study drug compliance. It did not mention explicitly how the pain scores collected after subjects discontinued the study drug should be handled. It is in my opinion that the pain scores collected after the discontinuation of the study drug should be included in the primary analysis. In contrast,

the applicant seemed to believe that the estimand only entails including all randomized subjects and excluding pain scores collected off study drug from in the primary analysis. The proposed primary analysis approach is conceptually analogous to the hybrid imputation method historically accepted by the division: baseline scores carried forward for subjects who discontinued due to AE and last observations carried forward for subjects who dropped out for other reasons. It appeared more like to estimate a utility based estimand: assigning high pain scores to discontinuations due to low utility of the drug. As sensitivity analyses including all collected pain scores yielded similar results, my concern on the ambiguity of the estimand was alleviated.

## 5.2 Collective Evidence

The collective evidence from Study ONU3701 was in support of the efficacy of OXN in comparison to placebo. There was statistically significant difference in pain response at Week 12 between the 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 OXN.

## 5.3 Conclusions and Recommendations

In my opinion, Study ONU3701 demonstrated that OXN was better than placebo in management of chronic pain. The review team will need to consider the totality of evidence including findings from safety analyses and abuse studies to decide whether the benefit-risk profile justify the approval of this combination product.

## 5.4 Labeling Recommendations

The applicant submitted the following wording to add to the clinical study section of the label for review:

### 14 CLINICAL STUDIES

*The efficacy of TARGINIQ was evaluated in one 12-week, randomized, double-blind, placebo-controlled clinical trial in opioid-experienced patients with uncontrolled moderate to severe chronic low back pain [redacted] (b)(4).*

#### 12-Week Study in Opioid-Experienced Patients with Uncontrolled Chronic Low Back Pain

*A total of 1095 patients (mean age = 52 years [range 20-88]; 45% male and 55% female) with uncontrolled moderate to severe chronic low back pain entered an open-label, dose-titration period for up to four weeks. Patients initiated TARGINIQ therapy at an oxycodone dose approximately equivalent to their current therapy [redacted] (b)(4) [see Dosage and Administration (2.1)]. The dose of TARGINIQ could be uptitrated to a maximum of 40/20 mg twice daily by the investigator every 1-2 days as needed based on efficacy, safety, and tolerability considerations or down-titrated at any time for safety and/or tolerability reasons. During open-label titration, subjects were allowed supplemental pain medication (immediate-release oxycodone HCl 5 mg capsules) for low back pain every 4 hours as needed up to 8 capsules per day.*

*Fifty-five percent (55%) of patients who entered the open-label titration period achieved adequate analgesia and tolerability on TARGINIQ and were then randomized to their final titrated dose of TARGINIQ or matching placebo for 12 weeks of double-blind treatment. Nine percent (9%) of patients discontinued from the open-label titration period due to an adverse event; 10% discontinued due to lack of a therapeutic effect, and 11% discontinued for other reasons. Sixteen (16%) percent did not qualify for randomization. During double-blind treatment, subjects were allowed one capsule of supplemental pain medication (immediate-release oxycodone HCl 5 mg capsules) for low back pain as needed, up to 2 capsules per day.*

*Of the 298 patients randomized to TARGINIQ, 73% of the patients completed the 12-week double-blind treatment on study drug. Of the 302 patients randomized to placebo, 60% of the patients completed the study. Fewer patients randomized to TARGINIQ discontinued due to lack of efficacy compared to placebo, 10% versus 24%.*

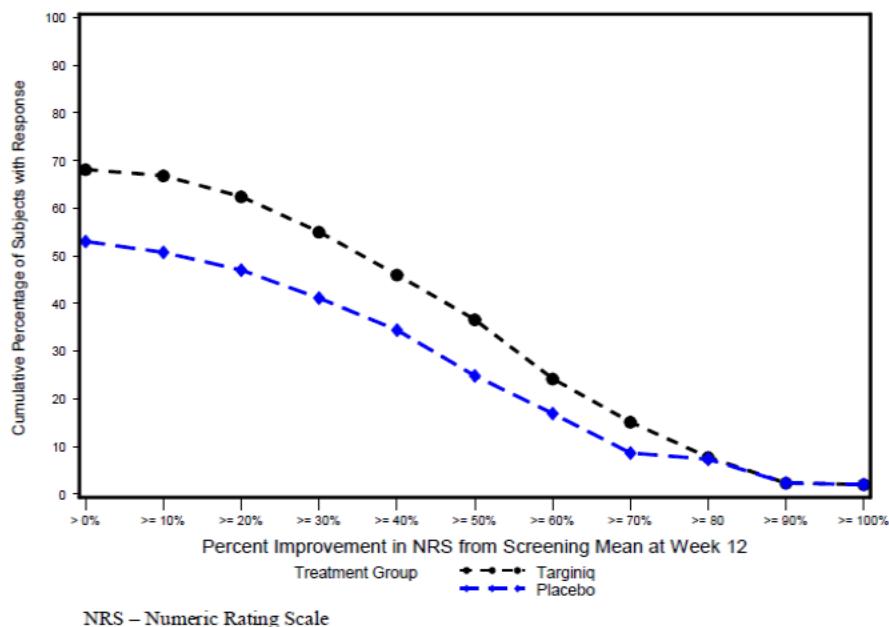
*Discontinuation due to adverse events was the same for both TARGINIQ (8%) and placebo (8%).*

*Of the patients who were randomized, pain scores were similar at screening and end of the open-label titration for TARGINIQ and placebo subjects. The mean “average pain over the last 24 hours” (SE) scores were [REDACTED] (b)(4) and [REDACTED] (b)(4) at screening and [REDACTED] (b)(4) and [REDACTED] (b)(4) at pre-randomization (beginning of double-blind phase) for the TARGINIQ and placebo groups, respectively.*

*The mean score of “average pain over the last 24 hours” at the end of the study (Week 12/Early Termination) was statistically significantly lower [REDACTED] (b)(4) in patients treated with TARGINIQ (SE), [REDACTED] (b)(4) compared to patients treated with placebo (SE), [REDACTED] (b)(4).*

(b) (4)



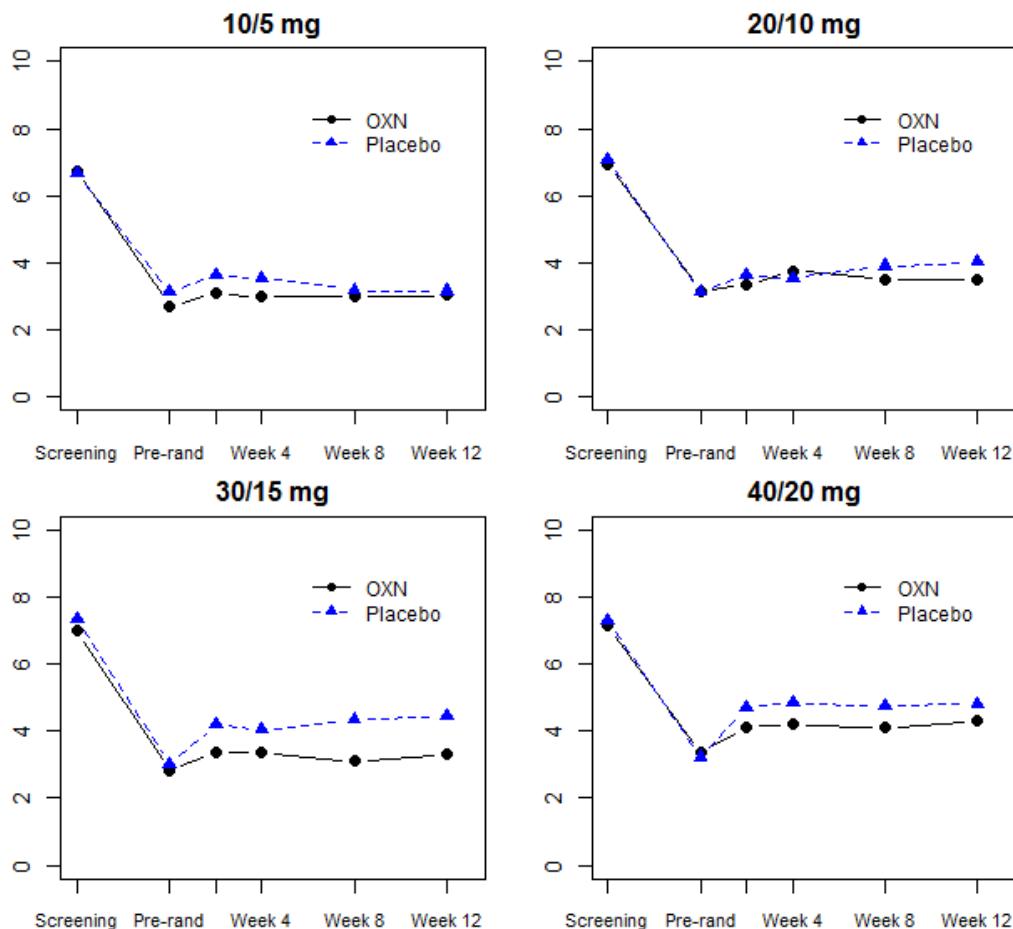


**Figure 4. Plot of Distribution of Responders Based on Pain Intensity at Week 12**

I suggest the applicant round the numbers to one decimal place. For example, round (b) (4) to be 7.0. Furthermore, the p-values, the words (b) (4) should be removed from the current sixth and seventh paragraphs. In addition, I suggest the applicant remove the (b) (4) as the plot has conveyed the relevant information.

## APPENDIX

**Figure 3: Average Pain intensity on Study Drug by Dose**



**Table 7: Summary and Analysis of MOS-Sleep Disturbance Subscale**

Visit	Statistics	Placebo (N=302)	OXN (N=298)	95% CI	P-value
Screening	Mean (SE)	52 (1)	49 (1)		
Pre-randomization	Mean (SE)	31 (1)	29 (1)		
Week 12	Mean (SE)	36 (2)	31 (2)		
Overall Week 12 Difference	Difference	5 (2)		(1,10)	0.02

Source: Clinical Study Report, Table 14.2.3.1; SE: standard error; CI: confidence interval

**Table 8: Summary of Patient Global Impression of Change**

<b>Variable</b>	<b>Placebo (N=302)</b>	<b>OXN (N=298)</b>	<b>P-value</b>
Proportion of Subjects Responding			
“Very Much Improved” or “Much Improved”			
Yes	109 (40%)	153 (56%)	0.0002
No	164 (60%)	122 (44%)	
Missing	29	23	

Source: Clinical Study Report, Table 14.2.4.1; SE: standard error; CI: confidence interval

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06/16/2014



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 #:** 205777

**Drug Name:** Targiniq (oxycodone hydrochloride and naloxone hydrochloride) extended release tablets

**Indication(s):** Management of [REDACTED] <sup>(b) (4)</sup> pain [REDACTED] <sup>(b) (4)</sup>, around-the-clock [REDACTED] <sup>(b) (4)</sup>, [REDACTED] <sup>(b) (4)</sup>, [REDACTED] <sup>(b) (4)</sup>, [REDACTED] <sup>(b) (4)</sup>

**Applicant:** Purdue Pharma, L.P.

**Date(s):** September 23, 2013 (submission date); November 20, 2013 (consult date); July 23, 2014 (PDUFA goal date)

**Review Priority:** Standard

**Biometrics Division:** Division of Biometrics VII

**Statistical Reviewer:** Janelle K. Charles, PhD

**Concurring Reviewers:** Mat Soukup, PhD  
Statistics Team Leader, DBVII  
Aloka Chakravarty, PhD  
Director, DBVII

**Medical Division:** Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

**Clinical Team:** Liz Kilgore, MD  
Medical Officer, DAAAP  
Ellen Fields, MD  
Medical Team Leader, DAAAP

**Project Manager:** Lisa Basham  
Senior Regulatory Health Project Manager, DAAAP

**Keywords:** cardiovascular safety, rare events, pooled analyses, observational study

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## 1 EXECUTIVE SUMMARY

This is a statistical safety review by the Division of Biometrics VII (DBVII), in response to a consult request from the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), of a report containing cardiovascular (CV) assessments for oxycodone/naloxone tablets that were conducted by drug manufacturer Purdue Pharma, L.P (PPLP). The New Drug Application (NDA 205777) for oxycodone/naloxone was submitted to the FDA on September 23, 2013.

Oxycodone/naloxone, hereafter referred to as OXN, is a fixed-dose combination of oxycodone (OXY) hydrochloride and naloxone hydrochloride. The proposed indication for OXN is for

(b)(4) chronic pain; the naloxone component is included as a deterrent to abuse of oxycodone. OXN has been approved for this indication in several European countries. Due to concerns about potential CV signals with products similar to OXN (for example, as observed with Entereg<sup>1</sup>), DAAAP requested that PPLP include analyses of CV events and their possible association with opioid withdrawal in the NDA. To this end, PPLP conducted analyses of CV events using data from their clinical trial database. Note that these events were collected as part of routine safety monitoring in the clinical trials and are not from trials prospectively designed to assess CV safety. The report, which is the subject of this statistical review, includes results from PPLP's analyses of the clinical trial database and results from assessments from other data sources, such as European postmarketing databases. The consult from DAAAP requested that DBVII review and comment on the statistical analysis methods that were used in the assessments, and discuss the statistical evidence in support of PPLP's conclusions. In accordance with the consult request from DAAAP, this review does not address findings from assessments contained in the study report that are not based on comparative statistical analyses, that is, findings from literature reviews and postmarketing surveillance. Therefore, this statistical review is based on pooled analyses and results from the clinical trial database and an epidemiologic study of the United Kingdom (UK) The Health Improvement Network (THIN) database.

### 1.1 Summary of Findings from the Clinical Trial Database

The clinical trial database comprised 29 phase 1 through 4 trials in the OXN development program. PPLP presented analyses based on all 29 trials as well as analyses using different subsets, or 'groupings' as denoted in the study report, of these trials. There are several issues identified with the designs or populations studied that limit the ability to perform adequate comparative CV safety assessments based on data from all the trials included in the clinical trial database; refer to Section 3.1.1 for detailed discussion of these issues. In brief, the majority of the trials included in the database lacked a parallel control arm, had small sample sizes (<40 subjects), was limited in follow-up data (<30 days of study duration), or were studied in healthy subject populations at low risk for CV adverse effects. Of the 29 clinical trials in the database, 6 randomized, double-blind controlled phase 2 and 3 trials in subjects with chronic pain were available for comparative statistical analyses of CV events. Only data from these 6 trials are presented in this review. The durations for these trials were up to 12-weeks (4 of which had uncontrolled extension phases of up to 52-weeks, during which subjects were treated with OXN only). There was no specified endpoint to evaluate CV risk; rather, assessment of CV safety was

<sup>1</sup> Refer to pre-NDA meeting minutes dated October 12, 2012

based on algorithm-defined endpoints which were not adjudicated. For analysis results, data are presented for an SMQ-based MACE and FDA custom MACE (cMACE) derived from MedDRA SMQs for MI, central nervous system, and CV death; see Section 3.1.2.1 for specific preferred terms included in these outcomes. Section 3.1.2.2 describes the opioid withdrawal symptoms defined by PPLP. The main groups compared are OXN and comparator (pooled placebo and OXY controls); results of subgroup analyses by comparator type are also presented. The analyses were based on all randomized subjects; subjects were analyzed according to the actual treatment received, regardless of assigned treatment.

Across the six trials, a total of 936 patients were treated with OXN of which 2 patients (0.2%) experienced SMQ-based MACE, whereas a total of 1106 were treated with a comparator product of which 7 patients (0.6%) experienced a SMQ-based MACE event. The estimated rate ratio for SMQ-based MACE was 0.3 with 95% CI (0.0, 1.7); consistent results were obtained for FDA cMACE. There were no events (SMQ-based or FDA cMACE) in OXN subjects from placebo-controlled trials; see Table 1.

**Table 1 Summary of Findings from Pooled Analyses of Phase 2 and 3 Clinical Trials  
 (Double-Blind Treatment Period)**

	OXN n (%)	Comparator n (%)	RR <sup>1</sup> (95% CI)
<u>All Trials</u>	N=936	N=1106	
SMQ-based MACE	2 (0.2)	7 (0.6)	0.3 (0.0, 1.7)
FDA cMACE	1 (0.1)	5 (0.4)	0.2 (0.0, 2.1)
<u>Placebo-Controlled Trials</u>	N=451	N=460	
SMQ-based MACE	0 (0.0)	2 (0.4)	--
FDA cMACE	0 (0.0)	2 (0.4)	--
<u>OXY-Controlled Trials</u>	N=638	N=646	
SMQ-based MACE	2 (0.3)	5 (0.8)	0.4 (0.1, 2.1)
FDA cMACE	1 (0.2)	3 (0.5)	0.3 (0.0, 3.2)

n=number of subjects with event, N=number of subjects treated, RR=rate ratio

<sup>1</sup> A null value of 1 is indicative of no difference

Source: Created by the reviewer using dataset “adaette.xpt” and study report Table 17 (page 72)

According to the study report, there were 12 additional OXN subjects who experienced SMQ-based MACE during the uncontrolled extension phases of the clinical trials. Of these 12 subjects, 7 were treated with OXN and 5 treated with a comparator during the double-blind treatment period. Nine of the 12 subjects were classified as having FDA cMACE during the extension

phase: 7 who were treated with OXN and 2 treated with a comparator during the double-blind treatment period.

Given the short trial duration and subject population that may not have been sufficiently enriched to assess CV, the ability to determine if a CV signal is present or absent is limited. In particular, a conclusion that there is no increased risk of CV events with OXN use cannot be made from this data source. It is important to note that the potential CV signal with Entereg, which prompted the CV assessments for OXN, was driven by data from a 12-month trial (52 weeks) in which 7 Entereg subjects compared to 0 placebo subjects experienced a CV event. While the results from the OXN clinical trials trend in the opposite direction, namely 2 events in placebo compared to 0 OXN in the placebo-controlled trials, these trials may not have had sufficient follow-up (most trials were 12-weeks in duration) or baseline CV risk to characterize the CV risk of OXN. Finally, with this few events observed, any association, or lack thereof, between opioid withdrawal and CV incidence cannot be demonstrated with this data source.

## 1.2 Summary of Findings from the UK THIN Database

The other data source evaluated in this statistical review was PPLP's epidemiologic study. This was a retrospective observational study of subjects, at least 18 years, who received at least 1 prescription for OXN, OXY or morphine extended release (MOR ER) from January 1, 2005 through August 1, 2012 retrieved from the UK THIN database. The THIN database is an anonymized patient record primary care database containing medical records for over 7 million patients in the UK. The database includes demographic information, medical diagnosis and free-text comments entered by the primary care physician, referral letters from consultants and hospital admissions and biochemical test results. Medical diagnoses were coded using READ codes (National Health Service Terminology Service 2007) and prescriptions were coded using British National Formulary codes. According to the study report, the quality of the data on diagnosis, medical event and prescription contained in THIN are comparable to the Clinical Practice Research Database (formally GPRD) and are generalizable to the UK primary care as a whole. There was no supporting information provided in the report to verify these assertions. The outcomes analyzed in this database were MACE comprising stroke, MI, or CV death, and all ischemic CV events composed of MACE, transient ischemic attack, angina, or coronary artery bypass graft. PPLP stated that there were no appropriate READ codes for opioid withdrawal, so this data source was not suitable for investigating association between opioid withdrawal and CV occurrence. Incidence rates for each outcome were provided for the treatment groups as well as pairwise comparative assessments (OXN to OXY, OXN to MOR ER and OXY to MOR ER). Note that a protocol or statistical analysis plan were not submitted for this study, and sufficient details were not provided in the study report to allow thorough assessments of the statistical analyses conducted. For this reason and issues identified with the design of this study, only estimates of the incidence of events for each treatment group are presented in this review.

There were a total of 49,226 subjects in the epidemiologic study: 2600 exposed to OXN; 35,636 exposed to MOR ER; and 10,990 exposed to OXY. The incidence of MACE was low and similar across the three treatment groups: 14 (0.5%) in the OXN subjects, 280 (0.8%) in the MOR ER subjects and 98 (0.9%) in the OXY CR subjects. The incidence of all ischemic events was also

low: 38 (1.5%) in OXN subjects, 715 (2.0%) in OXY CR subjects and 285 (2.6%) in OXY subjects. Several discrepancies were noted in the number of subjects included in the incidence rate calculations conducted by the PPLP compared to the number of subjects that were reported in each treatment arm; see Section 3.2.4. No explanations for these discrepancies were provided in the study report. Note that data for this study were not included in the submission, so further investigations of these discrepancies or independent analyses by DBVII could not be conducted.

The overall incidence of CV events in OXN subjects from this data source was small (<1%) for each of the outcomes assessed. Here again, it should not be inferred that this low event rate is indicative of a lack of CV safety concern. There are many well-known issues with observational studies, in particular, with retrospective studies of administrative databases not designed for clinical research that should be considered when interpreting the findings from this study. These issues include outcome misclassification, low predictive ability of diagnostic codes, and residual confounding. Sufficient details were not provided in the report to conclude that these issues were appropriately addressed in this study. Another important issue with this study is the small percentage of subjects exposed to OXN; only 5% of the study cohort had been exposed to OXN. Note that the study began in January 1, 2005, which is approximately 4 years prior to the 2008 approval of OXN in the UK<sup>2</sup>. Thus, for over 50% of the study time, no post-market data would have been available for OXN in the UK THIN database. This is a clear design flaw of this study; as such, the reliability of this data source for assessing CV safety of OXN is questionable.

### 1.3 Overall Conclusions and Recommendations

Overall, the Applicant concludes that “consistent findings across all methods of evaluation support the conclusion that there is no apparent increased CV risk with OXN treatment”. Given the concerns summarized in this section and described in detail throughout this review, a definitive conclusion that there is no CV safety concern with OXN use cannot be made from the data sources evaluated in this statistical review. Therefore, should OXN be approved, the recommendation is that further assessment of CV safety be conducted through a postmarketing controlled study, if there is a need to further characterize the CV risk of OXN. Some important characteristics to be considered for such a study are specific CV outcome definition, requirement for prospective blinded independent adjudication, and sufficient follow-up time to observe CV outcome in a population at risk for CV related events. Additionally, if OXN is approved, the recommendation is that findings from these CV assessments not be included in the product label.

## 2 INTRODUCTION

### 2.1 Background and Regulatory History

Oxycodone/naloxone, also referred to as OXN, is a fixed-dose combination of oxycodone (OXY) hydrochloride and naloxone hydrochloride. Oxycodone is an opioid analgesic used for the treatment of pain and naloxone is an opioid receptor antagonist. The New Drug Application,

<sup>2</sup> Mundipharma(2009-01-26). "[Targin \(oral oxycodone/naloxone prolonged-release tablet\) now launching across Europe to control severe chronic pain with significantly reduced risk of opioid-induced constipation](#)".

NDA 205777, for OXN was submitted to the FDA on September 23, 2013 by Purdue Pharma, L.P. (PPLP); PDUFA goal date: July 23, 2014. The proposed indication is for the management of [REDACTED] (b) (4) pain [REDACTED] (b) (4) around-the-clock [REDACTED] (b) (4)

[REDACTED] . OXN is being developed in three oxycodone/naloxone strengths (10/5 mg, 20/10 mg, and 40/20 mg) intended for twice daily dosing approximately every 12 hours. OXN was initially developed by Mundipharma Research Limited, an associated company of PPLP, and first approved in 2006 in Germany and in 2008 in 13 other European countries including United Kingdom (UK) for moderate to severe pain management.

During the pre-NDA meeting for OXN, the FDA<sup>3</sup> noted the following:

- A potential cardiovascular (CV) safety signal had been identified during the clinical development trials for Entereg (alvimopan) another peripheral mu-opioid antagonist.
- Pre-marketing randomized controlled trials were required to be conducted for similar products that are designed and powered to assess the risk of adverse CV events.

PPLP informed the FDA that no safety signal had been detected for OXN based on data from clinical trials and post-marketing use in Europe. To address the Agency's concerns, PPLP conducted analyses of the occurrence of CV events from various sources including analyses of the clinical trials database and an epidemiologic study of a United Kingdom (UK) database. The study report of these assessments is included in the NDA submission. The objectives of the assessments were to characterize the CV safety with OXN and to assess, if any, the relationship with opioid withdrawal and occurrence of CV outcomes. The study report includes 4 main sections that describe the various CV assessments and respective results, namely:

- Literature characterizing the effects of opioids and opioid antagonists in the CV system; Section 3 of the report
- CV events in the OXN clinical development program; Section 4 of the report.
- CV safety analyses of OXN and OXY controlled release (CR) from postmarketing surveillance data; Section 5 of the report
- Epidemiologic study to evaluate CV safety of OXN: United Kingdom The Health Improvement Network (THIN) database; Section 6 of the report

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Division of Biometrics VII (DBVII) on November 20, 2013 to review and comment on the statistical methods used in the report and to determine whether the statistical evidence supports PPLP's conclusions. This is the statistical safety review in response to the DAAAP consult.

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<sup>3</sup> Refer to pre-NDA meeting minutes dated October 12, 2012

**Reviewer's Comment:** *The literature review provides clinical characterization of the CV effects of opioids and naloxone and does not contain any statistical assessments. The postmarketing surveillance study provides descriptive statistics, which are based on reported CV events and not the number of subjects exposed. The concern with this type of study is the inadequacy of the denominator for comparative safety analyses. Therefore, information from the literature review and the postmarketing surveillance study are omitted from this statistical review, and this review focuses on the analyses and findings from the clinical trial database and the epidemiologic study.*

## 2.2 Data Sources

The study report was submitted electronically as part of the NDA, which included integrated analysis datasets comprising the clinical trials database for the CV assessment. All analysis datasets were provided in CDISC Analysis Dataset Model format. Data definition files containing the variable names and derivation rules for the respective datasets were also included in the application. In addition, a Reviewer's Guide that contains further details and content for specific data domains was also included.

**Reviewer's Comment:** *Data from the epidemiologic study of the UK THIN database were not included in the application. Therefore, the review of this study is based solely on the information included in the study report.*

The study report and analysis datasets pertinent to this review can be found at

EDR location: <\\cdsesub1\evsprod\nda205777\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\mgmt-mod-to-sev-pain\5353-rep-analys-data-more-one-stud\evaluation-cv-events>

In addition to the integrated CV study report, the following submitted documents were referenced for this review:

- Integrated CV Statistical Analysis Plan (SAP) dated August 1, 2013
- Plan for Adjudication of Subjects with Potential Opioid Withdrawal dated February 1, 2013
- Clinical study reports of trials included in the CV clinical database

The following integrated datasets were used to perform statistical analyses in this review:

- “adsl.xpt” which contains the subject baseline characteristics and disposition
- “adaette.xpt” which contains the CV events.

### 3 STATISTICAL SAFETY EVALUATION

This is a statistical review of the CV assessments for OXN tablets that were conducted by the Applicant, PPLP. As noted previously, this review focuses on the assessments conducted in the integrated CV clinical trial database (Section 3.1) and in the epidemiologic study using the UK THIN database (Section 3.2). Refer to separate statistical review by Dr. Feng Li for efficacy and overall safety assessments for OXN.

#### 3.1 Integrated CV Clinical Trial Database

According to the study report, the objectives of the CV assessments from the integrated clinical trial database were as follows:

- To characterize the CV safety profile of OXN based on studies of the OXN clinical development program during open-label titration, double-blind, and extension periods as appropriate
- To evaluate the effects of demographics and baseline CV risk factors on the safety profile of OXN compared to OXY and placebo
- To evaluate the relationship of opioid withdrawal symptoms to the CV safety profile of OXN

##### 3.1.1 Description of the CV Clinical Trial Database

The integrated clinical trial database comprised 29 trials:

- 6 placebo or OXY CR controlled, double-blind, multiple-dose, phase 2 and 3 trials in subjects with nonmalignant and malignant chronic pain. Four of these trials had open-label OXN only extension phases.
- 15 controlled and uncontrolled single- and multiple-dose phase 1 pharmacokinetic trials in healthy patients
- 4 single-dose crossover and pharmacodynamics/pharmacokinetic (PK/PD) studies in subjects that are either recreational users or opioid dependent users to assess abuse deterrence of OXN
- 3 single-dose and multiple-dose pharmacokinetic studies in subjects from special populations: one trial in subjects with hepatic impairment, one trial in subjects with renal impairment, and one trial in younger or elderly healthy subjects.

- 1 codeine/paracetamol controlled phase 4 study in subjects with chronic non-malignant pain.

All trials were complete at the time of the NDA submission. A summary of the trial designs for trials included in the CV clinical database is provided in Appendix I. The Applicant's assessments of CV outcomes included in the study report were based on four different trial groupings of the 29 trials included in the CV database as illustrated in Table 2.

There are several issues with the designs or populations studied that limit the ability to perform adequate comparative CV safety assessments based on all the trials included in the clinical trial database, denoted by Group C in Table 2. Of the 29 trials included in the CV database, 22 trials are considered inappropriate because they were phase 1 trials of insufficient follow-up (less than 40 days randomized treatment period), had small sample size (most trials randomized less than 30 subjects), or were conducted in healthy subjects who are thus at low CV risk and did not have chronic pain (the proposed indication for OXN). Another issue is that most of these trials were single-dose crossover designs in which patients were administered OXN along with other treatments in a randomized sequence; as such, there was no unique parallel control arm for meaningful safety comparisons. Inappropriately including these single-dose crossover design trials increases the denominator, therefore underestimating the CV incidence. Also, since subjects receive doses on multiple treatments in sequence, it is difficult to attribute any event that occurred to a particular treatment. Given these issues we do not recommend any statistical inference be made from Group C.

There were 7 trials that were designed as randomized, double-blind, placebo- or active-controlled trials in patients with chronic pain. Of these trials, one trial (OXN4502) was a phase 4 trial from which only data from the OXN patients were incorporated in the report. The specific reason for excluding the comparator arm (codeine/paracetamol) was not provided in the report. It is possible that this arm was excluded because the stated objective of the clinical trial assessments was to compare CV safety of OXN to OXY or placebo. However, we do not believe that including one arm of a trial in the assessments follows proper statistical principles as randomization is not preserved.

Therefore, out of the 29 trials included in the CV database, there are only six trials (5 phase 3: ONU 3701, OXN3001, OXN 3006, OXN3401, and OXN3503; 1 phase 2: OXN2001) in subjects with chronic pain, which may provide useful comparative information for assessing CV risk. However, the concern remains that these trials may not provide sufficient follow-up for observing CV outcomes; these trials were at most 12 weeks in duration. Three of the phase 3 trials (OXN3001, OXN3006, and OXN3401) had extension phases of up to 52 weeks and the phase 2 trial (OXN 2001) had an extension phase of 24 weeks during which patients received open-label OXN only. While extension phases do not provide comparative data, it may be important to consider the number of events that occur during the longer follow-up phases, see Section 3.1.4 for details.

Table 2 Summary of Applicant's Groupings of Trials in CV Database

<b>Analysis group/ Period analyzed</b>	<b>Studies included</b>
<b>Group A1A</b> Titration Double-blind Double-blind + extension	Placebo-controlled studies involving subjects with nonmalignant chronic pain (2 studies): <a href="#">ONU3701</a> , <a href="#">OXN3401</a>
<b>Group A1C =</b> <b>A1B<sup>a</sup> + OXN2001</b> Titration Double-blind Double-blind + extension	OXY CR-controlled studies involving subjects with nonmalignant pain and malignant chronic pain (5 studies): <a href="#">OXN3001</a> , <a href="#">OXN3006</a> , <a href="#">OXN3401</a> , <a href="#">OXN3503</a> , <a href="#">OXN2001</a>
<b>Group A1D =</b> <b>A1B<sup>a</sup> + OXN2001 + ONU3701</b> Titration + double-blind + extension	Studies to compare OXY (OXY CR and OXY IR) and OXN over the longest continuous period of time possible. Subjects who received different treatments during the titration, double-blind, or extension periods are excluded from these analyses (see <a href="#">Table 3</a> ) (6 studies): <a href="#">ONU3701</a> , <a href="#">OXN3001</a> , <a href="#">OXN3006</a> , <a href="#">OXN3401</a> , <a href="#">OXN3503</a> , <a href="#">OXN2001</a>
<b>Group C</b> Overall (titration, double-blind, extension)	Studies in chronic pain, healthy subjects, abuse liability, and in special populations and situations (29 studies): All studies defined in Group A1A and A1C, including the open-label titration and open-label extension period data.  Phase 1 studies involving healthy subjects: <a href="#">ONU1001</a> , <a href="#">ONU1002</a> , <a href="#">ONU1009</a> , <a href="#">OXN1003</a> , <a href="#">OXN1004</a> , <a href="#">OXN1005</a> , <a href="#">OXN1008</a> , <a href="#">OXN1009</a> , <a href="#">OXN1011</a> , <a href="#">OXN1013</a> , <a href="#">OXN1016</a> , <a href="#">OXN1018</a> , <a href="#">OXN1403</a> , <a href="#">OXN1505</a> , <a href="#">OXN1506</a>  Studies of abuse deterrence and other special populations and situations: <a href="#">ONU1003</a> , <a href="#">ONU1004</a> , <a href="#">ONU1007</a> , <a href="#">ONU1008</a> , <a href="#">OXN1006</a> , <a href="#">OXN1007</a> and <a href="#">OXN1017</a>  Active medication-controlled phase 4 study in nonmalignant cancer pain: <a href="#">OXN4502</a>  Note that only studies also included in groups A1A and A1C provide long-term data.

OXN = oxycodone hydrochloride/naloxone hydrochloride controlled-release tablets; OXY = oxycodone; OXY CR = oxycodone hydrochloride controlled-release tablets; OXY IR = oxycodone immediate release.

<sup>a</sup> Group A1B consists of 4 oxycodone CR-controlled studies in subjects with nonmalignant chronic pain ([OXN3001](#), [OXN3006](#), [OXN3401](#), and [OXN3503](#)).

Source: Extracted from PPLP's Integrated CV Report Table 2 page 40

We note that the remaining trial groupings defined by PPLP (A1A, A1C, and A1D) contain data from six double-blind, randomized, controlled phase 2 and 3 trials that we find most adequate for comparative safety analyses. Groups A1A and A1C represent subgroup analyses by comparator type (placebo or OXY, respectively). Note that data from trial OXN3401 was included in both of these groups because it studied both placebo and OXY as comparators. We acknowledge that Group A1D is based on all six phase 2 and 3 trials. However, we do not agree with combining data from multiple trial periods when forming treatment groups; for example, open-label titration with randomized double-blind for OXY treatment arm and randomized double-blind with open-label extension for OXN treatment arm, see Table 3.

With all the issues noted above, the remainder of this review is focused on information from the six phase 2 and 3 trials that were randomized, double-blind controlled trials, rather than all 29 trials in the CV clinical trial database. The results from PPLP's analyses of the double-blind periods for Groups A1A and A1C provide comparative safety analyses, by type of comparator, and these will also be discussed in this review.

Table 3 Summary of OXN and OXY

Study	Original study treatment arms			Treatment Arm Summarized for Safety Group A1D
	OLT	DB	OLE	
ONU3701	<b>OXN</b>	<b>OXN</b>		OXN
	<b>OXN</b>	<i>Placebo</i>		OXN (exclude data from DB)
OXN2001		<b>OXN</b>	<b>OXN</b>	OXN
		<b>OXY</b>	<b>OXN</b>	OXY (exclude data from OLE)
OXN3001	<i>OXY CR</i>	<b>OXN</b>	<b>OXN</b>	OXN (exclude data from OLT)
	<b>OXY CR</b>	<i>OXY CR</i>	<b>OXN</b>	OXY (exclude data from OLE)
OXN3006	<i>OXY CR</i>	<b>OXN</b>	<b>OXN</b>	OXN (exclude data from OLT)
	<b>OXY CR</b>	<i>OXY CR</i>	<b>OXN</b>	OXY (exclude data from OLE)
OXN3401	<i>OXY IR</i>	<b>OXN</b>	<b>OXN</b>	OXN (exclude data from OLT)
	<b>OXY IR</b>	<i>OXY CR</i>	<b>OXN</b>	OXY (exclude data from OLE)
	<i>OXY IR</i>	<i>Placebo</i>	<b>OXN</b>	Not included in the analysis
OXN3503	<i>OXY CR</i>	<b>OXN</b>		OXN (exclude data from OLT)
	<b>OXY CR</b>	<i>OXY CR</i>		OXY

DB = double-blind; OLT = open-label titration; OLE = open-label extension; OXN = oxycodone hydrochloride/naloxone hydrochloride controlled-release tablets; OXY = oxycodone; OXY CR = oxycodone hydrochloride controlled-release tablets; OXY IR = oxycodone immediate release.

Note: the periods with italicized text indicate where data is excluded.

Note: OXY IR and OXY CR are combined into a single OXY group for the analyses of Group A1D.

Note: subjects who withdrew during the open-label titration study arm are also included in the Group A1D analyses under the treatment taken during the open-label titration (OXY [IR or CR]).

Source: Extracted from PPLP's Integrated CV Report Table 3 page 43

### 3.1.2 Definition of Outcomes and Adjudication

#### 3.1.2.1 Cardiovascular Outcomes

Four sets of CV related outcomes were defined by PPLP based on MedDRA SMQs (Version 15.0) using broad and narrow terms:

- SMQ-based Major Adverse Cardiac Events (MACE): any adverse event (AE) coded to a preferred term in 1 of the following SMQs:
  - Myocardial infarction
  - Central nervous system (CNS) hemorrhages and cerebrovascular conditions
  - CV death (defined below)

Refer to Appendix 2 of the SAP for list of preferred terms included in this outcome.

- FDA custom MACE (cMACE): a subset comprising 34 preferred terms used to determine SMQ-based MACE as well as CV death, as shown in Table 4.

Table 4 Preferred Terms in the Definition of FDA-cMACE

Acute myocardial infarction	Embolic cerebral infarction
Myocardial infarction	Embolic stroke
Coronary artery thrombosis	Haemorrhagic cerebral infarction
Papillary muscle infarction	Haemorrhagic stroke
Post procedural myocardial infarction	Haemorrhagic transformation stroke
Silent myocardial infarction	Ischemic cerebral infarction
Basilar artery thrombosis	Ischemic stroke
Brain stem infarction	Lacunar infarction
Brain stem stroke	Lateral medullary syndrome
Brain stem thrombosis	Moyamoya disease
Carotid arterial embolus	Post procedural stroke
Carotid artery thrombosis	Stroke in evolution
Cerebellar infarction	Thalamic infarction
Cerebral artery embolism	Thrombotic cerebral infarction
Cerebral artery thrombosis	Thrombotic stroke
Cerebral infarction	Wallenberg syndrome
Cerebral thrombosis	Cardiovascular death (see definition below)
Cerebrovascular accident	

Source: Integrated CV Report Table 4 (page 50)

3. CV death: deaths were classified as CV-related if the associated preferred terms met one of the following criteria:
  - Fell under the system organ class of cardiac disorder
  - Were contained in the SMQ for CNS hemorrhages and cerebrovascular conditions
  - Were suggestive of sudden death or
  - Were related to other vascular events.
4. SMQ-based CV AE/SAEs: any AE coded to preferred term in SMQs for cardiac arrhythmias, cardiac failure, cardiomyopathy, CNS hemorrhages and cerebrovascular conditions, embolic and thrombotic events, hypertension, ischemic heart disease, or torsade de pointes/QT prolongation. Refer to Appendix 1 of the SAP for list of preferred terms included in this outcome.

Note that all CV outcomes were defined and analyzed by PPLP post hoc, that is, the trials included in the database were not designed prospectively to assess CV safety; rather these outcomes were collected in routine safety monitoring. There were no endpoints designated as primary or secondary endpoints. In response to request from PPLP regarding specific CV events to be assessed, the FDA recommended that the Applicant “cast a wide net in order to capture as much information as possible, however, the major events of interest are serious cardiac acute

cardiovascular events including MI, stroke, and sudden death”<sup>4</sup>. For this reason, this review focuses on outcomes 1 through 3 as defined above.

***Reviewer’s Comment: From the details provided in the study report and SAP, it does not appear that an independent committee was convened to ensure objective and unbiased adjudication of the CV outcomes.***

### 3.1.2.2 Opioid Withdrawal Symptoms

PPLP requested a committee of personnel from [REDACTED] <sup>(b)(4)</sup> to comprise an independent blinded adjudication committee to identify subjects with opioid withdrawal symptoms. The adjudication process<sup>5</sup> was conducted in a blinded retrospective manner for all trials, with the exception of trial ONU3701 for which adjudication was prospective. The committee comprised three members: 1 statistician and 2 clinicians. The committee used a SAS program to identify subjects with potential opioid withdrawal symptoms, if any of the following three criteria were met:

1. Clinical Opiate Withdrawal Scale Score ≥13
2. AE of opioid withdrawal reported on the case report form
3. Any 3 or more concurrent AE terms included in the Diagnostic and Statistical Manual of Mental Disorders, Version 4, diagnostic criteria for opioid withdrawal.

A subject profile for each patient with potential opioid withdrawal was then created. The committee members reviewed the profiles in batches of approximately 25 subjects at a time. After each batch of reviews, the committee met to discuss their findings. Each reviewed subject was classified as having evidence of opioid withdrawal symptoms or not having evidence of opioid withdrawal symptoms.

***Reviewer’s Comment: Defer to clinical expertise on the adequacy of the criteria used to identify potential opioid withdrawal symptoms.***

### 3.1.3 Analysis Population and Statistical Analyses

According to the SAP, the analysis population for the phase 2 and 3 trials comprised subjects who were randomized to treatment groups and who received at least one dose of the treatment. Subjects were analyzed according to the actual treatment received, even if it was not the same as the treatment to which they were randomized.

Incidence rates, expressed as the number of cases per 100 subject-years of exposure by treatment group, are provided in this review for the outcomes of SMQ-based MACE and FDA cMACE.

<sup>4</sup> Refer to pre-NDA meeting minutes dated October 10, 2012.

<sup>5</sup> Refer to the adjudication plan for opioid withdrawal located in Appendix 17.8.1 of the Integrated Safety Summary for details.

The Applicant defined a case as a subject with at least one occurrence of a preferred term comprising the CV events while exposed to study drug or within 7 days after last dose. This type of analyses is also known as on-treatment analyses. Incidence rate ratios (OXN relative to all comparators combined) and corresponding 95% confidence intervals (CIs) are also provided for each of the aforementioned endpoints. None of the analyses were stratified by trial because of the low number of events observed.

Note that the incidence rate estimates provided in this review that are based on all subjects in the phase 2 and 3 trials were calculated by the reviewer using the submitted data. Incidence rates for subgroup analyses by type of comparator are obtained from the study report, that is, for placebo only comparators (Group A1A in the study report) and for OXY only comparators (Group A1C in the study report). In these analyses, for trials that were placebo- and OXY-controlled, the OXN arm is considered in both analyses, without adjustments for multiplicity.

**Reviewer's Comments:**

1. *As mentioned above, only on-treatment analyses of CV outcomes were presented in the study report. Note that this is a limitation of the trial designs as most of the phase 2-3 trials (with the exception of one trial) discontinued subjects from study once they prematurely discontinued treatment. Typically, for trials used to assess CV safety, we recommend that subjects are followed through the end of the trial, regardless of treatment exposure status. Additionally, on-treatment analyses, such as those conducted when assessing CV safety in diabetes products, generally allow up to a 30-day ascertainment window after treatment discontinuation. It is unclear if a 7-day window is reasonable in this setting.*
2. *The Applicant presents results (including p-values) from numerous analyses in the report, none of which were specified as primary analyses and there were no adjustments for multiple comparisons. Therefore, the analyses conducted are considered exploratory in nature; as such, we advise against any conclusions or labelling based on statistically significant p-values, that is, p-values less than 0.05.*
3. *To evaluate the association between opioid withdrawal and CV event occurrence, PPLP presented the number and percentage of subjects with at least one FDA cMACE, or SMQ-based MACE for the entire double-blind period and within 28 days after opioid withdrawal symptoms. PPLP also conducted Cox proportional hazard model analysis for time to first occurrence of each of the CV outcomes. For each outcome, the model included treatment as a covariate and presence of opioid withdrawal as a time-dependent covariate. Baseline characteristics were included in the model using forward selection criteria. The low CV event rate limits our ability to interpret any association from these analyses. The Applicant also conducts analyses based on all SMQ-based CVAEs and SMQ-based SAEs which comprise a broad list of preferred terms thereby leading to higher event rates. However, the concern is how meaningful or relevant findings based on less specific outcomes are to understand association*

***between opioid withdrawal and CV occurrence. Thus, results from these assessments are omitted from this review.***

The incidence of all-cause deaths and deaths considered as CV-related are presented.

### 3.1.4 Baseline Characteristics and Subject Disposition

This section summarizes the baseline characteristics and subject disposition for all subjects in the 6 phase 2 and 3 trials. The analysis population consisted of 2042 subjects: 936 who were treated with OXN and 1106 treated with a comparator (646 with OXY and 460 with placebo). Note that all of the subjects, who were randomized to a comparator treatment, received the treatment to which they were assigned. There were 5 subjects who were randomized to OXN, but were erroneously treated with OXY. These errors all occurred in trial OXN3006; however, because they were in 4 different sites there is no cause for concern about the quality of the randomization procedures.

The overall study discontinuation rates were 18.9% for subjects treated with OXN and 23.2% for subjects treated with a comparator. Generally, the rates for the different reasons for discontinuations were similar between the OXN and comparator arms, with the exception of AE and lack of therapeutic effect for which the rate in the comparator arm was almost double that in the OXN arm, see Table 5. As shown in this table, within the comparator group most of the discontinuations due to lack of therapeutic effect were in subjects treated with placebo.

Table 5 Study Discontinuation Reason across All Phase 2-3 Trials

Reason for Discontinuation	OXN N=936 n (%)	Comparator		
		Placebo N=460 n (%)	OXY N=646 n (%)	All N=1106 n (%)
Administrative	22 (2.4)	10 (2.2)	9 (1.4)	19 (1.7)
Administrative and AE	3 (0.3)	0 (0.0)	2 (0.3)	2 (0.2)
AE	74 (4.9)	35 (7.6)	54 (8.4)	89 (8.1)
Confirmed or suspected diversion	5 (0.5)	6 (1.3)	0 (0.0)	6 (0.5)
Lack of therapeutic effect	40 (4.3)	75 (16.3)	13 (2.0)	88 (8.0)
Lack of therapeutic effect and AE	1 (0.1)	4 (0.9)	3 (0.5)	7 (0.6)
Lost to follow-up	4 (0.4)	1 (0.2)	2 (0.3)	3 (0.3)
Lost to follow-up and AE	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Subject choice	20 (2.1)	13 (2.8)	13 (2.0)	26 (2.4)
Subject choice and AE	6 (0.6)	1 (0.2)	16 (2.5)	17 (1.5)
Total	176 (18.9)	145 (31.5)	112 (17.3)	257 (23.2)

n=number of subjects discontinued

Source: Created by the reviewer using “adsl.xpt” dataset

The baseline demographic characteristics and CV risk factors were generally similar between the OXN and comparator arms; see Table 6 and Table 7, respectively. Note that height was not measured in all trials so weight is presented rather than BMI, and tobacco use or smoking status are not summarized as it does not appear that these were recorded in the submitted data. The majority of subjects were female (59% OXN and 62% comparator) and white (approximately 93% in both treatment groups). The mean age was approximately 57 years in the OXN and comparator groups with more than 70% of subjects in both treatment groups less than 65 years. Note that very few subjects (7.4% OXN and 6.6% comparator) were in the non-white race category, which comprised subjects recorded as black, Asian, or other. This may be due to the fact that most trials were conducted in Europe. Most subjects in both OXN and comparator groups had a pre-existing medical condition (hypertension, hyperlipidemia, or diabetes) that are known risk factors for CV outcomes.

Table 6 Baseline Demographic Characteristics across All Phase 2-3 Trials

Demographic Characteristic	OXN (N=936)	Comparator (N=1106)
<b><u>Sex, n (%)</u></b>		
Male	380 (40.6)	422 (38.2)
Female	556 (59.4)	684 (61.8)
<b><u>Age, in years</u></b>		
Mean (SD)	57.0 (11.6)	57.4 (11.6)
Range	20 – 85	20 – 87
<b><u>Age Group, n (%)</u></b>		
<65	697 (74.5)	793 (71.7)
≥65	239 (25.5)	313 (28.3)
<b><u>Race, n (%)</u></b>		
White	867 (92.6)	1033 (93.4)
Non-white	69 (7.4)	73 (6.6)
<b><u>Weight, in kg</u></b>		
Mean (SD)	84.7 (20.4)	84.6 (20.3)
Range	39.0 – 190.6	38.0 – 174.0

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Source: Created by the reviewer using “adsl.xpt” dataset

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Table 7 Baseline Cardiovascular Risk Factors across All Phase 2-3 Trials

CV Risk Factor	OXN (N=936)	Comparator (N=1106)
<b><u>CV History/Condition*, n (%)</u></b>		
Yes	258 (27.6)	293 (26.5)
No	678 (72.4)	813 (73.5)
<b><u>History of Hypertension, n (%)</u></b>		
Yes	462 (49.4)	551 (49.8)
No	474 (50.6)	555 (50.2)
<b><u>History of Hyperlipidemia, n (%)</u></b>		
Yes	300 (32.0)	320 (29.0)
No	636 (68.0)	786 (71.0)
<b><u>History of Diabetes Mellitus, n (%)</u></b>		
Yes	424 (45.3)	454 (41.1)
No	512 (54.7)	652 (58.9)

\*Preferred terms used to defined CV History/Condition defined in the SAP Appendix 1

Source: Created by the reviewer using dataset “adsl.xpt”

The distributions for treatment exposures were similar for the OXN and comparator subjects; mean durations of exposure were 68.7 days (range: 1 – 123) for OXN subjects and 66.8 days (range: 1 – 107) for comparator subjects. Most subjects were exposed for a period between 60-90 days, see Table 8. Recall that there was one trial in which the treatment period was 4 weeks and the remaining 5 trials had duration of 12 weeks.

Table 8 Summary of Treatment Exposure across All Phase 2-3 Trials

Duration of Exposure*	OXN N=936 n (%)	Comparator N=1106 n (%)
<30 days	178 (19.0)	243 (22.0)
30-60 days	57 (6.1)	61 (5.5)
60-90 days	645 (68.9)	709 (64.1)
>90 days	56 (6.0)	93 (8.4)

\*Duration of exposure defined as last dose date – first dose date +1.

Source: Created by the reviewer using dataset “adsl.xpt”

### 3.1.5 Results of Statistical Analyses of CV Outcomes

#### 3.1.5.1 SMQ-BASED MACE and FDA cMACE

The incidence of SMQ-based MACE or FDA cMACE in the OXY and comparator subjects was extremely low during the double-blind period of the 6 phase 2 and 3 trials. Overall, there were nine subjects, 2 OXN and 7 comparator subjects, who experienced SMQ-based MACE during the double-blind period. The estimated rate ratio was 0.3 with 95% CI (0.0, 1.7); consistent results were obtained for FDA cMACE, see Table 9.

Table 9 Results of Analyses of CV Outcomes in Phase 2-3 Trials  
(Double-Blind Treatment Period)

	OXN n (IR)	Comparator n (IR)	RR (95% CI)
<b>All Trials</b>			
SMQ-Based MACE	2 (1.1)	7 (3.2)	0.3 (0.0, 1.7)
FDA cMACE	1 (0.5)	5 (2.3)	0.2 (0.0, 2.1)
<b>Placebo-Controlled Trials</b>			
SMQ-Based MACE	0 (0.0)	2 (2.3)	--
FDA cMACE	0 (0.0)	2 (2.3)	--
<b>OXY-Controlled Trials</b>			
SMQ-Based MACE	2 (1.6)	5 (3.9)	0.4 (0.1, 2.1)
FDA cMACE	1 (0.8)	3 (2.4)	0.3 (0.0, 3.2)

n=number of subjects with event, IR=incident rate per 100 patient-years, RR=rate ratio

Source: Created by the reviewer using dataset “adaette.xpt” and study report Table 17 (page 72)

During the extension phases, when subjects were followed for up to 52 weeks, there was a notable increase in the number of observed CV events. According to the study report, there were 12 OXN subjects who experienced SMQ-based MACE during the extension phase. Of these 12 subjects, 7 were treated with OXN and 5 treated with a comparator during the double-blind treatment period. Nine of the 12 subjects who classified as having FDA cMACE during the extension phase: 7 were treated with OXN and 2 treated with a comparator during the double-blind treatment period.

#### 3.1.5.2 All-Cause and CV-Related Deaths

According to the study report, the incidences of all-cause deaths were similar between the treatment groups: 16/936 (1.7%) in OXN subjects and 13/1106 (1.2%) comparator subjects. Among these deaths, 3 were classified as CV deaths: 2 (0.2%) in OXN subjects and 1(0.1%) in comparator subjects. There were 2 CV deaths during the extension phase.

### 3.1.6 Results of Subgroup Analyses by Baseline Demographics and CV Risk Factors

Subgroup analyses (by baseline demographic or CV risk factors) are not presented in this review as interpretation of these analyses will be difficult with very few events. Therefore, refer to Appendix II for baseline characteristics of subjects with SMQ-Based MACE. Note that this includes subjects who were classified as having FDA cMACE.

## 3.2 Epidemiologic Database Study

The objectives of this epidemiologic study as described in the study report were:

- To characterize the incidence rate of ischemic CV events, including MI, cerebrovascular accident, revascularization, angina, thrombosis, and death among subjects prescribed OXN in the UK. These events were classified into two groups
  - MACE: MI, stroke or CV death
  - All ischemic CV events
- To compare the incidence rate of ischemic CV events among subjects prescribed OXN with subjects prescribed comparator opioids: extended release morphine (MOR ER), the most frequently used opioid in the UK, and OXY.

Note that there was no protocol, SAP, or data for this study included in the submission. Therefore, the review of this study consists of a critique of the submitted study report only.

### 3.2.1 Study Design and Description of Database

The study was a retrospective observational study of subjects, at least 18 years, who received at least 1 prescription for OXN, OXY or MOR ER from January 1, 2005 through August 1, 2012. According to the study report, only subjects without a history of CV disease at the time of first prescription of the respective opioid were included in the study because of the difficulty in distinguishing between second CV events and follow-up visits for the first CV event. The data source for this study was the THIN database, which is an anonymized patient record primary care database containing medical records for over 7 million patients in the UK. The database includes demographic information, medical diagnosis and free-text comments entered by the primary care physician, referral letters from consultants and hospital admissions and biochemical test results. Medical diagnoses were coded using READ codes (National Health Service Terminology Service 2007) and prescriptions were coded using British National Formulary codes. According to the study report, the quality of the data on diagnosis, medical event and prescription contained in THIN are comparable to the Clinical Practice Research Database (formally GPRD) and are generalizable to the UK primary care as a whole. No information was provided in the report to support these assertions.

**Reviewer's Comments:**

1. *There are many well-known issues that limit the reliability of data from observational studies, in particular retrospective studies in administrative databases not designed to assess the outcome. Among these issues is the predictive ability of diagnostic codes, such as ICD-9 codes or READ codes as used in this study, to determine the clinical event under investigation in the study. Sufficient details were not provided in the study report about the validity of these READ codes in determining CV events. There was no apparent medical chart reviews or adjudication committee to validate the codes. Additionally, because this is a retrospective database study some risk factors that may be associated with CV may not have been recorded. Therefore, there is a potential for residual confounding.*
2. *According to the report, the study began in January 2005. Note that this is approximately 4 years prior to approval of OXN in the UK<sup>6</sup>. In other words, for about half of the study time there would have been no post-market data available for OXN in the UK. This flaw in design calls into question the reliability of this study in assessing CV safety of OXN.*

### 3.2.2 Statistical Analyses

Incidence rates per 100 subject-years, along with corresponding 95% CIs, for MACE and all ischemic CV events were provided for each treatment group. Pairwise comparative incidence rate ratios (OXN to OXY, OXN to MOR ER, and OXY to MOR ER) were also provided in the report. Cox proportional hazards models were used to estimate the hazard ratio (OXN compared with each of other opioids) along with 95% CIs for each CV event of interest.

**Reviewer's Comments:**

1. *The Applicant does not provide sufficient details about the Cox modelling that was performed. It is unclear what censoring mechanism (and corresponding time at risk) was used, for example, if subjects were censored when there is a switch in prescriptions. There was no data submitted to investigate these issues; as such, hazard ratio estimates are not included in this review.*
2. *The Applicant conducts multiple covariate adjusted Cox analyses. Here again as with the clinical trial database, the issue of event rate needs to be considered. With few events these models will be unstable, therefore leading to inaccurate HR estimates.*

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<sup>6</sup> Mundipharma (2009-01-26). "[Targin \(oral oxycodone/naloxone prolonged-release tablet\) now launching across Europe to control severe chronic pain with significantly reduced risk of opioid-induced constipation](#)".

### 3.2.3 Demographics and Baseline Characteristics

There were 49,226 subjects included in the study: 2600 exposed to OXN; 35636 exposed to MOR ER; and 10,990 exposed to OXY. Note that only 5% of the subjects in this database were treated with OXN, the drug under investigation in this review. The demographics and baseline characteristics for subjects in the study are presented in Table 10. The distributions of these characteristics were generally similar across the three treatments with some minor differences in the age and sex distributions. The median durations of exposure, as reported by PPLP, were 42 days OXN, 65 days for MOR ER, and 65 days for OXY. Most subjects in each treatment group were exposed for less than 90 days and approximately 16% in the OXN and MOR ER and 19% in the OXY subjects were exposed for more than 1 year.

Table 10 Baseline Characteristics for the UK THIN Database Study

	<b>OXN</b> <b>N = 2600</b> <b>N (%)</b>	<b>MOR ER</b> <b>N = 35636</b> <b>N (%)</b>	<b>OXY CR</b> <b>N = 10990</b> <b>N (%)</b>
Age category			
< 65	1364 (52.5)	15696 (44.0)	5879 (53.5)
≥ 65	1236 (47.5)	19940 (56.0)	5111 (46.5)
Age group			
< 35	148 (5.7)	1290 (3.6)	718 (6.5)
35-54	731 (28.1)	7147 (20.1)	2895 (26.3)
55-64	485 (18.7)	7259 (20.4)	2266 (20.6)
65-74	542 (20.8)	8832 (24.8)	2500 (22.7)
≥ 75	694 (26.7)	11108 (31.2)	2611 (23.8)
Sex			
Male	925 (35.6)	16343 (45.9)	4616 (42.0)
Female	1675 (64.4)	19293 (54.1)	6374 (58.0)
Comorbidities			
History of CVD	259 (10.0)	4681 (13.1)	1238 (11.3)
Diabetes	337 (13.0)	5277 (14.8)	1594 (14.5)
Hypertension	1055 (40.6)	14324 (40.2)	4264 (38.8)
Hyperlipidemia	425 (16.3)	5635 (15.8)	1766 (16.1)
Obesity	762 (29.3)	8131 (22.8)	2868 (26.1)
Smoking	1621 (62.3)	24155 (67.8)	7051 (64.2)
History of drug abuse	51 (2.0)	915 (2.6)	268 (2.4)
Concomitant medications			
Anti-hypertensives	899 (34.6)	11214 (31.5)	3488 (31.7)
Anti-cholinesterases	3 (0.1)	22 (0.1)	3 (0.0)
Atypical antipsychotics	86 (3.3)	2062 (5.8)	608 (5.5)

CVD = cardiovascular disease; MOR ER = extended release morphine tablets; OXN = oxycodone hydrochloride/naloxone hydrochloride controlled-release tablets; OXY CR = oxycodone hydrochloride controlled-release tablets.

Note: smoking includes both current and ex-smokers.

Source: Extracted from the Integrated CV Report, Table 48 (page 145)

**Reviewer Comments:**

1. *The report states that patients with history of CV disease at time of 1<sup>st</sup> prescription (that is, at baseline) were not to be included in study. However, the table of baseline characteristics summarizes subjects with a history of CV disease. This seems to contradict the inclusion criteria for the study.*
2. *Because of the lack of randomization, typically statistical methods, such as, use of propensity scores or other matching strategy, are implemented to deal with confounding in observational studies. These methods are also employed when there are a low percentage of subjects exposed to the product studied relative to exposed to comparator products, as is the case with this study. It does not appear that any such methods were used in this study.*

### 3.2.4 Results of CV Assessments

The incidence of MACE was low and similar across the three treatment groups: 14 (0.5%) in the OXN subjects, 280 (0.8%) in the MOR ER subjects and 98 (0.9%) in the OXY CR subjects. The incidence of all ischemic events was also low: 38 (1.5%) in OXN subjects, 715 (2.0%) in OXY CR subjects and 285 (2.6%) in OXY subjects.

**Reviewer's Comment:** *The Applicant presented incidence rates for MACE as well as for all ischemic events for each treatment group. There is concern that these estimates are based on fewer subjects than the number reported to have been enrolled in the study. In the Tables 50 and 51 containing the incidence of MACE and ischemic events, the numbers of subjects treated with OXN were 2343 and 1703, respectively, compared to 2600 subjects that were reported to have been treated with OXN in the study. Similar discrepancies were noted in the OXY and MOR ER treatment groups. No explanation is provided in the report about the differences in the number of subjects enrolled and the number analyzed. As such, the validity of the incidence rate (and resulting rate ratio) estimates provided in the report is questionable. Therefore, these estimates are not included in this review. In addition, as noted previously, sufficient details about the Cox model analyses were not provided; therefore, hazard ratio estimates are not presented in this review.*

## 4 SUMMARY AND CONCLUSIONS

This statistical safety review was based on the CV assessments for OXN that were included in a study report that was included in the NDA for this product. These assessments were conducted by the Applicant, PPLP, in response to concerns raised by the Agency about a potential CV signal with Entereg, an approved product similar to OXN. The review focused on findings from pooled analyses of clinical trials in the OXN development program and an epidemiologic study of the UK THIN database. An important point to keep in mind is that none of these data sources were prospectively created to assess CV safety of OXN.

#### **4.1 Summary of Findings and Statistical Issues**

Overall, the incidence of CV events was extremely low in both data sources. In the subset of phase 2 and 3 clinical trials contained in the trial database, the incidence of SMQ-based MACE (one of the CV outcomes assessed) was 2 (0.2%) in OXN subjects compared to 7 (0.6%) in comparator subjects during the double-blind period. According to the study report, there were 12 OXN subjects who experienced SMQ-based MACE during the extension phase. Of these 12 subjects, 7 were treated with OXN and 5 treated with a comparator during the double-blind treatment period. In the UK THIN database study the incidence of MACE was 14 (0.5%) in the OXN subjects, 280 (0.8%) in the MOR ER subjects, and 98 (0.9%) in the OXY CR subjects.

There are several issues, discussed in detail throughout this review, which should be carefully considered when interpreting the findings from these data sources. A summary of the issues for each data source are provided below.

##### Summary of Statistical Issues in Clinical Trials Database

The majority of the trials included in the database lacked a parallel control arm, had small sample sizes (<40 subjects), were limited in follow-up data (<30 days study duration), or studied healthy subjects who are at low CV risk. Therefore, of the 29 clinical trials in the database, there are 6 randomized, double-blind controlled phase 2 and 3 trials in subjects with chronic pain that could be used for statistical analyses of CV events. The concern that remains with these 6 trials is that the follow-up time may be insufficient to observe CV events as most trials were 12 weeks in duration, as well as the population enrolled may not be sufficiently enriched to evaluate CV risk. It is important to note that the potential CV signal with Entereg, which prompted the CV assessments for OXN, was driven by data from a 12-month trial (52 weeks).

Another issue to keep in mind is that for most of these 6 trials, with the exception of one trial, subjects were discontinued from study once they prematurely discontinued treatment and only events that occurred while patients were still on treatment or within 7 days of treatment discontinuation were considered. It is unclear whether a 7-day window is meaningful in this setting.

Finally, with this few events observed, any association, or lack thereof, between opioid withdrawal and CV incidence cannot be demonstrated with this data source.

##### Summary of Statistical Issues in the UK THIN Database Study

There are many well-known issues with observational studies, in particular, with retrospective studies of administrative databases not designed for clinical research that should be considered when interpreting the findings from this study. These issues include outcome misclassification, low predictive ability of diagnostic codes, and residual confounding. The Applicant acknowledges these limitations of the study. Another important issue with this study is the small percentage of subjects exposed to OXN; only 5% of the study cohort had been exposed to OXN. Note that the study began in January 1, 2005, which is approximately 4 years prior to October

2008 approval of OXN in the UK. Thus, for over 50% of the study time, no post-market data would have been available for OXN in the UK database. This is a clear design flaw of this study; as such, the reliability of this data source for assessing CV safety of OXN is questionable.

There were apparent discrepancies identified with the study report. The study report states, on page 143, that only those subjects without a history of CV disease at the time of their index prescription were to be included in the database, but on page 145, patients with history of CVD are summarized among the baseline characteristics. Additionally, there are inconsistencies between the number of subjects reported to have been enrolled in the study and the number of subjects presented in the results of statistical analyses. No explanation is provided in the report for these inconsistencies.

## **4.2 Conclusions and Recommendations**

Given the concerns summarized in this section and described in detail throughout this review, a definitive conclusion that there is no CV safety concern with OXN use cannot be made from the data sources evaluated in this statistical review. Therefore, should OXN be approved, the recommendation is that further assessment of CV safety be conducted through a postmarketing controlled study, if there is a need to further characterize the CV risk of OXN. Some important characteristics to be considered for such a study are specific CV outcome definition, requirement for prospective blinded independent adjudication, and sufficient follow-up time to observe CV outcome in a population at risk for CV related events. Additionally, if OXN is approved, the recommendation is that findings from these CV assessments not be included in the product label.

## APPENDIX I Summary of Trial Designs in CV Clinical Trial Database

<b>Trial ID/Phase</b>	<b>Population/ Objective</b>	<b>Design</b>	<b>Treatments: Patients Randomized</b>	<b>Total Randomized</b>	<b>Location</b>
				<b>Treatment Duration</b>	
ONU1001 Phase 1	Healthy adults to determine fasting bioequivalence of OXN manufactured at 2 sites	OL,R, SD, 2-period CO	OXN 10/5 mg (US): 25 OXN 10/5 mg (UK): 25	16 days <sup>1</sup>	US, UK
ONU1002 Phase 1	Healthy adults to determine fasting bioequivalence of OXN manufactured at 2 sites	OL,R,SD, 2 period CO	OXN 40/20mg (UK): 26 OXN 40/20 mg (US): 29	16 days <sup>1</sup>	US, UK
ONU1009 Phase 1	Healthy adults to assess relative bioavailability of OXN	OL,R, SD, 4-period CO	OXN 20/10 mg, SUB 2/0.5 mg, OXY 20 mg, NAL 0.4mg : 30	30 days <sup>1</sup>	US
OXN1003 Phase 1	Healthy adults to assess effect of food (fasting or feeding) on PK of two doses of OXN	OL,R, SD, 4-period CO	OXN 10/5 mg, OXN 40/20 mg: 28	30 days <sup>1</sup>	Germany
OXN1004 Phase 1	Healthy adults to compare PK of OXN from two batch sizes of two doses	OL,R, SD, 4-period CO	OXN 10/5 mg, OXN 40/20 mg: 40	30 days <sup>1</sup>	Ireland
OXN1005 Phase 1	Healthy male adults to assess the effects of OXN on intestinal motility	OL, R, SD, 5-period CO	OXN 10/5 mg, OXN 20/10 mg, OXY 10 mg, OXY 20mg, PLA: 15	40 days <sup>1</sup>	UK
OXN1008 Phase 1	Healthy adults to assess the effect of food (fasting or feeding) on PK of OXN	OL, R, SD, 3-period CO	OXN 40/20 mg, OXY 20mg+NAL 10mg: 29	22 days <sup>1</sup>	Germany

<b>Trial ID/Phase</b>	<b>Population/ Objective</b>	<b>Design</b>	<b>Treatments: Patients Randomized</b>	<b>Total Randomized</b>	<b>Location</b>
				<b>Treatment Duration</b>	

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OXN1009 Phase 1	Healthy adults to assess the effect of food (fasting or feeding) on PK of OXN	OL, R, SD, 3-period CO	OXN 10/5 mg, OXY 10 mg + NAL 5mg: 20	22 days <sup>1</sup>	UK
OXN1011 Phase 1	Healthy adults to assess the bioequivalence of OXN	OL, R, MD, 3-period CO	OXN 40/20 mg, OXY 40mg, NAL 10 mg: 34	31 days <sup>1</sup>	Germany
OXN1013 Phase 1	Healthy males to assess PK of OXN from batches with difference release rates (slow, medium, fast)	OL, R, SD, 4-period CO	OXN 20/10 mg, OXY 10mg+NAL 5mg: 18	30 days <sup>1</sup>	UK
OXN1016 Phase 1	Healthy adults to assess the PK of OXN from two batch sizes	OL, R, SD, 5-period CO	OXN 10/5 mg, OXN 40/20 mg, OXN10/5 mg+ NALT 50mg: 30	36 days <sup>1</sup>	UK
OXN1018 Phase 1	Healthy adults to assess the effect of food (fasting or feeding) on PK and bioavailability of OXN	OL, R, SD, 4-period CO	OXN 5/2.5 mg, OXY 5mg+NAL 2.5 mg: 24	30 days <sup>1</sup>	Ireland
OXN 1403 Phase 1	Healthy adults to assess the PK and bioavailability of OXN	OL, R, SD, 4-period CO	OXN 10/5 mg, OXN 20/10 mg, OXN 40/20, OXY 20mg+NAL 10mg: 28	25 days (7-day wash out for periods 1-3)	Germany
OXN1505 Phase 1	Healthy adults to assess the effect of food (fasting or feeding) on PK of OXN	OL, R, SD, 3-period CO	OXN 80/40 mg, OXY 20 mg+ NAL 10mg: 28	21 days <sup>1</sup>	Ireland

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<b>Trial ID/Phase</b>	<b>Population/ Objective</b>	<b>Design</b>	<b>Treatments: Patients Randomized</b>	<b>Total Randomized</b>	<b>Treatment Duration</b>	<b>Location</b>
OXN1506 Phase 1	Healthy adults to assess the PK and dose proportionality of five new strengths of OXN compared to two existing strengths of OXN	OL, RD, SD, 5-period CO	OXN 2.5/1.25 mg, OXN 15/7.5 mg, OXN 30/15 mg, OXN 60/30 mg, OXN 80/40 mg, OXN 10/5 mg, OXN 40/20 mg: 48	36 days <sup>1</sup>		Ireland
ONU3701 Phase 3	Efficacy and safety of OXN in adults with moderate to severe pain due to chronic low back pain who require around-the-clock opioid therapy	R, DB, C, MD	OXN 10/5 mg or OXN 20/10 mg or OXN 40/20 mg: 298  PLA : 302	12 weeks		US
OXN3001 Phase 3	Improvement of symptoms of constipation in adults with non-malignant pain	R, DB, C, MD	OXN 10/5 mg or OXN 20/10 mg: 160  OXY 10 mg or 20 mg : 162	12 weeks		Europe
OXN3006 Phase 3	Improvement of symptoms of constipation in adults with non-malignant pain	R, DB, C, MD	OXN 10/5 mg or OXN 20/10 mg or OXN 40/20 mg: 130  OXY 10mg or OXY 20mg or OXY 40 mg: 135	12 weeks		Europe

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<b>Trial ID/Phase</b>	<b>Population/ Objective</b>	<b>Design</b>	<b>Treatments: Patients Randomized</b>	<b>Total Randomized</b>	<b>Location</b>
OXN3401 Phase 3	Safety and Efficacy of OXN in adults with moderate to severe chronic nonmalignant pain	R, DB, C, MD	OXN 10/5 mg or 20/10 mg: 154  OXY 10 mg or 20 mg: 151  PLA: 158	12 weeks	Europe
OXN3503 Phase 3	Demonstrate noninferiority in pain and locomotor function and improvement in symptoms in adults with moderate to severe pain due to osteoarthritis	R, DB, C, MD	OXN 5/2.5 mg, 10/5 mg, 20/10 mg, or 40/20 mg: 101  OXY 5mg, 10 mg, 20mg, or 40 mg:108	12 weeks	Europe
OXN2001 Phase 2/3	Safety and efficacy of OXN in adults with moderate to severe chronic malignant pain	R, DB, C, MD	OXN 5/2.5 mg ,10/5 mg, 20/10 mg, 40/20 mg: 92  OXY 5 mg, 10 mg, 20mg, or 40 mg : 92	4 weeks	Europe
ONU1004 Phase 1	Opioid dependent adults to assess the PD, PK, and safety of OXN	R, DB, SD 2 block order CO	OXN 30/15 mg, OXY 30 mg, PLA followed by OXN 60/30 mg, OXY 60 mg, PLA: 18	10 days (includes washout of 3 days)	Canada
ONU1007 Phase 1	Healthy non-dependent recreational drug users to evaluate the abuse potential of OXN (intact or chewed)	R, DB, SD, 4-period CO	OXN 40/20 mg, OXY 40mg, PLA: 37	30 days (includes washout of 5-7 days)	Canada

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<b>Trial ID/Phase</b>	<b>Population/ Objective</b>	<b>Design</b>	<b>Treatments: Patients Randomized</b>	<b>Total Randomized</b>	<b>Location</b>
ONU1008 Phase 1	Healthy adults to assess the PD, PK, and safety of OXN (chewed or intact)	R, DB, SD, 4-period CO	OXN 60/30 mg, OXY 60mg, PLA: 33	10 days (includes washout of 2 days)	Canada
ONU1003 Phase 1	Healthy non-dependent recreational drug users to evaluate the abuse potential of OXN	R, DB, SD, 3-period CO, parallel-group	<u>Oral</u> OXN 40/20mg, OXY 40mg, PLA:16  <u>Powder</u> OXN 40/20 mg, OXY 40 mg, PLA:27  <u>Intravenous</u> OXY 0.07mg, OXY 0.07 mg + NAL 0.035mg, PLA: 24	30 days (includes washout of 5-7 days)	Canada
OXN1006 Phase 1	Patients with hepatic impairment and healthy adults to assess the PK of OXN	OL, SD	OXN 10/5 mg: 24	3 days	Czech Republic
OXN1007 Phase 1	Patients with renal impairment and healthy adults to assess the PK of OXN	OL, SD	OXN 10/5 mg: 24	3 days	Czech Republic
OXN1017 Phase 1	Healthy elderly patients and young adults to assess PK of OXN	OL, MD	OXN 10/5 mg: 39	7 days	UK

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Trial ID/Phase	Population/ Objective	Design	Treatments: Patients Randomized	Total Randomized	Location
				Treatment Duration	
OXN4502 Phase 4	Efficacy and safety of OXN in adults with moderate to severe chronic low back pain or pain due to osteoarthritis	R, DB, MD	OXN 5/2.5 mg or 10/5mg or 20/10 mg: Codeine/paracetamol 15/500 mg or 30/500 mg : 123	12 weeks	UK

OL=open label, R=randomized, DB=double-blind, CO=crossover, C= controlled, SD=single-dose, MD=multiple-dose  
 US=United States, UK=United Kingdom

OXN=oxycodone/naloxone, SUB=sublingual naloxone, NAL=naloxone, OXY=Oxycodone, NALT= naltrexone, PLA=placebo

<sup>1</sup> Includes 7-day wash-out period between each treatment switch

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Source: Created by the reviewer from clinical trial reports included in the NDA

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## APPENDIX II Subjects with SMQ-BASED MACE OR FDA cMACE in Clinical Trial Database

Subject ID	Treatment	Age	Sex	CV Risk Factor	Time to Event (in Days)
ONU3701-0755A-0039002	PBO	40	Female	No	12
ONU3701-1175A-0070013	PBO	71	Female	Yes	11
OXN2001-0206A-0020601	OXY	71	Male	Yes	12
OXN2001-0408A-0040807	OXY	73	Female	Yes	30
OXN2001-0507A-0050703	OXY	51	Male	No	4
OXN2001-0602A-0060202	OXY	72	Male	No	1
OXN3001-0962A-0096219	OXY	51	Male	Yes	63
OXN2001-0409A-0040902	OXN	61	Male	No	9
OXN2001-0502A-0050205	OXN	78	Female	Yes	23

PBO=placebo, OXN=oxycodone/naloxone, OXY=oxycodone

Shaded region represents subjects classified as having SMQ-based and FDA cMACE, unshaded indicates with SMQ-based only.

Source: Created by the reviewer using “dataset adaette.xpt”

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Statistical Review of CV Safety  
Oxycodone/Naloxone, NDA 205777

## **SIGNATURE/DISTRIBUTION LIST**

Primary Statistical Reviewer: Janelle K. Charles  
Date: March 24, 2014

Concurring Reviewers: Mat Soukup, Team Leader DBVII  
Aloka Chakravarty, Division Director, DBVII

cc:

Liz Kilgore, Medical Officer, DAAAP  
Ellen Fields, Medical Team Leader, DAAAP  
Preston Dunnmon, Medical Officer, DCRP  
Lisa Basham, Project Manager, DAAAP  
Aloka Chakravarty, Director, DBVII  
Mat Soukup, Team Lead, DBVII  
Janelle Charles, Statistical Reviewer, DBVII  
Feng Li, Statistical Reviewer, DBII  
Janice Derr, Statistical Team Leader, DBII  
Lillian Patrician, Office of Biostatistics

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JANELLE K CHARLES  
03/24/2014

MATTHEW J SOUKUP  
03/25/2014  
Concur

ALOKA G CHAKRAVARTY  
03/25/2014



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

# Statistical Review and Evaluation

## CLINICAL STUDIES

<b>NDA/Serial Number:</b>	205777
<b>Drug Name:</b>	Oxycodone-Naloxone tablets (ONU)
<b>Indication:</b>	(b) (4)
<b>Study number:</b>	ONU1008 (UPN 1757)
<b>Applicant:</b>	Purdue Pharma L.P.
<b>Date(s):</b>	Date of Document: Sep 23,2013 Consult received date: Nov 11, 2013 Completion date: 02/11/2014
<b>Review Priority:</b>	S
<b>Biometrics Division:</b>	DBVI
<b>Statistical Reviewer:</b>	Anna Sun, Ph.D., Mathematical Statistician, OB/DBVI
<b>Concurring Reviewers:</b>	Yi Tsong, Ph.D., Acting Division Director, OB/DBVI
<b>Medical Division:</b>	Control Substance Staff
<b>The CSS Team:</b>	James Tolliver, Ph.D., Pharmacologist, OCD/CSS Silvia Calderon, Ph.D., Pharmacology Team Leader, OCD/CSS
<b>Project Manager:</b>	Sandra Saltz, Project Manager, CSS

**Keywords:** *Crossover design, Drug abuse potential study, Self-reported endpoint, Multiple endpoints*

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## 1. Executive Summary

Study ONU1008 (UPN 1757) was single-center, double-blind, triple-dummy, PBO-controlled, randomized, 4-way crossover study to evaluate the PD effects (subjective, physiologic and withdrawal), PK, and safety of oral ONU (chewed and intact) compared to Oxy API and PBO in methadone-maintained, opioid-dependent subjects.

The objectives of the study were to evaluate the following:

- The pharmacodynamic (PD) effects of intact and chewed ONU compared to the active pharmaceutical ingredient, oxycodone HCl (Oxy API), and PBO in methadone-maintained, opioid-dependent subjects
- The PK of oxycodone and naloxone in methadone-maintained, opioid-dependent subjects
- The safety and tolerability of intact and chewed ONU in methadone-maintained, opioid dependent Subjects

There were four treatments in the study. 33 subjects were randomized and 29 subjects were analyzed. Subjects received each of the treatments outlined below in a randomized, double-blinded, triple-dummy fashion (one per Treatment visit). Treatment A: ONU 60/30 mg intact; Treatment B: ONU 60/30 mg chewed; Treatment C: Oxy API, 60 mg oral solution; Treatment D: PBO

Primary PD outcome variable was High VAS .The reviewer analyzed the primary endpoint Drug High and the secondary endpoint Drug Liking VAS, Good Effects VAS, Bad Effects VAS, Pupil Diameter (mm), Overall Drug Liking VAS (at hour 12) and Take Drug Again VAS (at hour 12). The results from the statistical reviewer's analyses establish that:

- For the comparison of placebo and OXY, except for the Bad Effect VAS, there were statistically significant differences between these two treatments on all subjective measures. Pupil diameter was significantly lower following administration of OXY.
- For the comparison of ONU chewed and OXY, there were significant statistically differences on all subjective measures. ONU chewed was associated with greater Bad Effect VAS, higher pupil diameter and significantly lower Drug Liking, Good Effects, Bad Effects, Overall Drug Liking (at hour 12) and Take Drug Again VAS (at hour 12).
- For the comparison of ONU intact and OXY, except for the Bad Effect VAS, there were significant statistically differences on all subjective measures.
- There were few significant differences between ONU chewed and ONU intact. However, ONU chewed showed marginally higher Good Effect VAS, significantly higher score in Bad Effect VAS.
- For the comparison of ONU intact and placebo, no significant differences were observed on all subjective measures.
- Effects on the comparison of ONU chewed and placebo were minimal, no significant differences were observed, however, ONU chewed had marginally higher score on Good Effect VAS, significantly higher Bad Effect VAS

## **2. Review Report on Study ONU1008 (UPN 1757)**

### **2.1 Overview**

Oxycodone/naloxone (ONU) tablets ( [REDACTED]<sup>(b)(4)</sup>, [REDACTED]<sup>(b)(4)</sup>, 10/5 mg, 20/10 mg, and 40/20 mg combination formulation of oxycodone hydrochloride (HCl) and naloxone HCl that is [REDACTED]<sup>(b)(4)</sup> pain. Due to the inclusion of naloxone, it is expected that this combination product will be at reduced risk for abuse via the intranasal and intravenous routes of administration.

This study was designed to evaluate the abuse potential/agonist effects, withdrawal effects, PK profile, and safety of orally administered intact and chewed ONU tablets in methadone-maintained, opioid-dependent subjects.

#### **2.1.1 Objectives of the study**

The objectives of the study were to evaluate the following:

- The pharmacodynamic (PD) effects of intact and chewed ONU compared to the active pharmaceutical ingredient, oxycodone HCl (Oxy API), and PBO in methadone-maintained, opioid-dependent subjects
- The PK of oxycodone and naloxone in methadone-maintained, opioid-dependent subjects
- The safety and tolerability of intact and chewed ONU in methadone-maintained, opioid dependent Subjects

#### **2.1.2 Study design**

This was a single-center, double-blind, triple-dummy, PBO-controlled, randomized, 4-way crossover study. The study consisted of 4 phases: screening, qualification, treatment, and follow-up.

- Screening: Visit 1 for inclusion/exclusion screening was conducted within 30 days prior to admission to the qualification phase.
- Qualification: 1 visit (Visit 2) lasting 3 days (2 overnight stays). On the morning of days 1 and 2, subjects were administered single doses of Oxy API 60 mg, in oral solution and PBO in a randomized fashion (washout of 24 hours) to determine if they showed an appropriate response to PBO; this visit also determined if each subject was suitable for study entry.
- Treatment: 1 inpatient session (Visit 3) lasting 9 days (with 8 overnight stays). Subjects received each of the following treatments in a randomized, double-blind, triple-dummy fashion:
  - Treatment A: ONU 60/30 mg intact
  - Treatment B: ONU 60/30 mg chewed
  - Treatment C: Oxy API 60 mg, in oral solution

- Treatment D: PBO
- Follow-up: Visit 4 was a safety follow-up, 3 to 7 days after the last study drug administration.

### **Outcome Variables**

- Primary Pharmacodynamics outcome variable was High VAS (maximum effect [Emax], time-averaged area under the effect curve [TA\_AUE]).
- Secondary endpoints:

Subjective PD endpoints:

- Drug Liking VAS ‘at this moment’ (Emax, minimum effect [Emin], TA\_AUE)
- Overall Drug Liking VAS (end-of-session score)
- Take Drug Again VAS (end-of-session score)
- Good Effects VAS (Emax, TA\_AUE)
- Bad Effects VAS (Emax, TA\_AUE)
- Feeling Sick VAS (Emax, TA\_AUE)
- Drowsiness/Alertness VAS (Emin, TA\_AUE)
- Any Effects VAS (Emax, TA\_AUE)

Objective physiologic endpoints:

- Pupillometry (maximum pupil constriction [MPC], pupillometry area over the effect curve [PAOE] relative to baseline)

Withdrawal endpoints:

- Subjective Opioid Withdrawal Scale (SOWS) (Emax, TA\_AUE)
- Objective Opioid Withdrawal Scale (OOWS) (Emax, TA\_AUE)

#### **2.1.3 Abuse potential measure and data collection times**

Drug High VAS are the primary abuse potential variables, measured at pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 hours post-dose. The secondary variables VAS (Drug Liking, Good, Bad, Any Effects VAS) were measured at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 hours post-dose. Pupillometry was measured at pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 hours post-dose. Overall Drug Liking, Take Drug Again VAS were measured at 4 and 12 hours post-dose. SOWS, OOWS were measured at pre-dose, 1, 2, 3, 4, 8 and 12 hours post-dose.

#### **2.1.4 Number of subjects**

A total of 118 subjects were screened for enrollment. Of these, 74 (62.7%) subjects passed screening and were eligible for the qualification phase. 33 (44.6%) subjects passed qualification criteria and were randomized to the treatment phase. Four (12.1%) subjects did not complete the study as planned. Two subjects discontinued after treatment period 1, subject 01067 was discontinued post-dose during treatment period 2 for non-compliance, and Subject 01084 was discontinued for non-compliance after completing treatment period 2. In total, 29 (87.9%) subjects completed all 4 treatment periods and were included in the PK and PD Populations.

### **2.1.5 Statistical methodologies used in the Sponsor's analyses**

#### **Hypothesis Testing**

For each of the parameters, the null hypothesis was: there is no treatment effect, and the alternative hypothesis was: there is a treatment effect. For each of the contrasts or pairwise comparisons, the null hypothesis was: there is no treatment effect difference between the tested pair, the alternative hypothesis was: there is a treatment effect difference between the tested pair.

A 5% Type I error rate with a P value <0.05 was considered as statistically significant for all individual hypothesis tests. All statistical tests were performed using two-tailed significance criteria.

#### **Analysis of Pharmacodynamic Assessments**

PD data at each time point were summarized by descriptive statistics and presented graphically (where appropriate) for the PD Population. Derived endpoints were summarized using descriptive statistics and box-plots. Outliers were listed by measure and parameter.

PD endpoints (Emax, Emin, MPC and/or TA\_AUE or PAOE, as appropriate) were analyzed using a mixed-effect model for a crossover study. TEmax/TEmin was summarized descriptively; however, additional analyses may have been undertaken if appropriate. From each model, means, 95% confidence intervals and P values for treatments and treatment differences were computed. The Benjamini and Hochberg procedure was used to control for Type I error arising from the multiple comparisons. Tests for non-normality and homogeneity of variance were conducted and nonparametric methods were employed, if necessary.

The following contrasts were performed:

- Oxy API vs. PBO
- ONU (intact) vs. PBO
- ONU (intact) vs. Oxy API
- ONU (chewed) vs. PBO
- ONU (chewed) vs. Oxy API
- ONU (chewed) vs. ONU (intact)

A sensitivity analysis was also conducted for High VAS (primary endpoint), which included subjects who were considered 'responders' during the qualification phase, i.e., peak score (Emax)

in response to Oxy API greater than that of PBO ( $\geq 15$ -point difference) for High VAS and <10 points on High VAS for PBO.

## 2.1.6 Sponsor's Summary and Conclusions

### Pharmacodynamic Conclusions

- There were statistically significant differences between PBO and Oxy API 60 mg on all subjective measures with the exception of Bad Effects VAS. Pupil diameter and subjective withdrawal (SOWS) were statistically significantly lower following administration of Oxy API 60 mg.
- No statistically significant differences were observed between ONU 60/30 mg intact and PBO on measures of subjective drug effects; however, self-reported withdrawal effects were statistically significantly lower with ONU 60/30 mg intact.
- Relative to Oxy API 60 mg, ONU 60/30 mg intact showed statistically significantly lower scores on Positive and Balance of Effects measures, less high, and less effect on pupil diameter. Drowsiness/Alertness VAS scores were statistically significantly higher (less drowsy) with ONU 60/30 mg intact relative to Oxy API 60 mg.
- Effects of ONU 60/30 mg chewed in comparison to PBO were minimal; however, ONU 60/30 mg chewed showed statistically significantly greater disliking (Drug Liking VAS Emin), statistically significantly higher Bad Effects VAS and Any Effects VAS scores, and higher Good Effects VAS scores over time (TA\_AUE). There were no statistically significant effects on pupil diameter or measures of withdrawal relative to PBO.
- Compared to Oxy API 60 mg, ONU 60/30 mg chewed was associated with statistically significantly greater disliking (Drug Liking Emin), negative effects (Bad Effects VAS), and subjective withdrawal (SOWS), and statistically significantly lower balance (Drug Liking VAS, Take Drug Again VAS, and Overall Drug Liking), positive (Good Effects VAS, High VAS), other (Any Effects VAS over time [TA\_AUE]), drowsiness/alertness (less drowsy), and pupillary effects.
- There were few statistically significant differences between ONU 60/30 mg intact and ONU 60/30 mg chewed. However, ONU 60/30 mg chewed was associated with statistically significantly greater disliking (Drug Liking VAS Emin), higher scores on Bad Effects VAS, higher Any Effects VAS Emax, and greater self-reported withdrawal effects.
- Review of the distribution and individual subject responses on the OOWS, SOWS, and negative VAS measures suggests that most subjects experienced a mild negative effect of ONU 60/30 mg chewed, with a small subset of subjects showing mild withdrawal-like responses.

## 2.2 Data Location

The analysis datasets are located at

<\\CDSESUB1\evsprod\NDA205777\0000\m5\datasets\onu1008\analysis\adam\datasets>

## 2.3 Reviewer's Assessment

All analyses were conducted from the stand point of the pharmacodynamics analysis.

### 2.3.1 Descriptive Statistics

The descriptive statistics for the Emax endpoint for primary variable Drug High and secondary variable Drug Liking VAS are provided in Table 1 and Table 2. Mean score over time for Drug High and Drug Liking VAS are shown in Figure 1 and Figure 2. Heatmap of Emax for Drug High and Drug Liking VAS by Subject by Treatment are provided in Figure 3 and Figure 4.

Table 1 summarizes the mean, standard error, minimum, the first quartile (Q1), median, the third quartile (Q3), and maximum for four treatments in the study. Table 2 summarizes the treatment differences between ONU chewed vs. ONU intact, ONU chewed vs. Oxy, Oxy vs. ONU intact for Emax of Drug High and Drug Liking VAS.

**Table 1. E<sub>max</sub> Descriptive Statistics for Drug Liking, Drug High, PD population (N=29)**

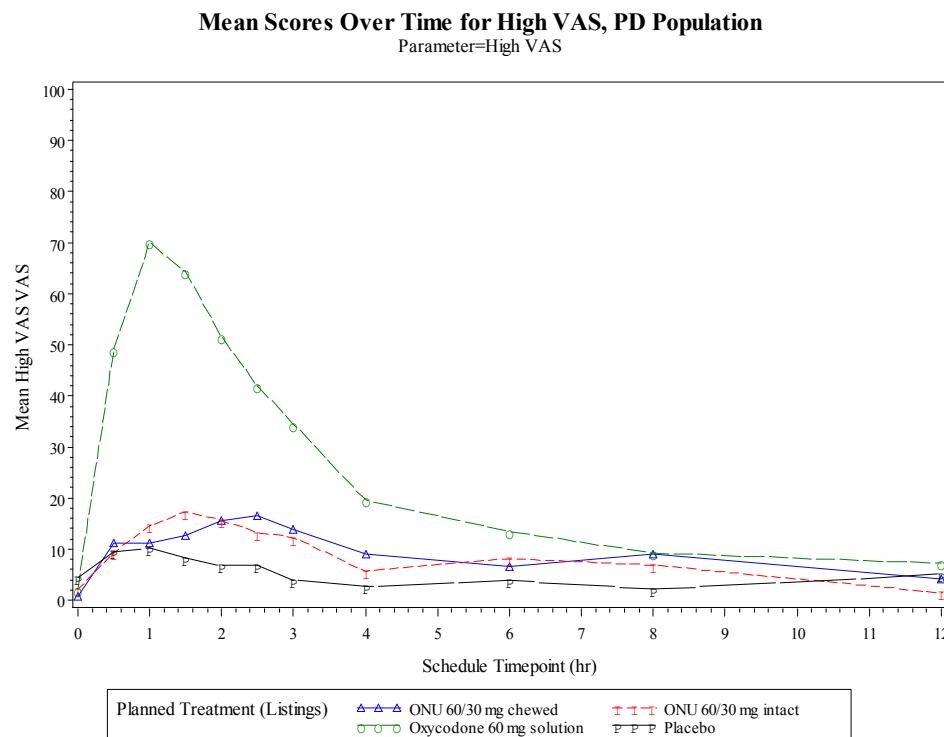
Parameter	Planned Treatment	Mean	Std Dev	Min	Q1	Median	Q3	Max
High VAS	ONU 60/30 mg chewed	27.7	35.1	0.0	0.0	1.0	51.0	100.0
	ONU 60/30 mg intact	20.6	27.7	0.0	0.0	1.0	51.0	73.0
	Oxycodone 60 mg solution	77.9	26.8	0.0	64.0	86.0	100.0	100.0
	Placebo	21.9	27.5	0.0	0.0	1.0	50.0	82.0
Drug Liking VAS	ONU 60/30 mg chewed	54.6	17.3	0.0	50.0	51.0	51.0	100.0
	ONU 60/30 mg intact	54.7	10.6	50.0	50.0	51.0	51.0	99.0
	Oxycodone 60 mg solution	77.9	20.2	50.0	60.0	78.0	100.0	100.0
	Placebo	54.4	11.5	50.0	50.0	51.0	51.0	100.0

For Drug High VAS, from table 1, mean E<sub>max</sub> score for placebo and ONU intact were low, 21.9 and 20.6 respectively, mean score for ONU chewed were slightly higher with score 27.7, while mean E<sub>max</sub> for Oxy API was very high with score 77.9, around 3 times as ONU chewed, ONU intact and placebo. Figure 1 shows mean scores for High VAS over time for the four treatments. Mean E<sub>max</sub> scores of Oxy API increased rapidly to the peak of ~70 at hour one post-dose. ONU intact, ONU chewed and placebo had similar mean E<sub>max</sub> score over the first 3 to 4 hours post-dose. Over the time, mean score of ONU intake and ONU chewed were only slight higher than the mean score of placebo.

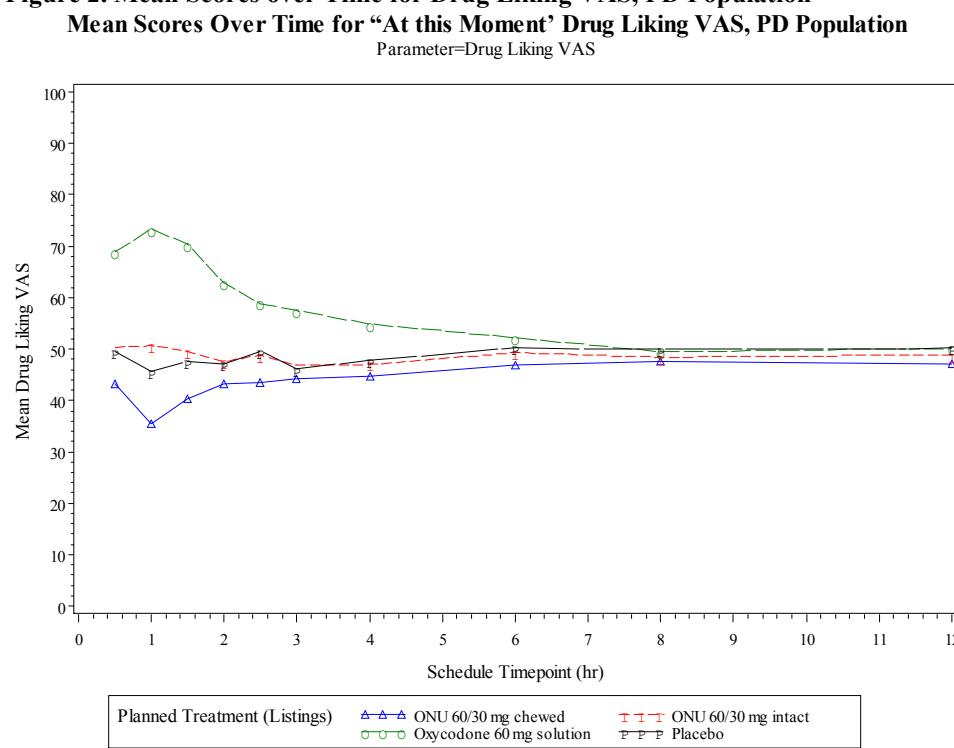
For Drug Liking VAS, as can be seen in table 1, the mean score of placebo (54.4) is slightly higher than the neutral range, first quartile, median and third quartile of placebo was within the neutral range which is ~50. Mean E<sub>max</sub> for ONU chewed and ONU intact are similar as placebo, but mean score for OXY API is high, with score 77.9.

We can further explore the individual's Emax score for each treatment from Figure 3 and Figure 4. For example, in Figure 4 the Drug Liking VAS for each subject, one subject has the score 100 in placebo group, 4 out of 29 subjects (13.8%) had the placebo score >60, these high score explained why the mean Emax score of placebo is higher than the neutral range.

**Figure 1. Mean Scores over Time for High VAS, PD Population**



**Figure 2. Mean Scores over Time for Drug Liking VAS, PD Population**



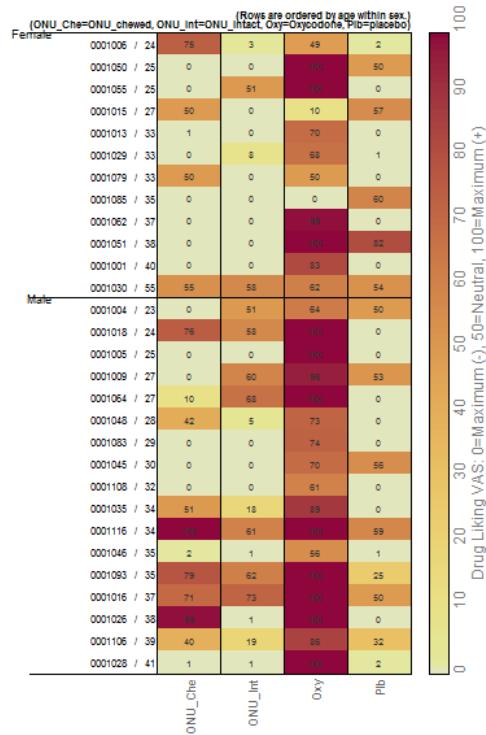
**Table 2. Treatment difference of Emax for Drug High, Drug Liking, PD population (N=29)**

Parameter	Variable	Mean	Std Dev	Min	Q1	Median	Q3	Max	t Value	Pr >  t
High VAS	ONU_chew_VS_ONU_intact	7.0	35.7	-60.0	0.0	0.0	21.0	98.0	1.06	0.2973
	ONU_chew_VS_OXY	-50.3	42.1	-100.0	-90.0	-61.0	-21.0	40.0	-6.43	<.0001
	OXY_VS_ONU_intact	57.3	30.4	0.0	38.0	60.0	74.0	100.0	10.15	<.0001
Drug Liking VAS	ONU_chew_VS_ONU_intact	-0.1	17.7	-51.0	0.0	0.0	1.0	49.0	-0.03	0.9751
	ONU_chew_VS_OXY	-23.3	24.2	-99.0	-44.0	-15.0	-1.0	5.0	-5.18	<.0001
	OXY_VS_ONU_intact	23.2	22.7	-48.0	8.0	23.0	44.0	50.0	5.50	<.0001

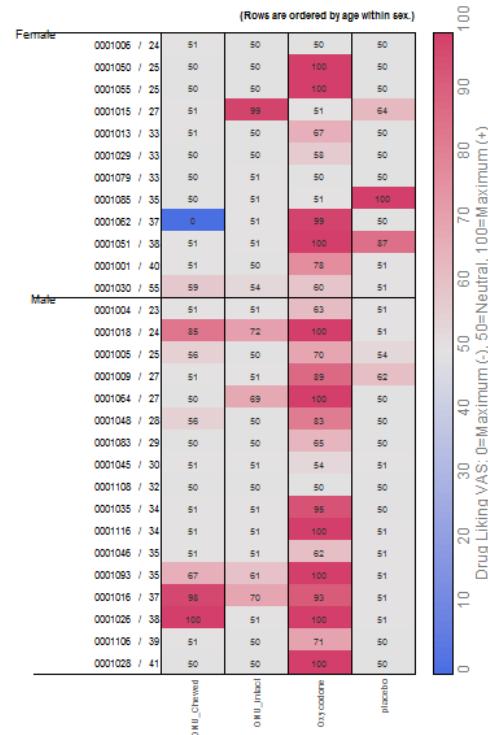
For the treatment difference comparison of high VAS, there is no significant difference between ONU chewed and ONU intact ( $p>0.05$ ), but there are significant statistically differences between the comparisons of ONU chewed and OXY ( $P<0.001$ ), ONU intact and OXY ( $P<0.001$ ). Similar results were observed for the Drug Liking VAS comparison.

Individual  $E_{max}$  scores are displayed by subject for all treatments in Figures 3-4, the rows of the table plot are ordered by age within sex. One can visually compare the  $E_{max}$  for each patient at different treatment, and the heat map also showed that more subjects had higher Drug High and Drug Liking VAS scores in OXY group comparing with ONU intact, ONU chewed and placebo.

**Figure 3. Emax for Drug High by Subject x Treat**



**Figure 4. Emax for Drug Liking by Subject x Treat**



### 2.3.2 Primary Analysis

#### Statistical model fitting

The reviewer analyzed the hypotheses of the primary objective using the mixed-effect model, the final model the reviewer used is treatment, period and sequence as fixed effects and subject

nested within sequence as a random effect. Table 3 is the analysis results for Emax of Drug High, Table 4 is the analysis results for Emax of Drug Liking VAS.

Table 3 shows that a significant treatment effect for this primary endpoint ( $p<0.0001$ ). Placebo and ONU intact have similar least square mean (21.8 and 20.28 respectively), ONU chewed has slightly higher least square mean (27.57), while OXY has the highest least square mean (77.48), around 2-3 times as the other treatments. From treatment contrast, the least square mean difference of ONU chewed, ONU intact and placebo are significant different from OXY ( $P<0.0001$ ). Similar results are observed from table 4.

Note: Sponsor didn't do the type I error rate adjustment in this study. Holm's procedure is recommended for the type I error rate adjustment for the multiple comparisons.

**Table 3. Analysis Results for High VAS Emax , PD Population.**

	LS Means	StdE	Pr >  t	Lower	Upper
Treatments					
ONU 60/30 mg chewed	27.57	4.82	<.0001	17.99	37.16
ONU 60/30 mg intact	20.28	4.82	<.0001	10.69	29.87
Oxycodone 60 mg solution	77.48	4.82	<.0001	67.90	87.07
Placebo	21.80	4.82	<.0001	12.21	31.38
Contrasts (difference)					
ONU 60/30 mg chewed - ONU 60/30 mg intact	7.30	6.70	0.2795	-6.04	20.63
ONU 60/30 mg chewed - Oxy 60 mg solution	-49.91	6.69	<.0001	-63.23	-36.59
ONU 60/30 mg chewed - Placebo	5.78	6.69	0.3906	-7.54	19.09
ONU 60/30 mg intact - Oxy 60 mg solution	-57.20	6.69	<.0001	-70.52	-43.89
ONU 60/30 mg intact - Placebo	-1.52	6.69	0.8211	-14.84	11.80
Oxy 60 mg solution - Placebo	55.69	6.70	<.0001	42.35	69.02

**Table 4. Analysis Results for Drug Liking VAS Emax , PD Population.**

	LS Mean	StdE	Pr >  t	Lower	Upper
Treatments					
ONU 60/30 mg chewed	54.09	2.59	<.0001	48.94	59.24
ONU 60/30 mg intact	54.16	2.59	<.0001	49.01	59.31
Oxycodone 60 mg solution	77.47	2.59	<.0001	72.32	82.62
Placebo	53.89	2.59	<.0001	48.74	59.04
Contrasts (difference)					
ONU 60/30 mg chewed - ONU 60/30 mg intact	-0.07	3.60	0.9841	-7.23	7.09
ONU 60/30 mg chewed - Oxy 60 mg solution	-23.38	3.60	<.0001	-30.53	-16.22
ONU 60/30 mg chewed - Placebo	0.20	3.60	0.9547	-6.95	7.36
ONU 60/30 mg intact - Oxy 60 mg solution	-23.30	3.60	<.0001	-30.46	-16.15
ONU 60/30 mg intact - Placebo	0.28	3.60	0.9389	-6.88	7.43
Oxy 60 mg solution - Placebo	23.58	3.60	<.0001	16.42	30.74

### 2.3.3 Secondary Analysis

Besides the analysis of the secondary endpoint Drug Liking VAS, the reviewer also analyzed the other secondary endpoints, they are: Good Effects VAS, Bad Effects VAS, Pupil Diameter (mm), Overall Drug Liking VAS and Take Drug Again VAS. The final mixture-effect model the reviewer used is treatment, period and sequence as fixed effects and subject nested within sequence as a random effect.

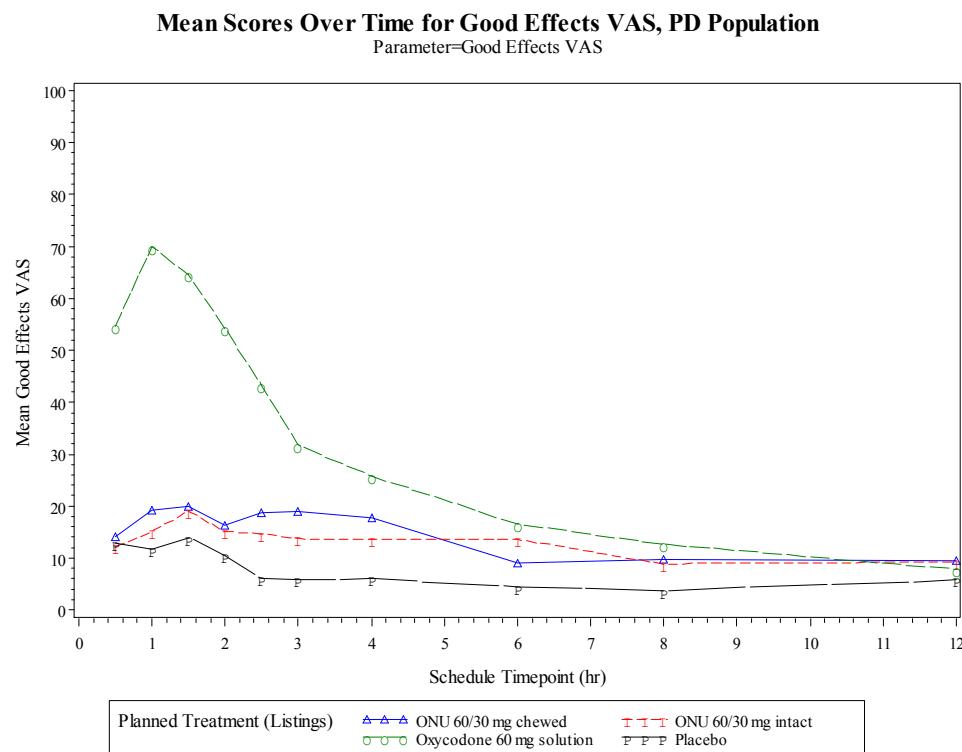
### Descriptive Statistics

The descriptive statistics of Emax for secondary endpoint variables: Good Effects VAS, Bad Effects VAS and Pupil Diameter, Overall Drug Liking VAS (at hour 12) and Take Drug Again VAS (at hour 12) are provided in Table 5. Mean score over time for Bad Effects VAS, Good Effects VAS and Pupil Diameter are shown in Figure 5, Figure 6 and Figure 7.

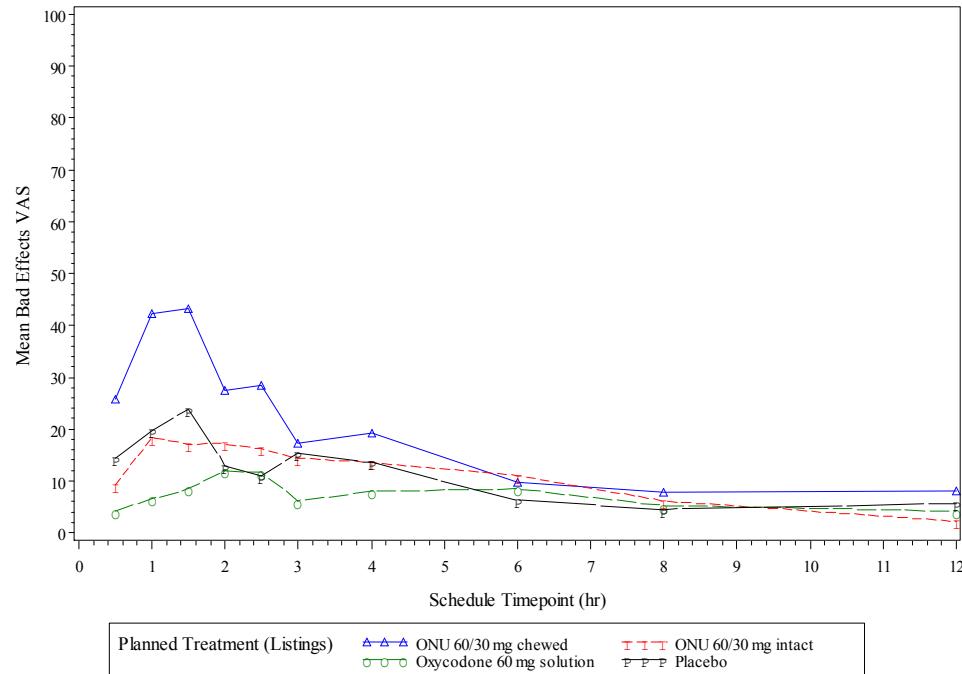
**Table 5. Emax Descriptive Statistics for Good Effects VAS, Bad Effects VAS, Pupil Diameter, Overall Drug Liking VAS (at hour 12) and Take Drug Again VAS (at hour 12), PD population (N=29)**

Parameter	Treatment	Mean	Std Dev	Min	Q1	Median	Q3	Max
Good Effects VAS	ONU 60/30 mg chewed	37	33.6	0	0	50	58	100
	ONU 60/30 mg intact	24.3	29.5	0	0	2	51	85
	OXY 60 mg solution	77.8	28.4	0	63	90	100	100
	Placebo	23.8	30.5	0	0	2	51	100
Bad Effects VAS	ONU 60/30 mg chewed	60.1	37.2	0	50	57	100	100
	ONU 60/30 mg intact	29.2	36.1	0	0	1	51	100
	OXY 60 mg solution	27.2	28.3	0	1	15	50	100
	Placebo	30.8	37	0	0	4	56	100
Pupil Diameter (mm)	ONU 60/30 mg chewed	5.9	1.1	3.3	5.1	6.4	6.6	7.4
	ONU 60/30 mg intact	5.9	0.9	4.0	5.4	6.2	6.6	7.1
	OXY 60 mg solution	5.5	1.1	3.5	4.6	6.0	6.4	6.9
	Placebo	6.0	0.9	3.9	5.5	6.2	6.6	7.2
Overall Drug Liking VAS (hour 12)	ONU 60/30 mg chewed	44.8	19	0	50	50	51	77
	ONU 60/30 mg intact	48.1	14.9	0	50	50	50	90
	OXY 60 mg solution	60.3	15.4	50	50	50	69	100
	Placebo	48.1	8.3	7	50	50	50	52
Take Drug Again VAS (hour 12)	ONU 60/30 mg chewed	32.6	31.7	0	0	50	51	100
	ONU 60/30 mg intact	38.5	30.7	0	0	50	51	100
	OXY 60 mg solution	61.4	31.6	0	50	50	100	100
	Placebo	41.5	27.1	0	33	50	50	100

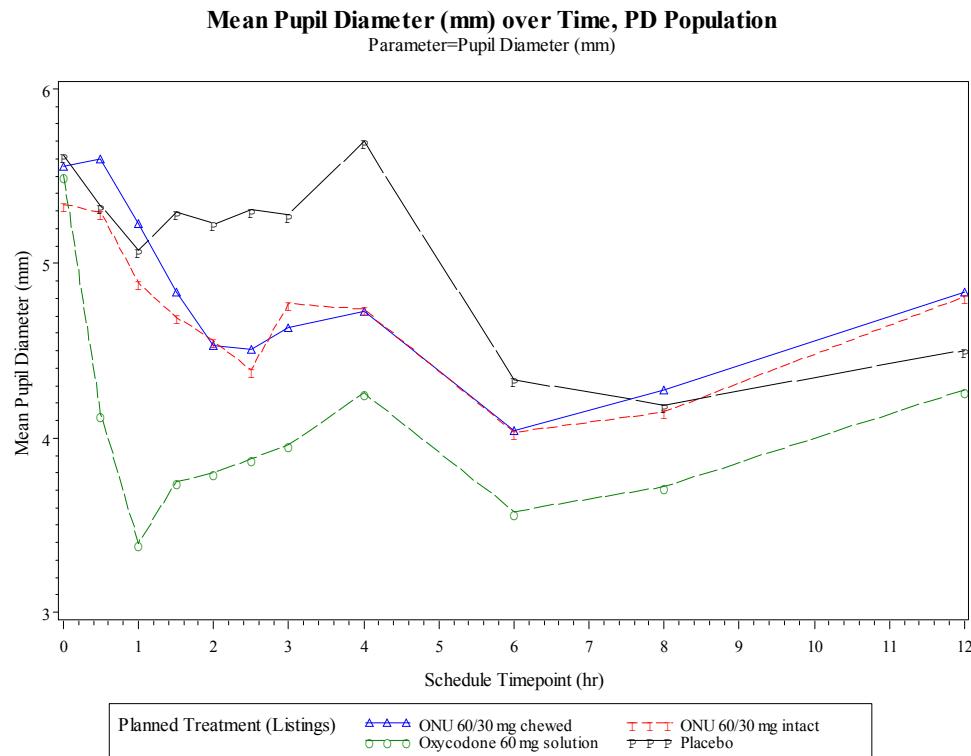
**Figure 5. Mean Scores over Time for Good Effects VAS, PD Population**



**Figure 6. Mean Scores over Time for Bad Effects VAS, PD Population**  
**Mean Scores Over Time for Bad Effects VAS, PD Population**  
Parameter=Bad Effects VAS



**Figure 7. Mean Pupil Diameter (mm) over Time, PD Population**



From table 5 we can see for the Good Effect VAS, Mean Emax score for OXY is significant higher than the other three treatments. For the Bad Effect VAS, there is no big difference among these four treatments after hour 3. The mean Pupil Diameter (mm) in OXY group is lower than the other three treatments over time. OXY mean score at hour 12 for Overall Drug Liking VAS is higher than the other three treatments, while there is no significant difference among these three treatments. Similar results are observed from Take Drug Again VAS at hour 12.

Figure 5 shows that for the mean scores over time for Good Effect VAS, OXY were much higher than the other three treatments from hour 1 to hour 3. For the Bad Effect VAS, Figure 6 shows there is no significant mean scores difference among ONU intact, OXY and placebo, however, ONU chewed had higher mean score for the first three hours. Figure 7 is the mean pupil diameter over time, OXY decreased rapidly in pupil diameter that peaked at 1 hour post-dose and remained lower than the other three treatments until approximately 8 hours post-dose.

### Statistical model fitting

The reviewer analyzed the hypotheses of the secondary objective using the mixed-effect model, the final model the reviewer used is treatment, period and sequence as fixed effects and subject nested within sequence as a random effect. Table 6 to Table 8 are the analysis results for  $E_{\max}$  of Good Effect VAS, Bad Effect VAS and Pupil Diameter (mm) respectively. Table 9 and Table 10 are the analysis result for Overall Drug Liking VAS and Take Drug Again VAS at hour 10 respectively.

Table 6 to Table 10 showed that all treatments are significant ( $P$  value<0.0001). Except for Bad Effect VAS, the analysis results for Good Effect VAS, Pupil Diameter, Overall Drug Liking VAS

and Take Drug Again VAS are similar, the OXY scores were significantly higher than the scores for the other three treatments. There were few significant differences between ONU chewed and ONU intact. For the comparison of ONU intact and placebo, no significant differences were observed. For the Bad Effect VAS, table 7 shows no significant difference between OXY and placebo ( $P$  value=0.5785), but there is significant different for the comparison of ONU chewed with the other three treatments.

**Table 6. Analysis Results for Good Effect VAS Emax , PD Population.**

	LS Mean	StdE	Pr >  t	Lower	Upper
Treatments					
ONU 60/30 mg chewed	35.63	4.97	<.0001	25.74	45.51
ONU 60/30 mg intact	23.04	4.97	<.0001	13.16	32.93
Oxycodone 60 mg solution	76.47	4.97	<.0001	66.58	86.35
Placebo	22.13	4.97	<.0001	12.25	32.02
Contrasts (difference)					
ONU 60/30 mg chewed - ONU 60/30 mg intact	12.58	6.91	0.0723	-1.17	26.33
ONU 60/30 mg chewed - Oxy 60 mg solution	-40.84	6.90	<.0001	-54.57	-27.11
ONU 60/30 mg chewed - Placebo	13.49	6.90	0.054	-0.24	27.23
ONU 60/30 mg intact - Oxy 60 mg solution	-53.42	6.90	<.0001	-67.15	-39.69
ONU 60/30 mg intact - Placebo	0.91	6.90	0.8951	-12.82	14.65
Oxy 60 mg solution - Placebo	54.33	6.91	<.0001	40.59	68.08

**Table 7. Analysis Results for Bad Effect VAS Emax , PD Population.**

	LS Mean	StdE	Pr >  t	Lower	Upper
Treatments					
ONU 60/30 mg chewed	58.23	5.31	<.0001	47.67	68.80
ONU 60/30 mg intact	26.05	5.31	<.0001	15.49	36.61
Oxycodone 60 mg solution	24.37	5.31	<.0001	13.80	34.93
Placebo	28.48	5.31	<.0001	17.92	39.05
Contrasts (difference)					
ONU 60/30 mg chewed - ONU 60/30 mg intact	32.19	7.38	<.0001	17.50	46.87
ONU 60/30 mg chewed - Oxy 60 mg solution	33.87	7.37	<.0001	19.20	48.54
ONU 60/30 mg chewed - Placebo	29.75	7.37	0.0001	15.08	44.42
ONU 60/30 mg intact - Oxy 60 mg solution	1.68	7.37	0.8201	-12.99	16.35
ONU 60/30 mg intact - Placebo	-2.44	7.37	0.7419	-17.11	12.24
Oxy 60 mg solution - Placebo	-4.12	7.38	0.5785	-18.81	10.57

**Table 8. Analysis Results for Pupil Diameter Emax , PD Population.**

	LS Mean	StdE	Pr >  t	Lower	Upper
Treatments					
ONU 60/30 mg chewed	5.98	0.15	<.0001	5.68	6.27
ONU 60/30 mg intact	5.95	0.15	<.0001	5.66	6.25
Oxycodone 60 mg solution	5.61	0.15	<.0001	5.32	5.90
Placebo	6.14	0.15	<.0001	5.85	6.43
Contrasts (difference)					
ONU 60/30 mg chewed - ONU 60/30 mg intact	0.02	0.11	0.845	-0.20	0.25
ONU 60/30 mg chewed - Oxy 60 mg solution	0.37	0.11	0.0018	0.14	0.59
ONU 60/30 mg chewed - Placebo	-0.16	0.11	0.1592	-0.39	0.06
ONU 60/30 mg intact - Oxy 60 mg solution	0.34	0.11	0.0033	0.12	0.57
ONU 60/30 mg intact - Placebo	-0.18	0.11	0.1097	-0.41	0.04
Oxy 60 mg solution - Placebo	-0.53	0.11	<.0001	-0.76	-0.30

**Table 9. Analysis Results for Overall Drug Liking VAS Emax at hour 12 , PD Population.**

	LS Mean	StdE	Pr >  t	Lower	Upper
Treatments					
ONU 60/30 mg chewed	44.72	2.58	<.0001	39.58	49.87
ONU 60/30 mg intact	48.67	2.58	<.0001	43.52	53.81
Oxycodone 60 mg solution	60.48	2.58	<.0001	55.34	65.62
Placebo	48.24	2.58	<.0001	43.09	53.38
Contrasts (difference)					
ONU 60/30 mg chewed - ONU 60/30 mg intact	-3.94	3.59	0.276	-11.09	3.21
ONU 60/30 mg chewed - Oxy 60 mg solution	-15.76	3.59	<.0001	-22.90	-8.61
ONU 60/30 mg chewed - Placebo	-3.51	3.59	0.331	-10.65	3.63
ONU 60/30 mg intact - Oxy 60 mg solution	-11.81	3.59	0.0015	-18.96	-4.67
ONU 60/30 mg intact - Placebo	0.43	3.59	0.9047	-6.71	7.58
Oxy 60 mg solution - Placebo	12.24	3.59	0.001	5.09	19.40

**Table 10. Analysis Results for Take Drug Again VAS Emax at hour 12 , PD Population**

	LS Mean	StdE	Pr >  t	Lower	Upper
Treatments					
ONU 60/30 mg chewed	29.65	4.46	<.0001	20.78	38.52
ONU 60/30 mg intact	37.13	4.46	<.0001	28.25	46.00
Oxycodone 60 mg solution	58.92	4.46	<.0001	50.05	67.79
Placebo	39.18	4.46	<.0001	30.31	48.06
Contrasts (difference)					
ONU 60/30 mg chewed - ONU 60/30 mg intact	-7.47	6.10	0.224	-19.61	4.66
ONU 60/30 mg chewed - Oxy 60 mg solution	-29.27	6.09	<.0001	-41.39	-17.15
ONU 60/30 mg chewed - Placebo	-9.53	6.09	0.1216	-21.65	2.59
ONU 60/30 mg intact - Oxy 60 mg solution	-21.79	6.09	0.0006	-33.92	-9.67
ONU 60/30 mg intact - Placebo	-2.06	6.09	0.7366	-14.18	10.07
Oxy 60 mg solution - Placebo	19.74	6.10	0.0018	7.60	31.88

### 3. Conclusion

The study was validated using mean statistical differences between the medicated products and the placebo. As to the primary and secondary analysis, the reviewer analyzed the primary endpoint Drug High and the secondary endpoint Drug Liking VAS, Good Effects VAS, Bad Effects VAS, Pupil Diameter (mm), Overall Drug Liking VAS (at hour 12) and Take Drug Again VAS (at hour 12). The results from the statistical reviewer's analyses establish that:

- For the comparison of placebo and OXY, except for the Bad Effect VAS, there were statistically significant differences between these two treatments on all subjective measures. Pupil diameter was significantly lower following administration of OXY.
- For the comparison of ONU chewed and OXY, there were significant statistically differences on all subjective measures. ONU chewed was associated with greater Bad Effect VAS, higher pupil diameter and significantly lower Drug Liking, Good Effects, Bad Effects, Overall Drug Liking (at hour 12) and Take Drug Again VAS (at hour 12).
- For the comparison of ONU intact and OXY, except for the Bad Effect VAS, there were significant statistically differences on all subjective measures.
- There were few significant differences between ONU chewed and ONU intact. However, ONU chewed showed marginally higher Good Effect VAS, significantly higher score in Bad Effect VAS.
- For the comparison of ONU intact and placebo, no significant differences were observed on all subjective measures.
- Effects on the comparison of ONU chewed and placebo were minimal, no significant differences were observed, however, ONU chewed had marginally higher score on Good Effect VAS, significantly higher Bad Effect VAS

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Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Science  
Office of Biostatistics

# Statistical Review and Evaluation

## CLINICAL STUDIES

<b>NDA/Serial Number:</b>	205777
<b>Drug Name:</b>	Oxycodone-Naloxone tablets (ONU)
<b>Indication:</b>	(b) (4)
<b>Study number:</b>	ONU1007 (UPN 1608)
<b>Applicant:</b>	Purdue Pharma L.P.
<b>Date(s):</b>	Date of Document: Sep 23,2013 Consult received date: Nov 11, 2013 PDUFA date: Completion date: 01/10/2014
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<b>Biometrics Division:</b>	DBVI
<b>Statistical Reviewer:</b>	Anna Sun, Ph.D., Mathematical Statistician, OB/DBVI
<b>Concurring Reviewers:</b>	Yi Tsong, Ph.D., Acting Division Director, OB/DBVI
<b>Medical Division:</b>	Control Substance Staff
<b>The CSS Team:</b>	James Tolliver, Ph.D., Pharmacologist, OCD/CSS Silvia Calderon, Ph.D., Pharmacology Team Leader, OCD/CSS
<b>Project Manager:</b>	Sandra Saltz, Project Manager, CSS

**Keywords:** *Crossover design, Drug abuse potential study, Self-reported endpoint, Multiple endpoints*

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## 1. Executive Summary

Study ONU1007 (UPN 1608) was a Single-Center, Randomized, Double-Blind Study in Recreational Opioid Users to Evaluate the Abuse Potential, Pharmacokinetics, and Safety of Oxycodone/Naloxone (ONU) Tablets when Chewed or Administered Intact via the Oral Route.

The objectives of the study were to evaluate the following:

- The oral abuse potential and pharmacodynamic (PD) effects of chewed ONU and intact ONU compared to oxycodone oral solution and placebo (PBO) in healthy, adult, non-physically dependent recreational opioid users with a history of oral chewing abuse/misuse.
- The safety and tolerability of orally administered chewed and intact ONU in healthy, adult, non-physically dependent recreational opioid users with a history of oral chewing abuse/misuse.
- The comparative PK profile of orally administered chewed and intact ONU compared to oxycodone oral solution

There were four treatments in the study. 37 subjects were randomized (including 1 replacement subject for an early withdrawal) and 36 subjects were analyzed. Subjects received each of the treatments outlined below in a randomized, double-blinded, triple-dummy fashion (one per Treatment visit):

Treatment A: ONU 40/20 mg tablet, intact + ONU PBO tablet, chewed + PBO oral solution

Treatment B: ONU PBO tablet, intact + ONU 40/20 mg tablet, chewed + PBO oral solution

Treatment C: ONU PBO tablet, intact + ONU PBO tablet, chewed + oxycodone oral solution

Treatment D: ONU PBO tablet, intact + ONU PBO tablet, chewed + PBO oral solution

Pharmacodynamic Conclusions:

The study was validated using mean statistical differences between the medicated products and the placebo for the primary endpoint  $E_{max}$  of the two primary measures of relative abuse potential, Drug Liking VAS and Drug High VAS.

$E_{max}$  values of Drug liking VAS for Oxy API and ONU chewed were both significantly higher than for ONU intact. In contrast, there is no significant difference between Oxy API and ONU chewed.  $E_{max}$  values of Drug high VAS for Oxy API and ONU chewed were both significantly higher than for ONU intact, but there is no significant differences between Oxy API and ONU chewed were observed.

In addition, mean peak scores of Drug liking VAS and Drug high VAS for ONU Intact were generally delayed compared to Oxy API and ONU chewed.

## **2. Review Report on Study ONU1007 (UPN 1608)**

### **2.1 Overview**

ONU ( [REDACTED] <sup>(b) (4)</sup> 10/5 mg, 20/10 mg, and 40/20 mg oxycodone/naloxone) is a [REDACTED] <sup>(b) (4)</sup> combination formulation of oxycodone hydrochloride and naloxone hydrochloride [REDACTED] <sup>(b) (4)</sup> pain.

This study was designed to evaluate the abuse potential, PK profile, and safety of orally-administered ONU tablets when chewed or intact in subjects with a history of recreational opioid use who are not physically dependent on opioids.

#### **2.1.1 Objectives of the study**

The objectives of the study were to evaluate the following:

- The oral abuse potential and pharmacodynamic (PD) effects of chewed ONU and intact ONU compared to oxycodone oral solution and placebo (PBO) in healthy, adult, non-physically dependent recreational opioid users with a history of oral chewing abuse/misuse.
- The safety and tolerability of orally administered chewed and intact ONU in healthy, adult, non-physically dependent recreational opioid users with a history of oral chewing abuse/misuse.
- The comparative PK profile of orally administered chewed and intact ONU compared to oxycodone oral solution.

#### **2.1.2 Study design**

This was a single-center, double-blind, randomized, crossover study. The study consisted of 4 phases:

- Screening: Visit 1 for inclusion/exclusion screening and Visit 2 for a naloxone challenge test to screen for symptoms of opioid withdrawal.
- Qualification: Visit 3 for a randomized, crossover pharmacologic qualification (oxycodone and PBO) to ensure tolerability, appropriate reporting of positive subjective effects, and to demonstrate that subjects were able to complete the study procedures (including the chewing procedures).
- Treatment: Visit 4 to Visit 7 where each of the following single-dose treatments were administered (1 per visit): ONU 40/20 mg tablet, intact + ONU PBO tablet, chewed + PBO oral solution; ONU PBO tablet, intact + ONU 40/20 mg tablet, chewed + PBO oral solution; ONU PBO tablet, intact + ONU PBO tablet, chewed + oxycodone oral solution; ONU PBO tablet, intact + ONU PBO tablet, chewed + PBO oral solution
- Follow-up: Visit 8 for a safety follow-up, 3 to 7 days after the last Treatment Phase drug administration

#### **Outcome Variables**

Primary Pharmacodynamics outcome variables were 'at this moment' Drug Liking visual analog scale (VAS) and High VAS ( $E_{max}$ , TA\_AUE). However, conclusions regarding the abuse

potential of ONU when administered via the oral route will consider responses on all measures, which can be categorized as follows:

Balance of effects:

- ‘At the moment’ Drug Liking VAS (maximum effect [ $E_{max}$ ], minimum effect [ $E_{min}$ ], time averaged area under the effect curve [TA\_AUE])
- Overall Drug Liking (ODL) VAS ( $E_{max}$ ,  $E_{min}$ , end-of-day [12 hours] and next day [24 hours] mean scores)
- Take Drug Again (TDA) VAS ( $E_{max}$ , end-of-day and next day mean scores)
- Subjective Drug Value (SDV) ( $E_{max}$  end-of-day and next day mean scores)

Positive/euphoric effects:

- High VAS ( $E_{max}$ , TA\_AUE)
- Good Effects VAS ( $E_{max}$ , TA\_AUE)
- ARCI MBG scale ( $E_{max}$ , TA\_AUE)

Negative effects:

- Bad Effects VAS ( $E_{max}$ , TA\_AUE)
- Feeling Sick VAS ( $E_{max}$ , TA\_AUE)

Sedative effects:

- Drowsiness/Alertness VAS ( $E_{min}$ , TA\_AUE)

Other effects:

Any Effects VAS ( $E_{max}$ , TA\_AUE)

Objective measure:

- Pupillometry (maximum pupil constriction [MPC], time-averaged pupillometry area over the curve [TA\_PAOC] relative to baseline)

Time to peak effect ( $TE_{max}$ ,  $TE_{min}$  and/or  $T_{MPC}$ , as applicable) will also be calculated for ARCI, VAS (excluding ODL and TDA), and pupillometry measures.

### **2.1.3 Abuse potential measure and data collection times**

Drug Liking VAS and Drug High VAS are the primary abuse potential variables, measured predose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hours post-dose. The secondary variable VAS (Overall Drug Liking, Take Drug Again) and Subjective Drug Value were measured at 12 and 24 hours post-dose, ARCI MBG was measured at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hours post-dose and pupillometry was measured at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hours post-dose.

### **2.1.4 Number of subjects**

A total of 114 subjects were screened of whom 65 subjects were eligible to proceed to the Qualification Phase. Of the 65 subjects who were dosed during the Qualification Phase, 28 (43.1%) subjects did not pass the Qualification Phase and 37 (56.9%) subjects were randomized to the Treatment Phase and received at least 1 dose of the study drug. One (2.7%) subject discontinued after Treatment Period 1 for administrative reasons. In total, 36 subjects completed all 4 Treatment Periods including all protocol-specified procedures and assessments. All 36 subjects were included in the PK and PD populations.

## **2.1.5 Statistical methodologies used in the Sponsor's analyses**

### **Hypothesis Testing**

For each of the parameters, the null hypothesis was: there is no treatment effect, and the alternative hypothesis was: there is a treatment effect. For each of the contrasts or pairwise comparisons, the null hypothesis was: there is no treatment effect difference between the tested pair, and the alternative hypothesis was: there is a treatment effect difference between the tested pair.

A 5% Type I error rate with a P value less than 0.05 was considered as statistically significant for all individual hypothesis tests. All statistical tests were performed using two-tailed significance criteria.

### **Analysis of Pharmacodynamic Assessments**

Pharmacodynamic data at each time point were summarized by descriptive statistics and presented graphically (where appropriate) for the Qualification Phase and for the Treatment Phase. Derived endpoints were summarized using descriptive statistics and box-plots. Outliers were listed by measure and parameter.

Pharmacodynamic endpoints for the Treatment Phase (maximum effect [ $E_{max}$ ], minimum effect [ $E_{min}$ ], maximum pupil constriction [MPC] and/or time-averaged area under the effect curve [TA\_AUE]/ time-averaged pupillometry area over the curve [TA\_PAOC], as appropriate) were analyzed using a mixed-effect model for a crossover study. Time to maximum effect and time to minimum effect ( $TE_{max}$  and  $TE_{min}$ ) were summarized descriptively; however, additional analyses could have been undertaken, if appropriate. From each model, means, 95% confidence intervals, and P values for treatments and treatment differences were computed. The Benjamini and Hochberg procedure was used to control for Type I error arising from the multiple comparisons, as necessary. Tests for non-normality and homogeneity of variance were conducted for the primary measures. Nonparametric sensitivity analyses were employed, as necessary.

The contrasts to assess the abuse potential for the ONU formulation included:

- Oxycodone oral solution vs. PBO (reference)
- ONU (intact) vs. PBO
- ONU (intact) vs. oxycodone oral solution
- ONU (chewed) vs. PBO
- ONU (chewed) vs. oxycodone oral solution
- ONU (chewed) vs. ONU (intact)

## **2.1.6 Sponsor's Summary and Conclusions**

### **Pharmacodynamic Conclusions**

This study demonstrated that Oxy API showed significantly greater effects compared to PBO on the majority of endpoints, thereby confirming the validity of the study. ONU administered via the intended route (oral ONU intact) showed greater effects than PBO but significantly lower effects compared to Oxy API and ONU chewed. In addition, effects of ONU were generally delayed compared to Oxy API and ONU chewed. However, chewed ONU tablets showed significantly

greater effects than ONU intact and were not significantly different from Oxy API. Brief summary conclusions are provided below for each type of measure:

#### Balance of Effects

- ‘At this moment’ Drug Liking  $E_{max}$  values (primary) for Oxy API and ONU tablets (both intact and chewed) were significantly higher compared to PBO.  $E_{max}$  values for Oxy API and ONU chewed were both significantly higher than that for ONU intact, and no significant differences between Oxy API and ONU chewed were observed.
- For secondary global measures (Overall Drug Liking VAS, Take Drug Again VAS, and SDV), administration of Oxy API and ONU (intact and chewed) resulted in a significantly higher  $E_{max}$  compared to PBO on all measures.  $E_{max}$  values for intact ONU were significantly lower than those for Oxy API and ONU chewed, which were not significantly different from each other.

#### Positive Effects

- $E_{max}$  on the High VAS (primary) was significantly higher than PBO for Oxy API and ONU (intact and chewed).  $E_{max}$  values for Oxy API and ONU chewed were also significantly higher than that for ONU intact and not significantly different from each other.
- For ARCI MBG and Good Effects VAS, the secondary measures of positive effects, the same pattern of results was observed as for High VAS.

#### Negative Effects

- Negative effects were modest in this study. For both measures of negative effects (Bad Effects and Feeling Sick VAS),  $E_{max}$  for Oxy API and ONU chewed did not differ from each other and each was significantly higher than that for PBO. For ONU intact,  $E_{max}$  was not significantly different from PBO for either measure. For Bad Effects,  $E_{max}$  for ONU intact was significantly lower than that for ONU chewed but not significantly different from that for Oxy API. For Feeling Sick,  $E_{max}$  for ONU intact was significantly different than those for Oxy API and ONU chewed.

#### Sedative and Other Effects

- For sedative and any effects, all active treatments (Oxy API and ONU intact and chewed) had significantly greater effects compared to PBO. As with other measures, administration of Oxy API and ONU chewed resulted in peak effects ( $E_{min}$  for Drowsiness/Alertness and  $E_{max}$  for Any Effects) that were significantly greater than those for ONU intact but not significantly different from each other.

#### Objective Effects

- For the objective measure of pupillometry, MPC was observed to be significantly higher for Oxy API and ONU (intact and chewed) compared to PBO. Consistent with results from most subjective effects, MPC measurements for Oxy API and ONU chewed were significantly greater than those for ONU intact and not significantly different from each other.

## 2.2 Data Location

The analysis datasets are located at  
<\\CDSESUB1\evsprod\NDA20577\0000\m5\datasets\onu1007\analysis\adam\datasets>

## 2.3 Reviewer's Assessment

All analyses were conducted from the stand point of the pharmacodynamics analysis.

### 2.3.1 Descriptive Statistics

The descriptive statistics for the Emax endpoint for primary variables Drug Liking and Drug High are provided in Table 1 and Table 2.  $E_{max}$  is calculated as the maximum effect in the first 8 hours in the review's analysis.

Table 1 summarizes the mean, standard error, minimum, the first quartile (Q1), median, the third quartile (Q3), and maximum for four treatments in the study. Table 2 summarizes the treatment differences between ONU chewed vs. ONU intact, ONU chewed vs. Oxy API, Oxy API vs. ONU intact for  $E_{max}$  of Drug Liking VAS and Drug High.

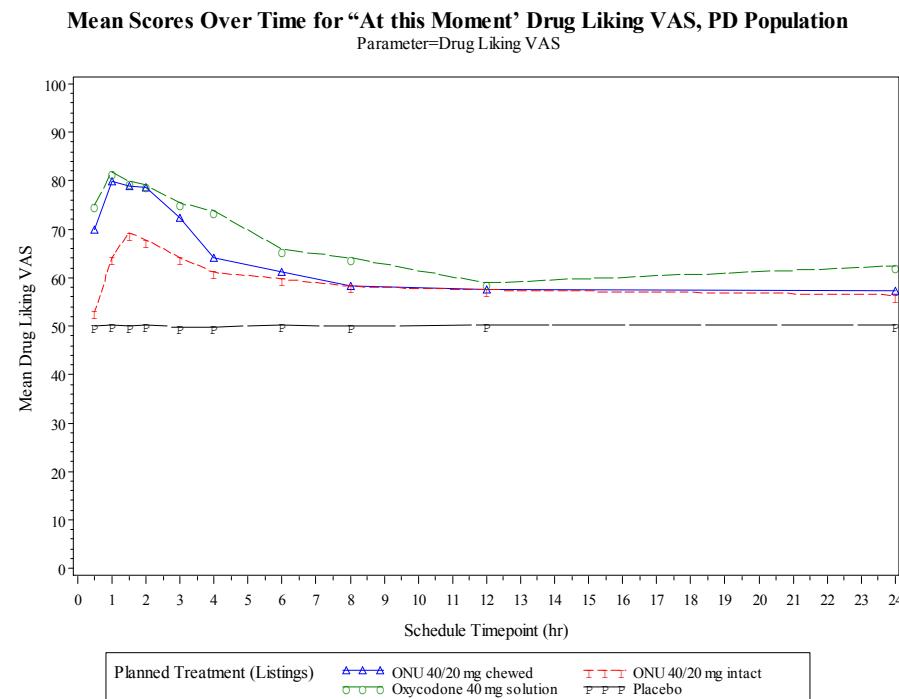
**Table 1.  $E_{max}$  Descriptive Statistics for Drug Liking, Drug High, PD population (N=36)**

Parameter	Planned Treatment	Mean	Std Dev	Min	Q1	Median	Q3	Max
Drug Liking VAS	ONU 40/20 mg chewed	86.3	16.0	51.0	72.5	96.0	100.0	100.0
	ONU 40/20 mg intact	72.5	19.0	50.0	53.5	73.5	86.0	100.0
	Oxy API 40 mg	88.5	16.9	50.0	79.0	100.0	100.0	100.0
	Placebo	50.8	0.6	50.0	50.0	51.0	51.0	52.0
High VAS	ONU 40/20 mg chewed	87.2	17.8	22.0	76.5	100.0	100.0	100.0
	ONU 40/20 mg intact	59.2	37.4	0.0	28.5	66.5	94.0	100.0
	Oxy API 40 mg	90.5	18.4	15.0	91.5	100.0	100.0	100.0
	Placebo	13.4	24.5	0.0	0.0	0.5	6.0	91.0

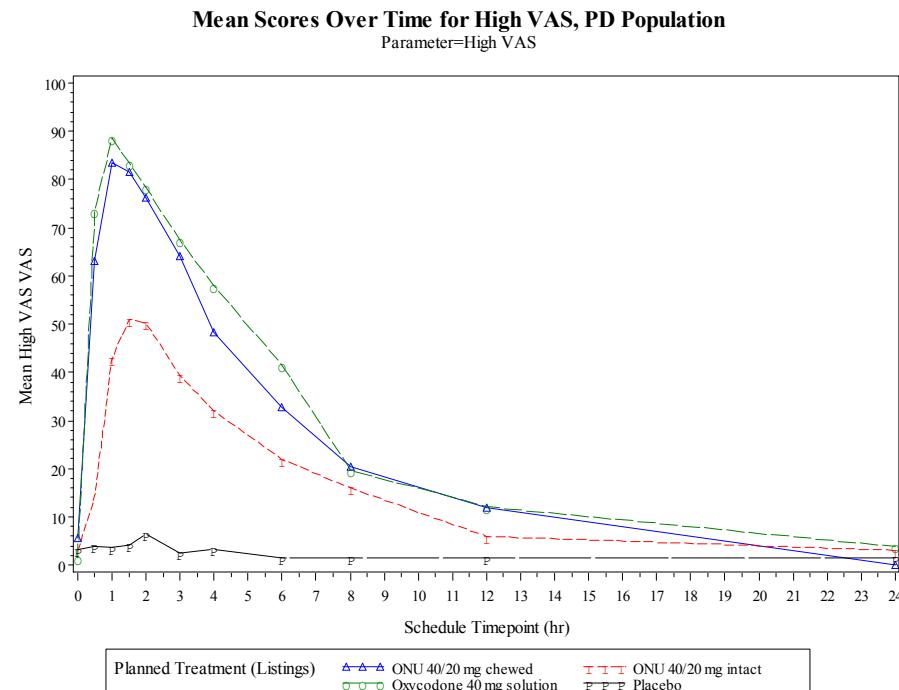
For Drug Liking VAS, as can be seen in table 1, the mean, first quartile, median and third quartile of placebo was within the neutral range (~50). Mean  $E_{max}$  for ONU chewed and Oxycodone 40 mg oral solution (Oxy API) are close with values 86.3 and 88.5 respectively. Mean  $E_{max}$  for ONU intact is 72.5, which is relatively lower than ONU chewed and Oxy API. From Figure 1, it can be seen that, the  $E_{max}$  of ONU is occurred at around 1.5 hours post-dose, slightly later than ONU chewed and Oxy API.

For Drug High VAS, from table 1, mean  $E_{max}$  for placebo was low (~13), while mean  $E_{max}$  for ONU chewed and Oxy API were high, 87.2 and 90.5 respectively. The median scores for both ONU chewed and Oxy API are 100. Figure 2 shows mean scores for placebo remained less than 10. Mean scores of ONU chewed and Oxy API increased rapidly to the peak of ~89 and ~83. Mean peak scores of ONU intact (~50) also increased to high scores compared with placebo but lower than ONU chewed and Oxy API, and occurred with slower onset, around 1.5 to 2 hours post-dose.

**Figure 1. Mean Scores over Time for Drug Liking VAS, PD Population**



**Figure 2. Mean Scores over Time for High VAS, PD Population**



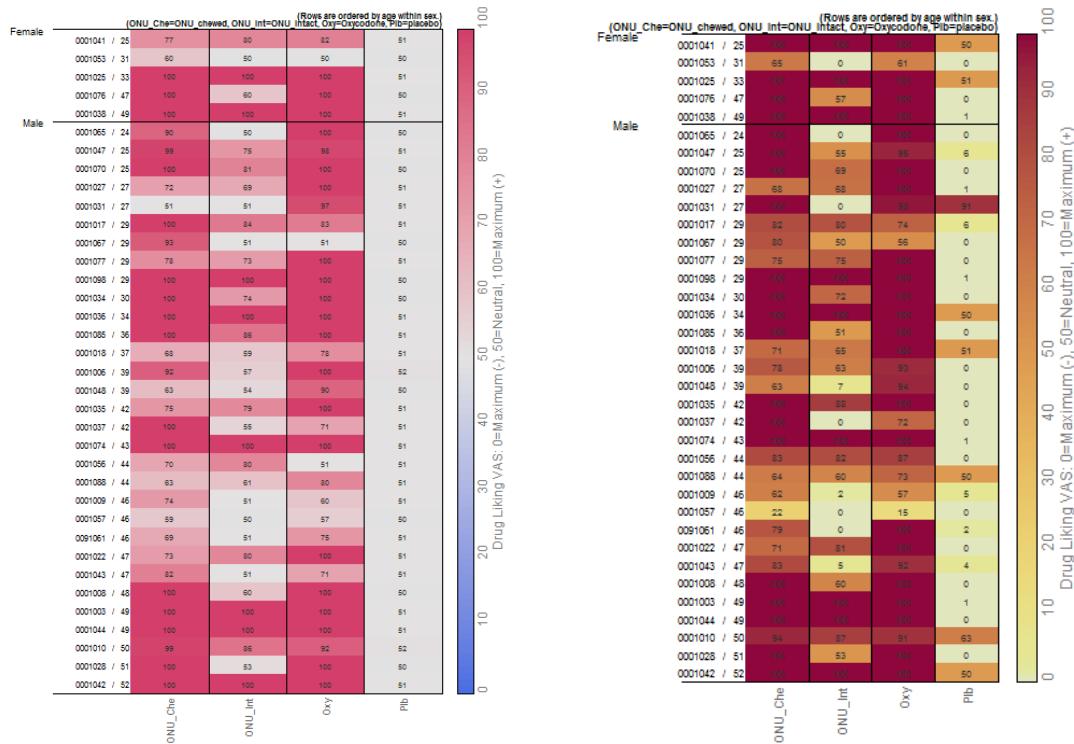
**Table 2. Treatment difference of E<sub>max</sub> for Drug Liking, Drug High, PD population (N=36)**

Parameter	Treatment difference	Mean	Std Dev	Min	Q1	Median	Q3	Max	t Value	Pr >  t
Drug Liking VAS	ONU_chew_VS_ONU_intact	13.8	16.7	-10.0	0.0	9.0	25.0	47.0	4.94	<.0001
	ONU_chew_VS_OXY	-2.2	16.6	-46.0	-9.0	0.0	1.5	42.0	-0.79	0.4328
	OXY_VS_ONU_intact	16.0	17.9	-29.0	0.0	17.5	26.5	50.0	5.35	<.0001
High VAS	ONU_chew_VS_ONU_intact	28.1	33.3	-10.0	0.0	13.5	48.0	100.0	5.06	<.0001
	ONU_chew_VS_OXY	-3.3	13.4	-32.0	-6.5	0.0	1.0	28.0	-1.47	0.1517
	OXY_VS_ONU_intact	31.3	32.7	-6.0	0.0	26.5	48.0	100.0	5.74	<.0001

For the Drug Liking VAS and high VAS difference, ONU intact showed a significantly lower E<sub>max</sub> value compared to both ONU chewed and Oxy API (P-value <0.0001), indicating less liking of ONU intact.

Individual E<sub>max</sub> scores are displayed by subject for all treatments in Figures 3-4, the rows of the table plot are ordered by age within sex. One may see the E<sub>max</sub> for each patient at different treatment, and the heat map also show that less liking of ONU intact.

**Figure 3. Emax for Drug Liking by Subject x Treatment      Figure 4. Emax for Drug High by Subject x Treatment**



### 2.3.2 Statistical Analysis

#### Statistical model fitting

The reviewer analyzed the hypotheses of the primary objective using the mixed-effect model, the final model the reviewer used is treatment as fixed effects and subject nested within sequence as a random effect. Table 3 is the analysis results for E<sub>max</sub> of Drug Liking VAS, Table 4 is the analysis results for E<sub>max</sub> of Drug high.

Table 3 shows that a significant treatment effect for this primary endpoint ( $p<0.0001$ ). From treatment contrast, ONU 40/20 mg chewed and ONU 40/20 mg intact are significant different, but there is no significant difference between ONU 40/20 mg chewed and Oxy 40 mg solution ( $P=0.4383$ ). Similar results are seen from table 4.

Note: In the proposal page 59 table 12, sponsor adjusted the p values using the Benjamini and Hochberg procedure. A more appropriate type I error rate adjusting procedure is Holm's procedure.

**Table 3. Analysis Results for Drug Liking VAS Emax , PD Population.**

	LS Mean	StdE	Pr >  t	Lower	Upper
Treatments					
ONU 40/20 mg chewed	86.31	2.46	<.0001	81.42	91.19
ONU 40/20 mg intact	72.53	2.46	<.0001	67.64	77.41
Oxy 40 mg solution	88.50	2.46	<.0001	83.61	93.39
Placebo	50.75	2.46	<.0001	45.86	55.64
Contrasts (difference)					
ONU 40/20 mg chewed - ONU 40/20 mg intact	13.78	2.82	<.0001	8.19	19.37
ONU 40/20 mg chewed - Oxy 40 mg solution	-2.19	2.82	0.4383	-7.79	3.40
ONU 40/20 mg chewed - Placebo	35.56	2.82	<.0001	29.96	41.15
ONU 40/20 mg intact - Oxy 40 mg solution	-15.97	2.82	<.0001	-21.56	-10.38
ONU 40/20 mg intact - Placebo	21.78	2.82	<.0001	16.19	27.37
Oxy 40 mg solution - Placebo	37.75	2.82	<.0001	32.16	43.34

**Table 4. Analysis Results for High VAS Emax ,PD Population**

	LS Mean	StdE	Pr >  t	Lower	Upper
Treatments					
ONU 40/20 mg chewed	87.22	4.23	<.0001	78.83	95.62
ONU 40/20 mg intact	59.17	4.23	<.0001	50.77	67.56
Oxy 40 mg solution	90.50	4.23	<.0001	82.11	98.89
Placebo	13.44	4.23	0.002	5.05	21.84
Contrasts (difference)					
ONU 40/20 mg chewed - ONU 40/20 mg intact	28.06	5.07	<.0001	18.00	38.12
ONU 40/20 mg chewed - Oxy 40 mg solution	-3.28	5.07	0.5197	-13.34	6.78
ONU 40/20 mg chewed - Placebo	73.78	5.07	<.0001	63.72	83.84
ONU 40/20 mg intact - Oxy 40 mg solution	-31.33	5.07	<.0001	-41.39	-21.27
ONU 40/20 mg intact - Placebo	45.72	5.07	<.0001	35.66	55.78
Oxy 40 mg solution - Placebo	77.06	5.07	<.0001	67.00	87.12

## Percentage Reduction Analysis

Percent reduction analysis is an important abuse potential measure, and it is recommended for the clinical abuse potential studies. Generally the percent reduction formula is defined as:

$$\% \text{ reduction} = \frac{c_i - t_i}{c_i - 50}, \quad i = 1, 2 \dots n \quad (1)$$

This formula does not include an adjustment factor for placebo responses.

Chen, Klein and Calderon [3] gave an example for the definition of the percentage reduction for the test drug relative to the active control for Drug Liking VAS in their poster presentation at the 74th College on Problems of Drug Dependence (CPDD) annual scientific meeting held in Palm Spring in June of 2012 as follows:

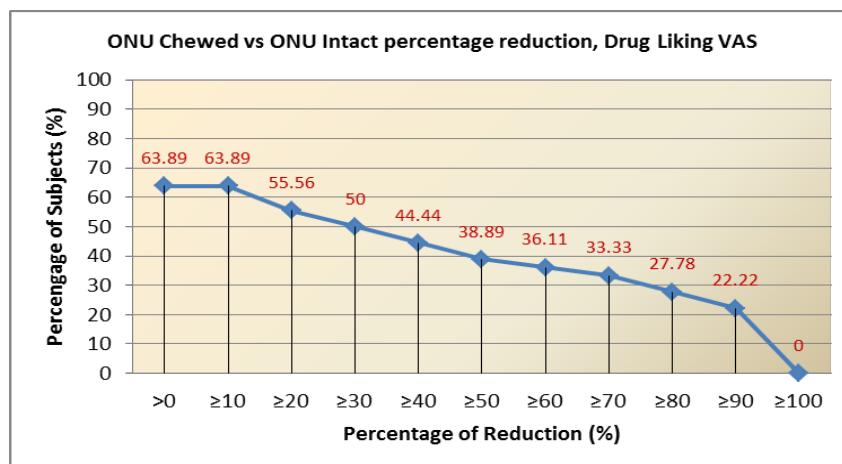
$$\% \text{ reduction} = \begin{cases} \frac{C-T}{C-50} \times \left(1 - \frac{P-50}{50}\right) \times 100\%, & \text{if } P > 55; \\ \frac{C-T}{C-50} \times 100\%, & \text{if } P \leq 55. \end{cases} \quad (2)$$

where T, C, and P denote  $E_{max}$  of the test drug, the active control drug and placebo, respectively.

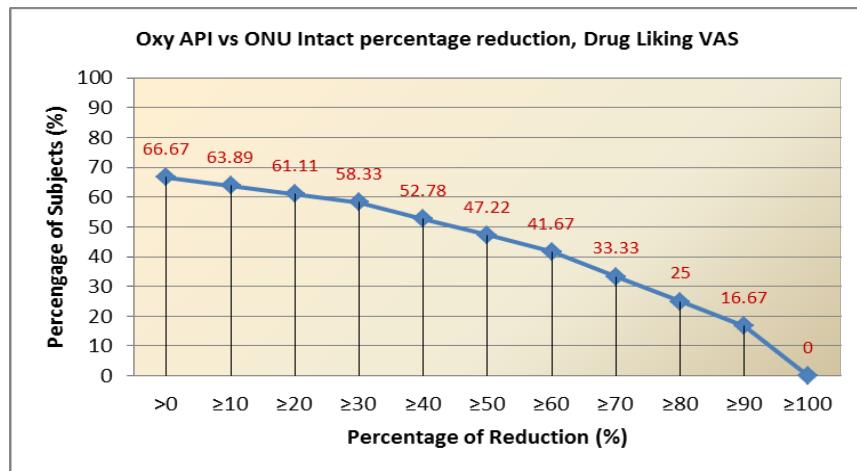
The reviewer use formula (2) to calculate the percent reduction between treatments.

The following three figures summary the percentage reductions of the three treatment comparisons for Drug Liking VAS. Figure 5 shows that for the comparison of ONU chewed and ONU intact, around 64% patients had drug liking VAS reduction for taking ONU intact, around 39% patients had more than 50% reduction. Figure 6 shows that for the comparison of Oxy API and ONU intact, around 67% patients had percentage reduction for taking ONU intact, and more than 47% patients had more than 50% percentage reduction. Figure 7 is the percentage reduction between Oxy API and ONU chewed, there is no big difference between these two treatment for Drug Liking VAS.

**Figure 5. ONU Chewed vs. ONU Intact percentage reduction, Drug Liking VAS.**



**Figure 6. Oxy API vs. ONU Intact percentage reduction, Drug Liking VAS**



**Figure 7. Oxy API vs. ONU Chewed percentage reduction, Drug Liking VAS**

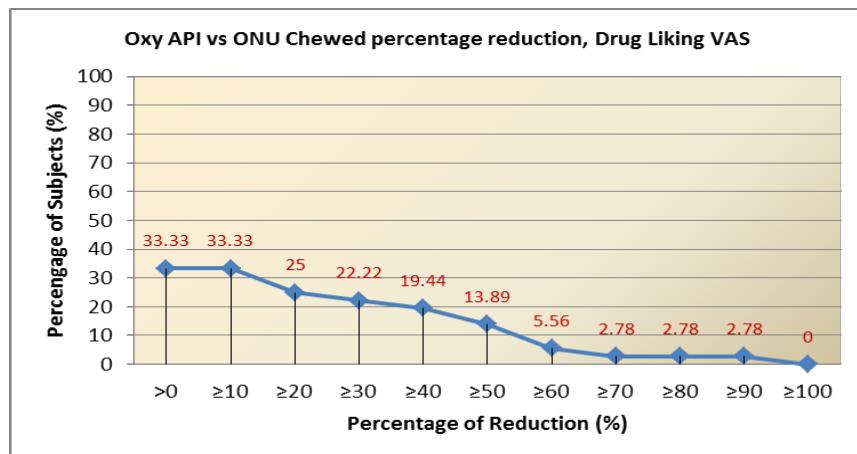
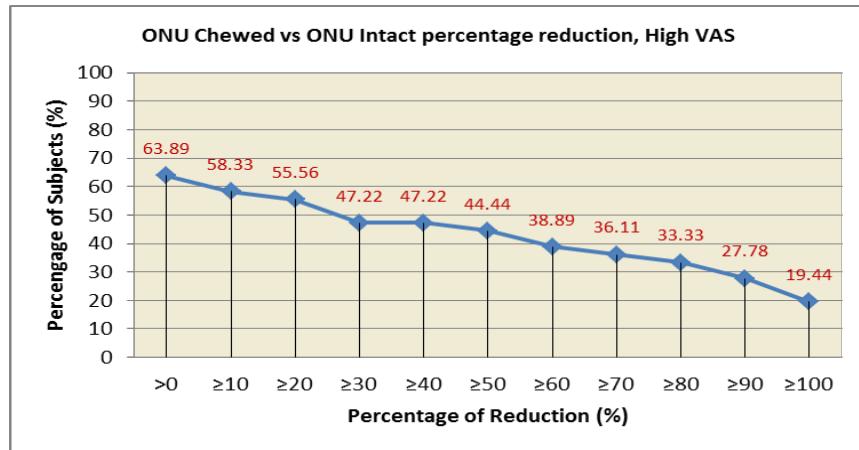
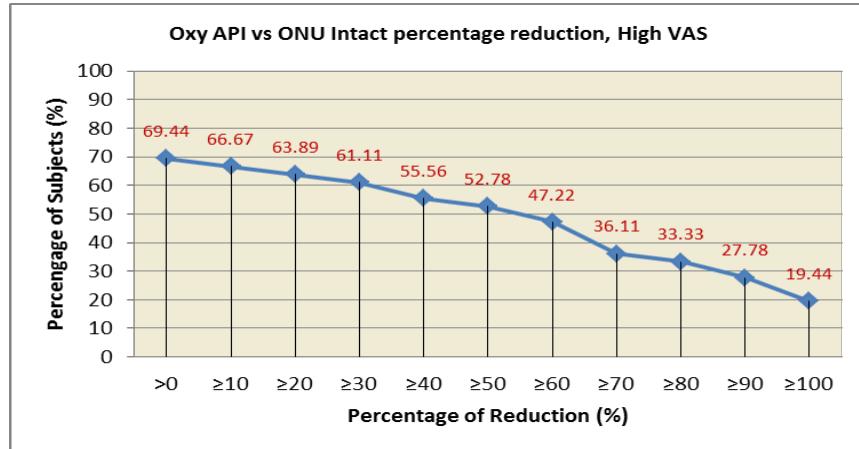


Figure 8 to Figure 10 summary the percentage reductions of the three treatment comparisons for the Drug High VAS. The results are similar as Drug Liking VAS. For the comparison of ONU chewed and ONU intact, Figure 8 shows around 64% patients showed drug high VAS reduction, and 44% patients had more than 50% reduction. Figure 9 shows that for the comparison of Oxy API and ONU intact, around 69% patients had percentage reduction for taking ONU intact, and more than 52% patients had more than 50% percentage reduction. Figure 10 is the percentage reduction between Oxy API and ONU chewed, there is no big difference between these two treatment for Drug High VAS.

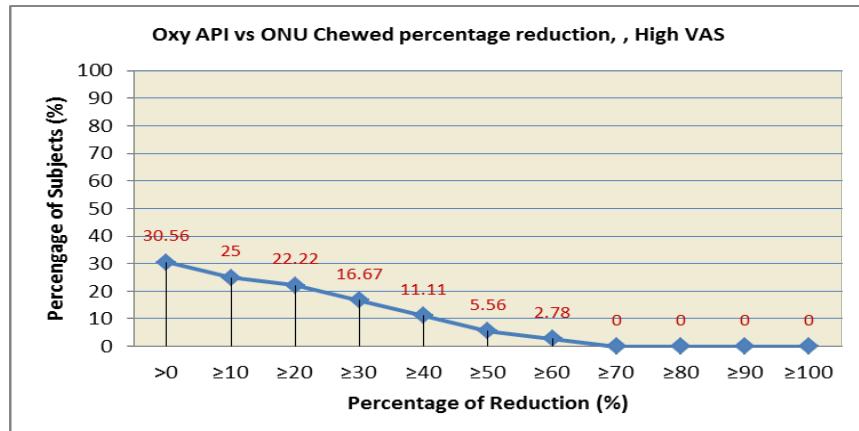
**Figure 8. ONU Chewed vs. ONU Intact percentage reduction, High VAS**



**Figure 9. Oxy API vs. ONU Intact percentage reduction, High VAS**



**Figure 10. . Oxy API vs. ONU Chewed percentage reduction, , High VAS**



### **3. Conclusion**

The primary objective of the study is to evaluate oral abuse potential and pharmacodynamic (PD) effects of chewed ONU and intact ONU compared to Oxy API oral solution 40 mg and placebo. The results from the statistical reviewer's analyses establish that:

- The study was validated using mean statistical differences between the medicated products and the placebo for the primary endpoint  $E_{max}$  of the two primary measures of relative abuse potential, Drug Liking VAS and Drug High VAS.
- $E_{max}$  values of Drug liking VAS for Oxy API and ONU chewed were both significantly higher than for ONU intact. In contrast, there is no significant difference between Oxy API and ONU chewed.
- $E_{max}$  values of Drug high VAS for Oxy API and ONU chewed were both significantly higher than for ONU intact, but there is no significant differences between Oxy API and ONU chewed were observed.
- In addition, mean peak scores of Drug liking VAS and Drug high VAS for ONU Intact were generally delayed compared to Oxy API and ONU chewed.

### **4. References**

- 1) Guidance for Industry: Assessment of Abuse Potential for Drugs (January 2010)  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>
- 2) Guidance for Industry: Abuse Deterrent Opioids – Evaluation and Labeling (January 2013)  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf>
- 3) Chen, Klein and Calderon (2012) poster presentation at the 74th College on Problems of Drug Dependence (CPDD) annual scientific meeting held in Palm Springs.
- 4) Holm, S. (1979). "A simple sequentially rejective multiple test procedure". *Scandinavian Journal of Statistics* **6** (2): 65–70

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

# Statistical Review and Evaluation

## CLINICAL STUDIES

<b>NDA/Serial Number:</b>	205,777
<b>Drug Name:</b>	Oxycodone/naloxone ER tablets
<b>Indication:</b>	(b) (4)
<b>Study number:</b>	ONU1003 and ONU1004
<b>Applicant:</b>	Purdue Pharma
<b>Date(s):</b>	Date of Document: 9/23/2013 Consult received date: 10/22/2013 PDUFA date: 3/23/2014 Completion date: 1/31/13
<b>Review Priority:</b>	P
<b>Biometrics Division:</b>	DB VI
<b>Statistical Reviewer:</b>	Ling Chen, Ph.D., Mathematical Statistician, Special Projects Team, DBVI/OB/OTS
<b>Concurring Reviewers:</b>	Yi Tsong, Ph.D., Acting Division Director, DBVI/OB/OTS
<b>Medical Division:</b>	Controlled Substance Staff
<b>The CSS Team:</b>	James Tolliver, Ph.D., Pharmacologist, OD/CSS Silvia Calderon, Team Leader, Pharmacologist, OD/CSS Michael Klein, Ph.D., Director, OD/CSS
<b>Project Manager:</b>	Sandra Saltz, OD/CSS
<b>Keywords:</b>	Crossover design; Clinical abuse potential study; Self-reported endpoint; Multiple endpoints

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## **1. Executive Summary**

Study ONU1003 was a single-center, randomized, double-blind, placebo- and positive controlled 3 way crossover study to evaluate the abuse potential, pharmacokinetics, and safety of oxycodone/naloxone (ONU) tablets administered via the oral, intranasal and intravenous routes in recreational opioid users.

This study included three groups of subjects for the oral, intranasal and intravenous assessment. The following treatments were used in these groups.

Group 1: ONU 40/20 mg tablet, chewed, oxycodone oral solution 40 mg, and placebo

Group 2: ONU 40/20 mg, finely crushed, Oxy API powder 40 mg, and placebo

Group 3: Oxycodone 0.07 mg/kg/naloxone 0.035 mg/kg, Oxycodone 0.07 mg/kg, and placebo

The numbers of completers were 14, 23 and 22 in Group 1, Group 2 and Group 3, respectively.

The reviewer's primary analysis was based on Emax of Drug Liking VAS. The results from the primary analysis show that the oral abuse potential of chewed ONU 40/20 mg is similar to that of oxycodone oral solution 40 mg, and the intranasal and intravenous abuse potential of ONU (oxycodone co-administered with naloxone in a 2:1 ratio) is significantly reduced to near placebo-like levels. The comparison between the positive control and the test drug validated the primary analysis for the oral, intranasal and intravenous studies.

The reviewer's secondary analysis was performed on the percent reduction in liking for the test drug relative to the positive control for intranasal and intravenous studies. The analysis results show that 74% of subjects had at least 60% reduction for finely crushed ONU 40/20 mg relative to Oxy API powder 40 mg in the intranasal study, and 77% of subjects had at least 90% reduction for oxycodone 0.07 mg/kg/ naloxone 0.035 mg/kg relative to oxycodone 0.07 mg/kg in the intravenous study. If a responder is defined as a subject who had at least 30% reduction, the responder rates are 78% and 91% for intranasal and intravenous studies, respectively. These responder rates are significantly greater than 50% with p-values 0.0013 and <0.0001, respectively.

Study ONU1004 was a single-center, randomized, double-blind placebo- and positive controlled 3 way crossover study to evaluate the pharmacodynamics, pharmacokinetics, and safety of oxycodone/naloxone (ONU) in opioid-dependent individuals maintained on a relatively low stable daily dose of methadone (20 mg/day to 40 mg/day).

The study included two treatment sessions. Treatments were chewed ONU 30/15 mg, Oxy API 30 mg solution and placebo in Treatment Session 1, and chewed ONU 60/30 mg, Oxy API 60 mg solution and placebo in Treatment Session 2. The same study subjects were used in both treatment sessions with at least 3 days washout period between these sessions. The numbers of completers were 18 and 16 in Treatment Sessions 1 and 2, respectively.

There was no Qualification Phase in this study. The reviewer found that 78% (14/18) and 56% (7/16) of subjects had Emax of Drug Liking VAS for Oxy API 30 mg and Oxy API 60 mg less than 60, respectively. Due to no significant difference between Oxy API and placebo on Drug Liking VAS in both treatment sessions as well as for other positive subjective abuse potential measures in Treatment Session 1, and Overall Drug Liking VAS and Take Drug Again VAS in

Treatment Session 2, the results from the comparisons between ONU and Oxy API on these measures are not meaningful.

The reviewer evaluated Objective Opioid Withdrawal Scale (OOWS) and Subjective Opiate Withdrawal Scale (SOWS). There was no significant difference among three treatments for both OOWS and SOWS in Treatment Session 1 and for OOWS in Treatment 2. For SOWS in Treatment Session 2, there was no significant difference between Oxy API 60 mg and placebo. ONU 60/30 mg had significantly larger mean than both Oxy API 60 and placebo. The least square means were 5.63, 0.37 and 1.83 for ONU 60/30 mg, Oxy API 60 mg and placebo, respectively. The 95% confidence intervals of the mean difference in Emax were (0.72, 6.88) and (2.16, 8.35) when comparing ONU 60/30 mg to placebo and to Oxy API 60 mg, respectively. Note that SOWS is ranged from 0 to 64. The CSS may comment on the clinical significance of these differences on SOWS.

## **2. Review report on Study ONU1003**

### **2.1 Overview**

Study ONU1003 was a single-center, randomized, double-blind, placebo- and positive controlled 3 way crossover study to evaluate the abuse potential, pharmacokinetics, and safety of oxycodone/naloxone (ONU) tablets administered via the oral, intranasal and intravenous routes in recreational opioid users.

This study included three groups of subjects for the oral, intranasal and intravenous assessment. The following treatments were used in these groups.

Group 1: ONU 40/20 mg tablet, chewed, oxycodone oral solution 40 mg, and placebo.

Group 2: ONU 40/20 mg, finely crushed, Oxy API powder 40 mg, and placebo (lactose powder)

Group 3: Oxycodone 0.07 mg/kg/naloxone 0.035 mg/kg, Oxycodone 0.07 mg/kg, and placebo

#### **2.1.1 Objectives of the study**

Objectives - Oral Administration (Group 1)

- To evaluate oral abuse potential and pharmacodynamic (PD) effects of chewed ONU compared to oxycodone oral solution and placebo in healthy, adult recreational opioid users with a history of oral chewing abuse/misuse
- To evaluate the safety and tolerability of orally administered chewed ONU in healthy, adult recreational opioid users with a history of oral chewing abuse/misuse
- To determine the comparative pharmacokinetic (PK) profile of orally administered chewed ONU compared to oxycodone oral solution Secondary objectives

Objectives - Intranasal (IN) Administration (Group 2)

- To evaluate intranasal abuse potential and PD effects of crushed ONU compared to oxycodone active pharmaceutical ingredient (Oxy API) and placebo in healthy, adult recreational opioid users with a history of intranasal abuse/misuse
- To evaluate the safety and tolerability of intranasally administered crushed ONU in healthy, adult recreational opioid users with a history of intranasal abuse/misuse
- To determine the comparative PK profile of intranasally administered crushed ONU compared to Oxy API

Objectives - Intravenous (IV) Administration (Group 3)

- To evaluate intravenous abuse potential and PD effects of oxycodone/naloxone compared to oxycodone alone, and placebo in healthy, adult recreational opioid users
- To evaluate the safety and tolerability of intravenously administered oxycodone/naloxone in healthy, adult recreational opioid users
- To determine the comparative PK profile of intravenously administered oxycodone/naloxone compared to oxycodone alone

### **2.1.2 Study design**

This was a single-center, double-blind, parallel-group, randomized crossover study to evaluate the abuse potential of ONU in healthy non-dependent recreational drug users with moderate experience with opioids and to evaluate the safety and PK profiles of both oxycodone and naloxone, when administered orally, IN, or IV. Subjects were divided into 3 parallel groups, separated by route of administration.

The study consisted of 4 phases: screening, qualification, treatment, and follow-up. The study design is summarized in Figure 1 on page 21 of the study report. The Screening Phase included 2 visits: a Screening visit (Visit 1), conducted within 21 days of the first study drug administration of the Qualification Phase, and a Naloxone Challenge visit lasting 1 day (Visit 2). All subjects completed the naloxone challenge test at least 12 hours prior to drug administration in the Qualification Phase, to confirm that they were not opioid-dependent.

The Qualification Phase consisted of 1 visit (Visit 3) lasting 4 days (3 overnight stays) for Group 1 and Group 2, and 3 days (2 overnight stays) for Group 3. 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 oxycodone and placebo in a randomized fashion (washout of 24 hours) via the oral (Group 1), IN (Group 2), or IV (Group 3) route to determine if subjects liked and could tolerate the effects of oxycodone and could discriminate these from placebo; this visit also determined if each subject was suitable for entry into the study.

The washout period from the last drug administration in the Qualification Phase and the first study drug administration in the Treatment Phase was to be at least 5 days and no more than 21 days.

The Treatment Phase consisted of 3 visits, each lasting 3 days (2 overnight stays) for Group 1 and Group 2, and 2 days (1 overnight stay) for Group 3.

A follow-up visit was scheduled to be between 3 to 7 days after the last study drug administration of the Treatment Phase.

### **2.1.3 Abuse potential measures**

The following abuse potential measures were administered to evaluate the subjective and objective effects of ONU.

#### Primary measures

Drug Liking VAS, Overall Drug Liking VAS, Subjective Drug Value (SDV) (\$) and ARCI MBG Scale

#### Secondary measures

High VAS, Good Effects VAS and others

#### **2.1.4 Number of subjects**

The numbers of completers were 14, 23 and 22 in Group 1, Group 2 and Group 3, respectively. The statistical analyses were based on completers.

#### **2.1.5 Statistical methodologies used in the Sponsor's analyses**

Pharmacodynamic parameters (maximum effect [Emax], minimum effect [Emin] and/or time-averaged area under the effect curves [TA\_AUE], as appropriate) were analyzed using a mixed-effect model for a crossover study; maximum pupil constriction (MPC) was the derived parameter of peak effect for pupillometry. The model included treatment, period, sequence, and first-order carryover effect as fixed effects, baseline (pre-dose) measurement as covariate where applicable, and subject nested within treatment sequence as random effect. A washout of at least 3 days was used in order to minimize the potential for carryover effects. If the carryover effect was found to be non-significant at the 25% level, then the term was dropped from the analysis model. Baseline and carryover were included as applicable. Least square means, standard errors (SE), and 95% two-sided confidence intervals for treatments and treatment differences were derived from the mixed-effects model. P values were provided for the effects and the contrasts. The residuals from the mixed-effect model were investigated for normality using the Shapiro-Wilk W-test. Parameters were analyzed as having a normal distribution if the probability value was  $\geq 0.05$ . Parameters that did not meet this criterion were analyzed non-parametrically using Friedman's test. The Benjamini and Hochberg procedure was used to control for Type I errors arising from the multiple comparisons.

#### 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.

#### **2.1.6 Sponsor's Summary and Conclusions**

##### Group 1 (oral)

- Mean Drug Liking VAS Emax (primary) for chewed ONU and oxycodone oral solution were similar and within the “strong liking” range, and were clearly distinct from PBO, which was near neutral;
- The time course and magnitude of mean Drug Liking scores were similar for ONU when chewed prior to ingestion compared to oxycodone oral solution;
- Both oxycodone oral solution and chewed ONU showed prominent responses on the primary and secondary global measures of balance of effects (Overall Drug Liking VAS, Take Drug Again VAS, SDV) compared to PBO, but did not differ notably from each other;
- As observed with measures of balance of effects, positive, sedative and any effects of chewed ONU were similar to those reported for oxycodone oral solution, though slightly lower. Both active treatments separated from placebo;

- Overall, negative effects were minimal for all treatments;
- The miotic response to chewed ONU was slightly weaker compared to that observed with oxycodone oral solution, though both produced considerable pupil constriction.

#### Group 2 (Intranasal)

- ‘At the moment’ Drug Liking (primary) of intranasally administered Oxy API was significantly higher compared to PBO and crushed ONU. While crushed ONU was significantly liked relative to PBO, the median difference in peak Drug Liking scores was 0. In addition to lower Emax, Emin of Drug Liking for crushed ONU was significantly lower compared to Oxy API, and in the disliking range (<50);
- Administration of Oxy API resulted in a significantly higher Emax compared to PBO and crushed ONU on SDV, Take Drug Again VAS, and Overall Drug Liking VAS measures. In contrast with the ‘at the moment’ Drug Liking VAS results, Emax for crushed ONU were observed to be not statistically different from that of PBO for any of these global measures of balance of effects;
- On ARCI MBG, the primary measure of positive effects, Emax for Oxy API was significantly higher than PBO and crushed ONU, which did not differ from each other. For both secondary measures of positive effects, Emax for intranasally administered Oxy API and crushed ONU were significantly higher than PBO, and Emax was significantly lower for crushed ONU compared to Oxy API;
- Oxy API and crushed ONU had larger negative effects relative to PBO, but were not different from each other. Overall, negative effects were minimal and there was little intranasal irritation observed for any of the treatments, though nasal burning and congestion were observed to be higher for crushed ONU compared to PBO;
- For sedative and any effects , both Oxy API and crushed ONU had significantly greater effects compared to PBO; however, the magnitude of sedative and any effects was significantly lower for crushed ONU compared to Oxy API;
- For the objective measure of pupillometry, MPC was observed to be statistically significantly higher for both Oxy API and crushed ONU compared to PBO, but MPC was significantly lower following intranasal administration of crushed ONU versus Oxy API.

#### Group 3 (Intravenous)

- ‘At the moment’ Drug Liking VAS (primary) Emax values for both oxycodone alone and oxycodone/naloxone co-administration were significantly higher than PBO. However, the median difference between Emax of oxycodone/naloxone and PBO was 0, demonstrating that the effect of oxycodone/naloxone on Drug Liking was marginal. As expected, co-administration of naloxone significantly reduced Emax of Drug Liking for oxycodone;
- Intravenous administration of oxycodone resulted in a significantly higher Emax compared to PBO and oxycodone/naloxone on all global measures of balance of effects. Emax for oxycodone/naloxone were observed to be not statistically different from that of PBO for any of these measures;
- For ARCI MBG, Emax values for oxycodone alone were significantly higher than PBO and oxycodone/naloxone co-administration, whereas Emax for oxycodone/naloxone was not statistically different from PBO;
- For the measures of positive, sedative and any effects, peak scores for oxycodone alone were significantly higher than both PBO and oxycodone/naloxone co-administration, which did not differ from each other. Negative effects of all treatments were minimal and no significant main effect was observed for any of the derived parameters;

- MPC was observed to be statistically significantly higher for oxycodone alone compared to PBO and significantly lower for oxycodone/naloxone compared to oxycodone alone, whereas MPC derived for oxycodone/naloxone was not statistically different from PBO.

## Conclusion

Based on the overall pattern of response on the measures evaluated in this study, the intranasal and intravenous abuse potential of oxycodone is significantly reduced to near placebo-like levels when co-administered with naloxone in a 2:1 ratio. The oral abuse potential of chewed ONU appears to be similar to that of oxycodone solution, which is an expected result based on the extremely low oral bioavailability of naloxone. It can be concluded that ONU (or oxycodone/naloxone solution) has less potential for intranasal and intravenous abuse compared to Oxy API and oxycodone solution, respectively.

## **2.2 Data Location**

The analysis datasets are located at

<\\cdsesub1\evsprod\nda205777\0000\m5\datasets\onu1003\analysis\adam\datasets\adpd.xpt>

## **2.3 Reviewer's Assessment**

### **2.3.1 Statistical analysis for the oral study (Group 1)**

#### **2.3.1.1 Descriptive statistics**

Table 1 summarizes the mean, standard error, minimum, the first quartile ( $Q_1$ ), median, the third quartile ( $Q_3$ ), and maximum for three treatments in the study and for the treatment differences between ONU 40/20 mg tablet, chewed and oxycodone oral solution 40 mg or placebo for the primary endpoint Emax of Drug Liking VAS. The similar tables for High VAS, ARCI MBG, Good Effect VAS, Bad Effect VAS, Overall Drug Liking VAS, and Take Drug Again VAS for the oral study can be found in Appendix I.

**Table 1: Summary statistics for Emax of Drug Liking VAS (N=14)**

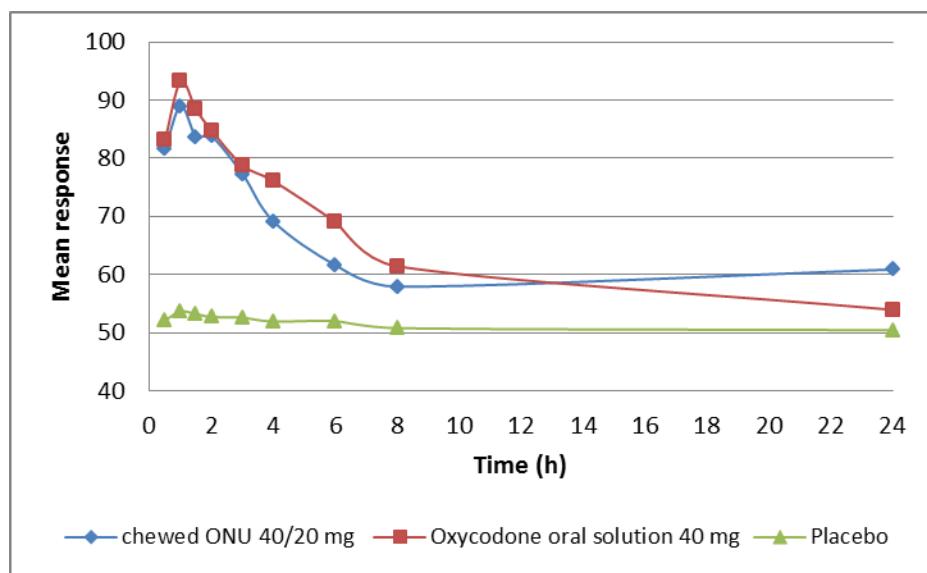
TRT	Mean	StdErr	Min	Q1	Med	Q3	Max
ONU 40/20 mg *	92.36	4.16	51	92	100	100	100
Oxy 40 mg**	94.43	3.09	66	95.8	100	100	100
Placebo	54.50	2.48	50	51	51	52.3	83
Oxy-P	39.93	4.96	-17	32.8	49	49	50
Oxy-ONU	2.07	3.89	-27	0	0	6.8	34
ONU-P	37.86	6.02	-32	32	49	49	50

\*: chewed ONU 40/20 mg

\*\*: oxycodone oral solution 40 mg

Table 1 shows the first quartiles of the primary endpoint are 92 and 95.8 for chewed ONU 40/20 mg and oxycodone oral solution 40 mg, respectively. The mean difference and the median difference between these treatments are 2.07 and 0, respectively.

Figure 1 is the mean time course profiles by treatment. The profile of chewed ONU 40/20 mg is very similar to that of oxycodone oral solution 40 mg.



**Figure 1: The mean time course profiles on Drug Liking VAS by treatment (N=14)**

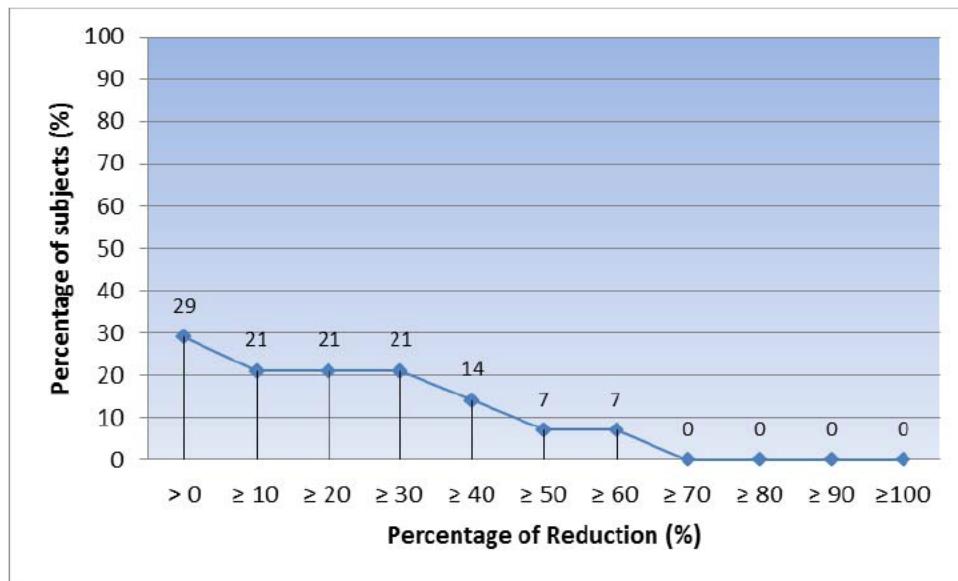
Table 2 shows the frequency distribution of subjects in terms of their responses to the positive control as well as their percent reductions for the test drug relative to the positive control. Only 21% of subjects had at least 30% reduction in liking.

**Table 2: Contingency Table for Emax of Drug Liking VAS of the positive control by percent reduction (chewed ONU 40/20 mg vs. Oxycodone oral solution 40 mg)**

Oxy 40 mg (Emax)	Percent of Reduction (%)												total
	<0	0	(0, 10)	[10, 20]	[20, 30]	[30, 40]	[40, 50]	[50, 60]	[60, 70]	[70, 80]	[80, 90]	[90, 100]	
≤55													
(55, 60]													
(60, 65]													
(65, 70]						1							1
(70, 75]	1												1
(75, 80]													
(80, 85]	1												1
(85, 90]													
(90, 95]													
(95, 100]		8	1				1		1				11
Total	2	8	1			1	1		1				14
pct(%)	14.3	57.1	7.1	0.0	0.0	7.1	7.1	0.0	7.1	0.0	0.0	0.0	100.0
cptc (%)	100	86	29	21	21	21	14	7	7	0	0	0	0

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

Figure 2 is the percent reduction profile for Emax of Drug Liking VAS for the oral study.



**Figure 2: Percent Reduction Profiles for Emax of Drug Liking VAS (N=14, Group 1)**

Note: The adjustment for placebo response is included in the calculation of the percent reduction.

### **2.3.1.2 Inferential Statistics**

Due to the small sample size, the inferential statistics was not conducted by the sponsor for Group 1. Because the results presented in Section 2.3.1.1 clearly show that the responses to treatments chewed ONU 40/20 mg and Oxycodone oral solution 40 mg on Drug Liking VAS were not much different, with such a small sample size (N=14), the inferential statistics are not needed for the primary and secondary analysis on Drug Liking VAS.

### **2.3.2 Statistical analysis for the intranasal study (Group 2)**

#### **92.3.2.1 Descriptive statistics**

Table 3 summarizes the mean, standard error, minimum, the first quartile (Q1), median, the third quartile (Q3), and maximum for three treatments in the study and for the treatment differences between finely crushed ONU 40/20 mg and Oxy API powder 40 mg or placebo for Emax of Drug Liking VAS. The similar tables for High VAS, ARCI MBG, Good Effect VAS, Bad Effect VAS, Overall Drug Liking VAS, and Take Drug Again VAS for the intranasal study can be found in Appendix I.

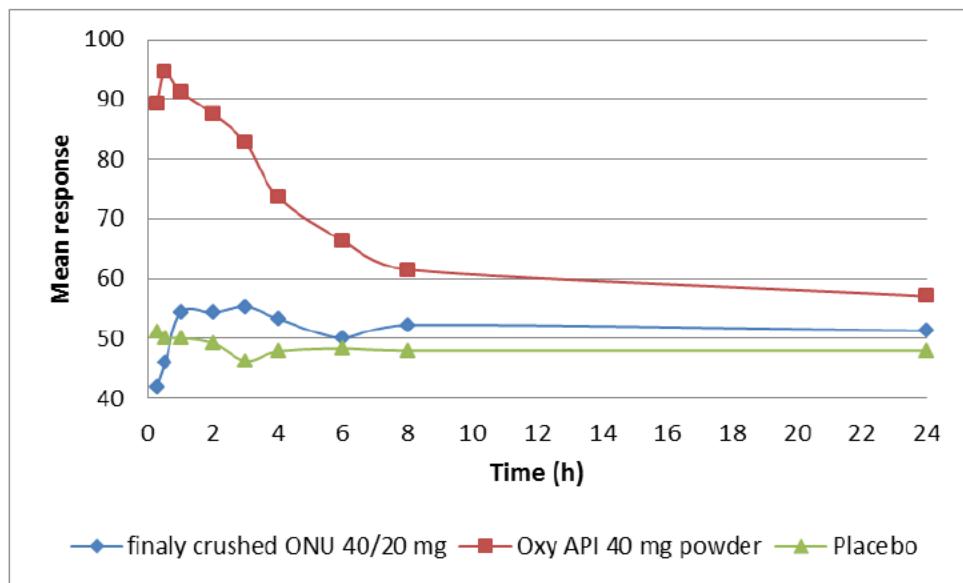
**Table 3: Summary statistics for Emax of Drug Liking VAS (N=23, Group 2)**

TRT	Mean	StdErr	Min	Q1	Med	Q3	Max
ONU*	59.13	2.84	50	51	51	65	100
OxyAPI**	94.83	2.18	61	93	100	100	100
P	53.17	2.14	50	51	51	51	100
OxyAPI-ONU	41.65	2.91	0	38	49	49	50
ONU-P	35.70	3.71	0	26	43	49	50
ONU-P	5.96	3.75	-49	0	0	12	49

\*:Finely crushed ONU 40/20 mg

\*\*: Oxy API 40 mg powder.

Table 3 shows the median and the third quartile of the primary endpoint for finely crushed ONU 40/20 mg are 51 and 65, respectively. For Oxy API 40 mg powder, the median is 100. The magnitude of the difference in responses to finely crushed ONU 40/20 mg and Oxy API 40 mg powder is large. Such a large difference also can be seen from the mean time course profiles in Figure 3.



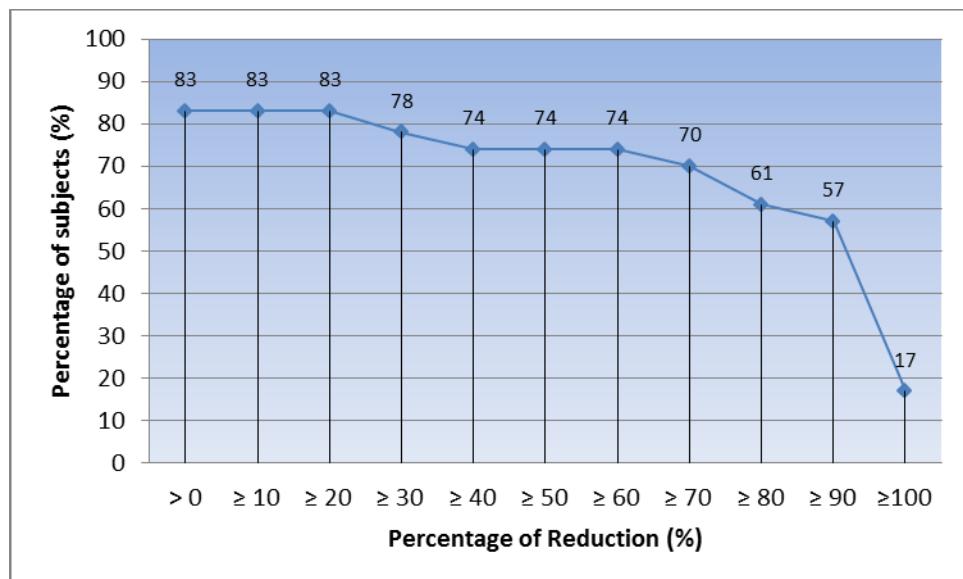
**Figure 3: The mean time course profiles on Drug Liking VAS by treatment (N=23, Group 2)**

Table 4 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 percent reduction profile is shown in Figure 4.

**Table 4: Contingency Table for Emax of the positive control by percent reduction for Emax of Drug Liking VAS (ONU 40/20 mg finely crushed vs. Oxy API powder 40 mg, Group 2)**

OxyAPI (Emax)	Percent of Reduction (%)													total
	<0	0	(0, 10)	[10, 20)	[20, 30)	[30, 40)	[40, 50)	[50, 60)	[60, 70)	[70, 80)	[80, 90)	[90, 100)	≥100	
≤55														
(55, 60]														
(60, 65]	1													1
(65, 70]	1													1
(70, 75]														
(75, 80]														
(80, 85]												1		1
(85, 90]													1	1
(90, 95]					1				1			1		3
(95, 100]	2				1					2	1	7	3	16
Total		4			1	1			1	2	1	9	4	23
pct (%)	0.0	17.4	0.0	0.0	4.3	4.3	0.0	0.0	4.3	8.7	4.3	39.1	17.4	100.0
cpct (%)	100	100	83	83	83	78	74	74	74	70	61	57	17	

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



**Figure 4: Percent Reduction Profiles for Emax of Drug Liking VAS (N=23, Group 2)**

Note: The adjustment for placebo response is included in the calculation of the percent reduction.

### 2.3.2.2 Inferential Statistics

The reviewer did not repeat the sponsor's primary analysis based on the median difference in Emax between treatments, because the deterrent effect for finely crushed ONU 40/20 mg relative to Oxy API 40 mg powder is evident in the intranasal study based on the results in the previous section. The following Table 23 is from the sponsor's study report.

Table 23. Analysis Results for Drug Liking VAS Emax (Maximum Liking) (Group 2 - PD Population)

	Median difference		P value	Adjusted P value
Overall Treatment Effect	--	--	<.001	
Pairwise comparisons				
Oxy API 40 mg – PBO	49.	(38.0 - 49.0)	<.001	<.001
ONU 40/20 mg – PBO	0.	(0.0 - 12.0)	0.036	0.052
ONU 40/20 mg - Oxy API 40 mg	-43.0	(-49.0 - -26.0)	<.001	<.001

The sponsor did not perform responder analysis. If we define a responder as a subject who had at least 30% reduction, the responder rate is 78%. The result from the responder analysis shows that the responder rate in this group is significantly greater than 50% ( $p=0.0013$ ). In this case, even if we define a responder as a subject who had at least 60% reduction, the responder rate is 74% which is also significantly greater than 50% ( $p=0.0053$ ).

### **2.3.3 Review report on the Intravenous study (Group 3)**

#### **2.3.3.1 Descriptive statistics for Group 3**

Table 5 summarizes the mean, standard error, minimum, the first quartile (Q1), median, the third quartile (Q3), and maximum for three treatments in the study and for the treatment differences between oxycodone 0.07 mg/kg/naloxone 0.035 mg/kg and oxycodone 0.07 mg/kg, or placebo for Emax of Drug Liking VAS. The similar tables for High VAS, ARCI MBG, Good Effect VAS, Bad Effect VAS, Overall Drug Liking VAS, and Take Drug Again VAS for the Intravenous study can be found in Appendix I.

**Table 5: Summary statistics for Emax of Drug Liking VAS (N=22, Group 3)**

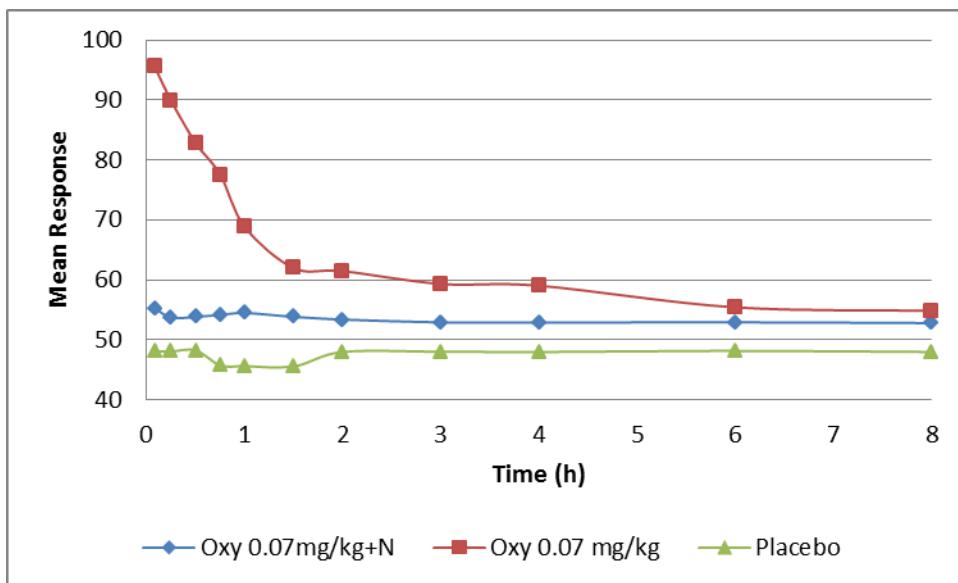
TRT	Mean	StdErr	Min	Q1	Med	Q3	Max
ONU*	56.55	2.85	50	51	51	52.75	100
Oxy**	96.36	2.30	50	98.75	100	100	100
P	48.68	2.32	0	51	51	51	53
Oxy-P	47.68	0.73	38	48.75	49	49	50
Oxy-ONU	39.82	4.71	-50	39	49	49	50
ONU-P	7.86	4.80	-2	0	0	1.75	100

\*: oxycodone 0.07 mg/kg/naloxone 0.035 mg/kg

\*\*: oxycodone 0.07 mg/kg

Table 5 shows that the third quartile of oxycodone 0.07 mg/kg/naloxone 0.035 mg/kg is 52.75 while the first quartile of oxycodone 0.07 mg/kg is 98.75 for Emax of Drug Liking VAS. The reduction in liking by the test drug is very impressive. One may notice that the minimum difference between oxycodone 0.07 mg/kg and oxycodone 0.07 mg/kg/naloxone 0.035 mg/kg is – 50 . This is because a Subject (ID 0001015) had Emaxs 100 and 50 to oxycodone 0.07 mg/kg/naloxone 0.035 mg/kg and oxycodone 0.07 mg/kg, respectively.

Figure 5 is the mean time course profiles by treatment for the intranasal study. The mean time course profile of oxycodone 0.07 mg/kg/naloxone 0.035 mg/kg is very similar to that of placebo.



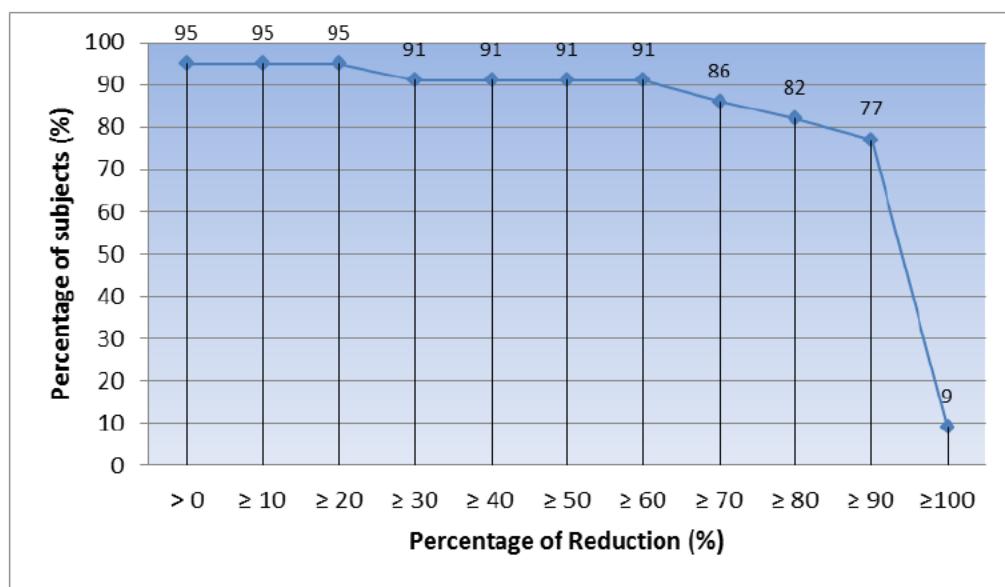
**Figure 5: The mean time course profiles for Drug Liking VAS by treatment (N=23, Group 3)**

Table 6 shows the frequency distribution of subjects in terms of their responses to the positive control as well as their percent reduction for the test drug relative to the positive control. Even though the study included a qualification phase, one subject did not respond to the positive control (see blue cell). Among 21 subjects whose Emaxx to the positive control were greater than 85, 20 of them (95%) had at least 60% reduction in liking for oxycodone 0.07 mg/kg/naloxone 0.035 mg/kg relative to oxycodone 0.07 mg/kg (see pink cells). The percent reduction profile is provided in Figure 6.

**Table 6: Contingency Table for Emax of the positive control by percent reduction for Emax of Drug Liking VAS (oxycodone 0.07 mg/kg/naloxone 0.035 mg/kg vs. oxycodone 0.07 mg/kg, Group 3)**

Oxy 0.07mg/kg (Emax)	Percent of Reduction (%)												total
	<0	0	(0, 10)	[10, 20)	[20, 30)	[30, 40)	[40, 50)	[50, 60)	[60, 70)	[70, 80)	[80, 90)	[90, 100)	
≤55	1												1
(55, 60]													
(60, 65]													
(65, 70]													
(70, 75]													
(75, 80]													
(80, 85]													
(85, 90]												1	1
(90, 95]											1	2	3
(95, 100]				1					1	1		12	2
Total	1			1				1	1	1	15	2	22
pct (%)	4.6	0.0	0.0	0.0	4.6	0.0	0.0	0.0	4.6	4.6	4.6	68.2	9.1
cpt (%)	100	95	95	95	95	91	91	91	91	86	82	77	9

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



**Figure 6: Percent Reduction Profiles for Emax of Drug Liking VAS (N=22, Group 3)**

Note: The adjustment for placebo response is included in the calculation of the percent reduction.

### 2.3.3.2 Inferential Statistics

The reviewer did not repeat the sponsor's primary analysis based on the median difference in Emax of Drug Liking VAS between treatments, because the deterrent effect for oxycodone 0.07 mg/kg/naloxone 0.035 mg/kg relative to oxycodone 0.07 mg/kg is evident in the intravenous study based on the results in the previous section. The following table is from the study report.

Table 37. Analysis Results for Drug Liking VAS  $E_{max}$  (Maximum Liking) (Group 3 - PD Population)

	Median Difference IQR		P value	Adjusted P value
Overall Treatment Effect	-	-	<.001	
Pairwise comparisons				
Oxycodone – PBO	49.0	(49.0 - 49.0)	<b>&lt;.001</b>	<b>&lt;.001</b>
Oxycodone/haloxone – PBO	0	(0.0 - 1.0)	<b>0.039</b>	0.053
Oxycodone/haloxone - Oxycodone	-49.0	(-49.0 - -39.0)	<b>&lt;.001</b>	<b>&lt;.001</b>

The sponsor did not perform responder analysis. In this study even if we define a responder as a subject who had at least 90% reduction, the responder rate is 77% which is significantly greater than 50% ( $p=0.0022$ ).

### 2.4 Conclusion

Study ONU 1003 shows that the oral abuse potential of chewed ONU 40/20 mg is similar to that of oxycodone oral solution 40 mg, and the intranasal and intravenous abuse potential of ONU (oxycodone co-administered with naloxone in a 2:1 ratio) is significantly reduced to near placebo-like levels.

### **3. Review report on Study ONU1004**

#### **3.1 Overview**

##### **3.1.1 Objectives of the study**

The objectives of the study were to evaluate the following:

- The pharmacodynamic effects of chewed ONU compared to the active pharmaceutical ingredient oxycodone HCl (Oxy API) and placebo in methadone-maintained opioid dependent subjects
- The pharmacokinetics of oxycodone and naloxone in methadone-maintained opioid dependent subjects
- The safety and tolerability of chewed ONU in methadone-maintained opioid-dependent subjects

##### **3.1.2 Study design**

This was a single-center, double-blind, placebo-controlled, randomized, block-order crossover study to evaluate the pharmacodynamic effects (subjective, physiologic, and withdrawal), pharmacokinetics, and safety of oral ONU (chewed) compared to Oxy API in methadone-maintained opioid-dependent subjects.

The study consisted of 3 phases: screening, treatment, and follow-up. The study design is summarized in Figure 1 on page 16 of the study report. The Screening Visit (Visit 1) was conducted within 30 days of first study drug administration.

The Treatment Phase consisted of 2 sessions, each lasting 4 days (with 3 overnight stays). Subjects received study drugs according to a randomized block-order design, with each block consisting of two 3 × 3 Williams squares. In the first block, subjects received the following study drugs, each separated by an interval of approximately 24 hours:

- Chewed 30/15 mg ONU (oxycodone/naloxone) + placebo solution
- 30 mg Oxy API in solution + chewed placebo
- Placebo solution + chewed placebo

Following an interval of at least 3 days, subjects were randomized to Session 2, where they received the following study drugs:

- Chewed 60/30 mg ONU (oxycodone/naloxone) + placebo solution
- 60 mg Oxy API in solution + chewed placebo
- Placebo solution + chewed placebo

Pharmacodynamic assessments were performed up to 4 hours post-dose.

Subjects were requested to return for a Follow-up Visit 3 to 7 days following the last study drug administration.

### **3.1.3 Pharmacodynamic endpoints**

The subjective pharmacodynamic endpoints were as follows:

Drug Liking visual analog scale (VAS) at the moment score (maximum effect [Emax], minimum effect [Emin], time-averaged area under the effect curve [TA\_AUE])

Overall Drug Liking VAS (end-of-session score)

Take Drug Again VAS (end-of-session score)

High VAS (Emax, TA\_AUE)

Good Effects VAS (Emax, TA\_AUE)

Bad Effects VAS (Emax, TA\_AUE)

Feeling Sick VAS (Emax, TA\_AUE)

Drowsiness/Alertness VAS (Emin, TA\_AUE)

Any Effects VAS (Emax, TA\_AUE)

The objective physiologic endpoints were as follows:

Pupillometry (maximum pupil constriction [MPC], time-averaged pupillometry area over the effect curve relative to baseline [TA\_PAOE])

The withdrawal endpoints were as follows:

Subjective Opiate Withdrawal Scale (SOWS) (Emax, TA\_AUE)

Objective Opioid Withdrawal Scale (OOWS) (Emax, TA\_AUE)

### **3.1.4 Number of Subjects**

A total of 18 subjects were randomized to Treatment Session 1 and completed all 3 doses (100%). Two subjects withdrew after completing Treatment Session 1 but prior to enrolling in Treatment Session 2. One subject (Subject 01013) withdrew consent and the other subject (Subject 01001) was withdrawn due to an AE of thrombocytopenia (attributed to the last treatment received, Oxy API 30 mg, but occurring almost 4 months after receiving this treatment in Treatment Session 1).

### **3.1.5 Statistical methodologies used in the Sponsor's analyses**

Derived pharmacodynamic endpoints and data at each time point were summarized by descriptive statistics and presented graphically. Pharmacodynamic endpoints were analyzed using a mixed effect model for a crossover study. From each model, means, 95% confidence intervals and P values for treatments and treatment differences were computed. The Benjamini and Hochberg procedure was used to control for Type I error arising from the multiple comparisons. Tests for non-normality and homogeneity of variance were conducted and non-parametric methods were employed, as necessary. Comparisons were performed primarily between the treatments within blocks/sessions.

### **3.1.6 Sponsor's Summary and Conclusions**

#### Summary of results for pharmacodynamic, physiological, and withdrawal endpoints

Treatment Session 1:

- There were no significant differences between placebo and Oxy API on subjective measures; however, pupil diameter was significantly lower with Oxy API 30 mg compared to placebo.

- Effects of ONU 30/15 mg were also minimal; however, compared with placebo, ONU 30/15 mg showed significantly higher Bad Effects VAS scores over time (TA\_AUE) and significantly lower Overall Drug Liking VAS (ie, overall disliking), but no effect on pupil diameter or other subjective measures.
- Relative to Oxy API 30 mg, ONU 30/15 mg showed significant greater disliking (Drug Liking VAS Emax and TA\_AUE and Overall Drug Liking VAS) and less willingness to take the drug again. Bad Effects VAS scores were significantly greater with ONU 30/15 mg relative to Oxy API 30 mg.

Treatment Session 2:

- Oxy API 60 mg showed no statistically significant treatment effects on Drug Liking, Overall Drug Liking VAS or Take Drug Again VAS, but did show significant effects relative to placebo on Good Effects VAS, High VAS, and Any Effects VAS endpoints (particularly TA\_AUE), as well pupil diameter. In addition, peak Feeling Sick VAS was lower with Oxy API 60 mg compared to placebo.
- There were few significant differences between ONU 60/30 mg and placebo. However, ONU 60/30mg was associated with lower Drug Liking VAS Emax, and higher negative effects (including Bad Effects VAS, Feeling Sick VAS, and SOWS). There was no effect of ONU 60/30 mg on peak pupil diameter, but over time (TA\_PAOE), there was a small but significant miotic effect compared to placebo.
- Compared to Oxy API 60 mg, ONU 60/30 mg was associated with fewer balance (Drug Liking VAS, Take Drug Again VAS), positive (Good Effects VAS, High VAS), and pupillary effects and greater negative effects (Bad Effects VAS, Feeling Sick VAS, and SOWS).
- Examination of the distribution and individual subject responses suggests that most subjects experienced little or no effect of ONU at either dose, while a small subset of subjects showed mild negative/withdrawal-like responses.

### Conclusion

In conclusion, ONU 30/15 mg was associated with few subjective or withdrawal effects, while ONU 60/30 mg was associated with lower abuse-related subjective effects compared to Oxy API. In addition, ONU 60/30 mg was associated with significant negative subjective effects compared to Oxy API and placebo in methadone maintained, opioid dependent subjects. In some subjects, ONU 60/30 mg was associated with mild subjective withdrawal effects and gastrointestinal TEAEs potentially related to naloxone blockade. These results demonstrate that the naloxone component reduces the abuse potential of chewed ONU in opioid-dependent individuals.

### **3.2 Data location**

The analysis datasets are located at

<\\cdsesub1\evsprod\nda205777\0000\m5\datasets\onu1004\analysis\adam\datasets\adpd.xpt>

### **3.3 Reviewer's assessment**

There was no Qualification Phase in this study. This reviewer found that 78% (14/18) and 56% (7/16) of subjects had Emax of Drug Liking VAS for Oxy API 30 mg and Oxy API 60 mg less than 60, respectively. Due to no significant difference between Oxy API and placebo on Drug Liking VAS as well as on other positive subjective abuse potential measures in Treatment Session 1, and Overall Drug Liking VAS and Take Drug Again VAS in Treatment Session 2, the results from the comparisons between ONU and Oxy API on these measures are not meaningful. Per the team leader in the CSS, Dr. Silvia Calderon's suggestion, the reviewer evaluated Subjective Opiate Withdrawal Scale (SOWS) and Objective Opioid Withdrawal Scale (OOWS) in both sessions. Note that SOWS is ranged from 0 to 64, and OOWS is range from 0 to 13.

#### **3.3.1 Statistical analysis for data from Treatment Session 1**

In the reviewer's report Oxy30, ONU30, Oxy 60, ONU60, and P denote Oxy API 30 mg, chewed ONU 30/15 mg, Oxy API 60 mg, chewed ONU 60/30 mg and placebo, respectively. In addition, the word "chewed" was omitted in some tables for the new drug.

##### **3.3.1.1 Descriptive statistics**

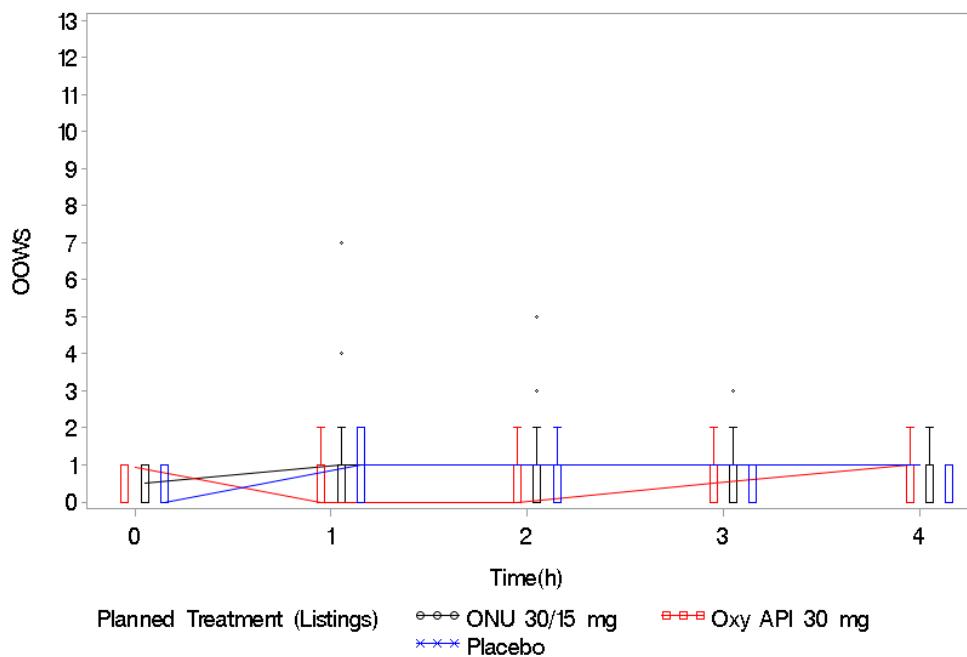
Table 7 summarizes the mean, standard error, minimum, the first quartile ( $Q_1$ ), median, the third quartile ( $Q_3$ ), and maximum for three treatments in the study and for the treatment differences in Emax on OOWS and SOWS.

**Table 7: Summary Statistics for Emax of OOWS and Emax of SOWS in Treatment Session 1**

Measure	TRT/Diff	N	Mean	StdErr	Min	Q1	Med	Q3	Max
OOWS	ONU30	18	1.06	0.45	-1	0	0	1.25	7
	Oxy30	18	0.17	0.17	-1	0	0	0.25	2
	P	18	0.72	0.19	0	0	0.5	1.25	2
	Oxy30-P	18	-0.56	0.28	-2	-2	-0.5	0	2
	Oxy-ONU30	18	-0.89	0.43	-6	-1.25	-0.5	0	2
	ONU30-P	18	0.33	0.49	-2	-1	0	1	6
SOWS	ONU30	18	6.44	2.42	-3	0	2	9.25	38
	Oxy30	18	1.67	1.14	-3	0	0	1.25	16
	P	18	3.28	1.07	-3	0	2	6.25	16
	Oxy30-P	18	-1.61	1.61	-16	-4.5	-1.5	0	15
	Oxy-ONU30	18	-4.78	2.06	-22	-9.25	-1	0.25	8
	ONU30-P	18	3.17	2.52	-16	-4	1	7.75	31

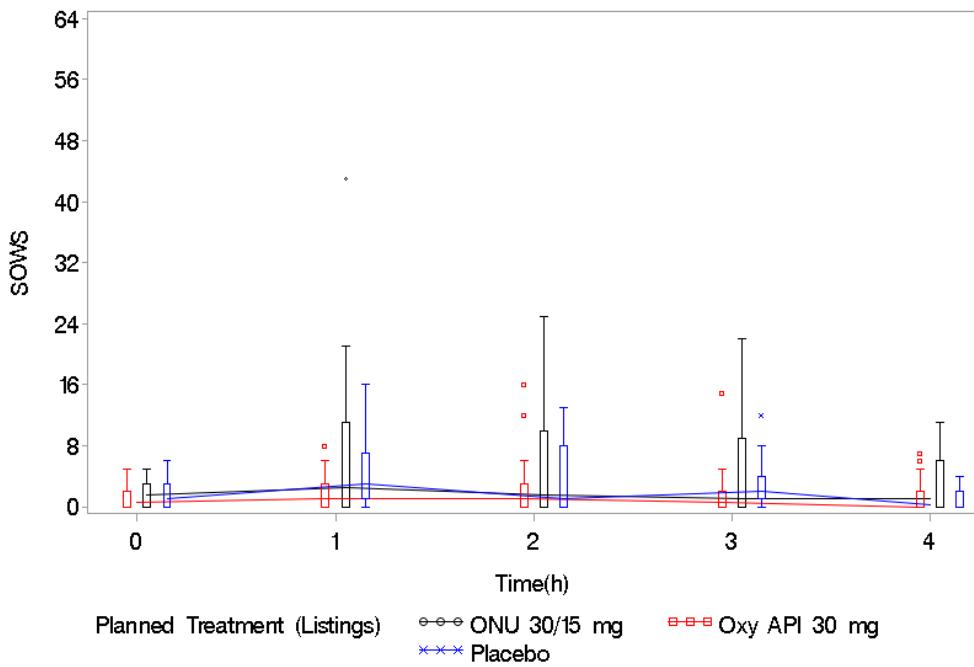
Figures 7 and 8 are the boxplots of OOWS and SOWS by time, respectively. The line on the graphs connects the medians at each time point for each treatment.

Because Oxy API will not cause withdraw syndrome, this reviewer focuses on the comparison between chewed ONU 30/15 mg tablet and placebo.



**Figure 7: Boxplots of OOWS by Time for Treatment Session 1**

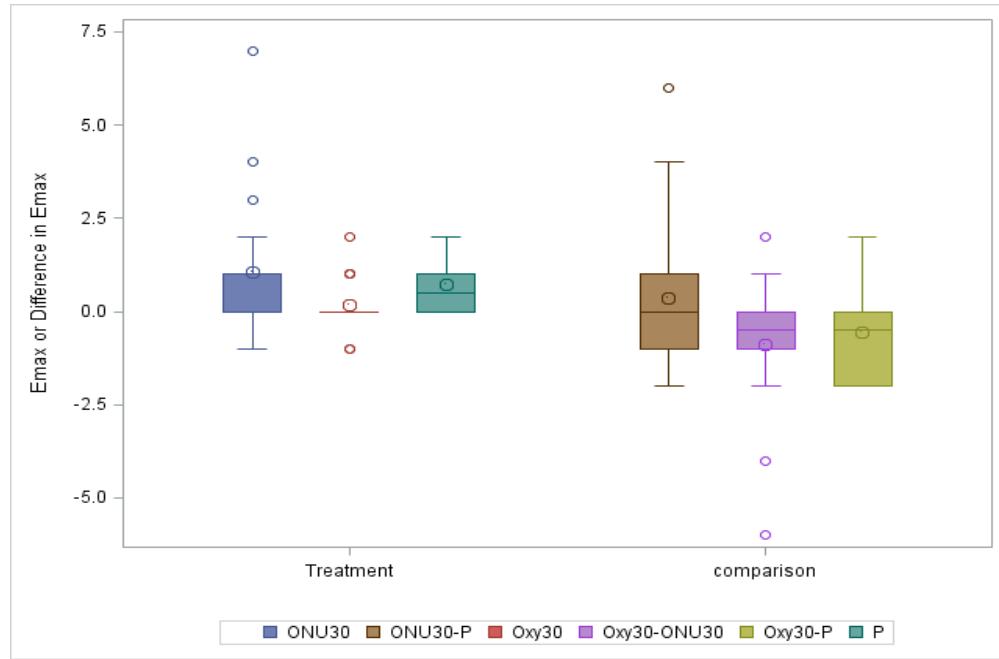
Note: The black line and blue line overlapped from hour 1 to hour 4.



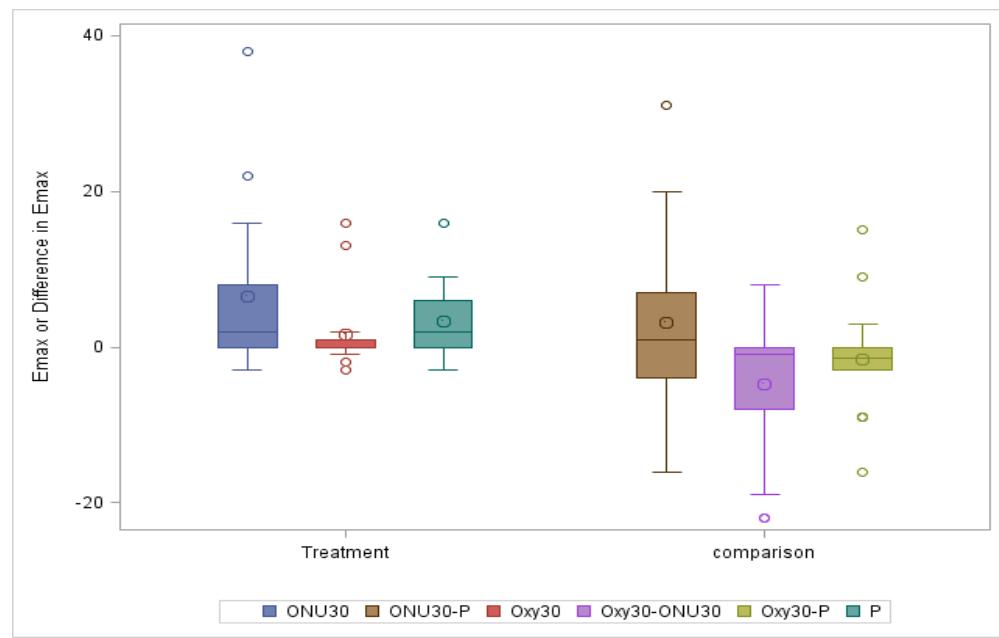
**Figure 8: Boxplots of SOWS by Time for Treatment Session 1**

Table 7 and Figures 7 and 8 show that the mean and median differences between chewed ONU 30/15 mg and placebo on OOWS and SOWS are very small.

Figures 9 and 10 are boxplots for Emax and difference in Emax between treatments on OOWS and SOWS respectively. The line in each box denotes the median and the big circle in each boxplot is for the mean. Note that the scales of these two measures are different. OOWS is ranged from 0 to 13 and SOWS is ranged from 0 to 64.



**Figure 9: Boxplot for each treatment and each treatment comparison for Emax of OOWS in Treatment Session 1**



**Figure 10: Boxplot for each treatment and each treatment comparison for Emax of SOWS in Treatment Session 1**

It can be seen from Figures 9 and 10 that only a few subjects had mild or moderate large score relative to the scale of the measures. The median difference in Emax between chewed ONU30 mg and placebo are around zero.

### 3.3.1.2 Statistical testing

The statistical model used in the reviewer's analysis was the mixed-effect model with treatment, period, sequence as fixed effects, baseline (pre-dose) measurement as covariate, and subject grouped in sequence as a random effect. The reviewer checked assumptions in the model for the equal variances and the normality. If the assumption of equal variances was not satisfied, Tukey-Kramer's method was used for adjusting the unequal variance. If the normal assumption of the model was violated, the reviewer did the following: If the normality was satisfied, the paired t-test was used in the comparison otherwise the reviewer checked the assumption for the symmetry of the distribution of paired differences, if the distribution was approximately symmetric, Wilcoxon Signed-Rank test was used, otherwise the Sign-test was used.

Tables 8 and 9 show the statistical testing results for Emax of OOWS and Emax of SOWS in Treatment Session 1, respectively. No significant difference was found in any comparison for both OOWS and SOWS.

**Table 8: Analysis Results for Emax of OOWS in Treatment Section 1**

Treatment Session 1 (N=18)	Total OOWS Score (Emax)		
	Mean /Median diff	StdErr/IQR	p-Value
<b>Pairwise comparisons</b>			
Oxy API 30 mg - Placebo	-0.56	0.2826	0.0659
ONU 30/15 mg – Placebo*	0	(-1, 1)	0.9028
ONU 30/15 mg - Oxy API 30 mg*	0.5	(0, 2)	0.0635

\*: Nonparametric method is used. The table reports the median difference and interquartile range instead of the mean difference and the standard error for such a case.

**Table 9: Analysis Results for Emax of SOWS in Treatment Section 1**

Treatment Session 1 (N=18)	SOWS (Emax)		
	Mean /Median diff	StdErr/IQR	p-Value
<b>Pairwise comparisons</b>			
Oxy API 30 mg - Placebo	-1.61	1.61	0.3313
ONU 30/15 mg - Placebo	3.17	2.52	0.2258
ONU 30/15 mg - Oxy API 30 mg*	1	(0, 8)	0.1796

\*: Nonparametric method is used. Table reports the median difference and interquartile range instead of the mean difference and the standard error for such a case.

### 3.3.2 Statistical analysis for data from Treatment Session 2

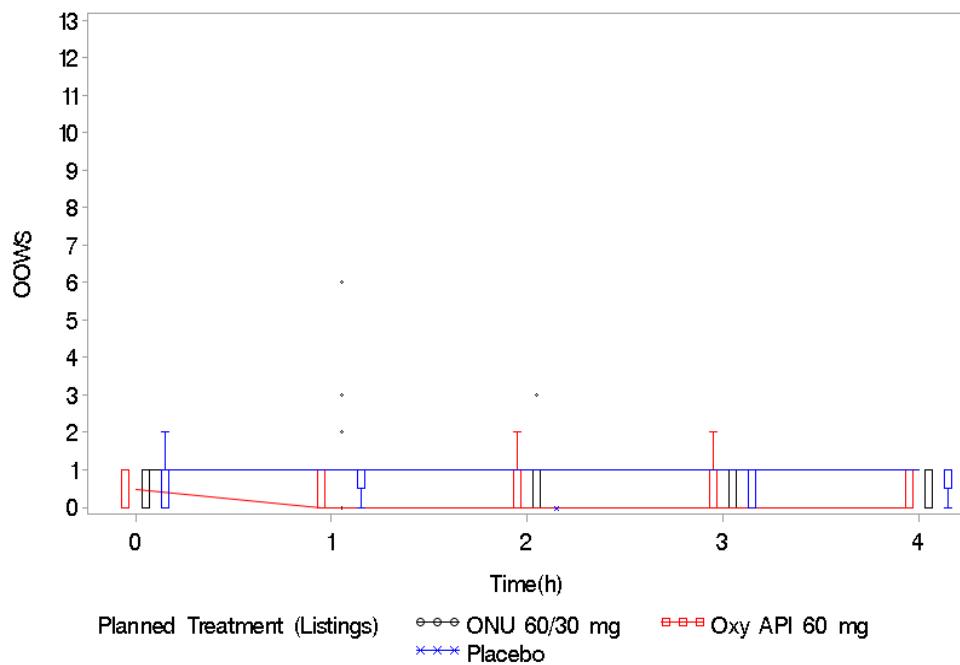
#### 3.3.2.1 Descriptive statistics

Table 7 summarizes the mean, standard error, minimum, the first quartile ( $Q_1$ ), median, the third quartile ( $Q_3$ ), and maximum for three treatments in the study and for the treatment differences between chewed ONU 60/30 mg tablet and Oxy API 60 mg solution or placebo on OOWS and SOWS.

**Table 10: Summary Statistics for Emax of OOWS and Emax of SOWS in Treatment Session 2**

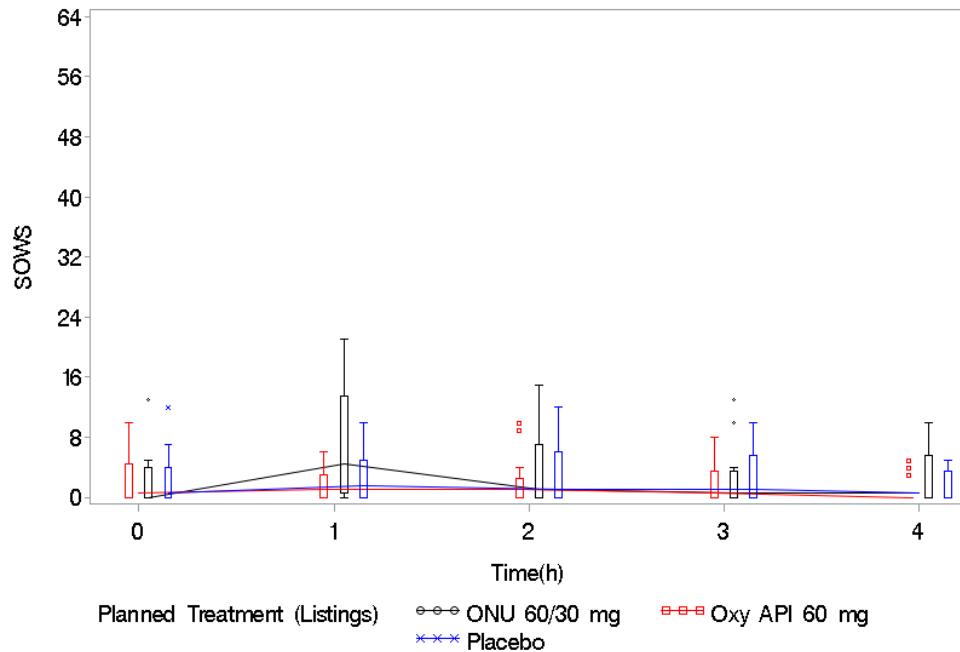
Measure	TRT/Diff	N	Mean	StdErr	Min	Q1	Med	Q3	Max
OOWS	ONU60	16	0.63	0.38	-1	0	0	0.75	5
	Oxy60	16	0.06	0.11	-1	0	0	0	1
	P	16	0.19	0.14	-1	0	0	0.75	1
	Oxy60-P	16	-0.13	0.18	-1	-1	0	0	1
	Oxy-ONU60	16	-0.56	0.45	-6	-0.75	0	0	1
	ONU60-P	16	0.44	0.45	-2	-0.75	0	0.75	5
SOWS	ONU60	16	5.63	1.15	0	1	4	9.75	14
	Oxy60	16	0.13	1.03	-12	0	0	0	9
	P	16	1.75	0.66	-2	0	1	4.25	8
	Oxy60-P	16	-1.63	1.33	-17	-2.5	-1	0	8
	Oxy-ONU60	16	-5.50	1.38	-14	-10	-5	-1	5
	ONU60-P	16	3.88	1.30	-4	-0.75	3.5	7.75	14

Figures 11 and 12 are the boxplots of OOWS and SOWS by time, respectively. The line on the graphs connects the medians at each time point for each treatment.



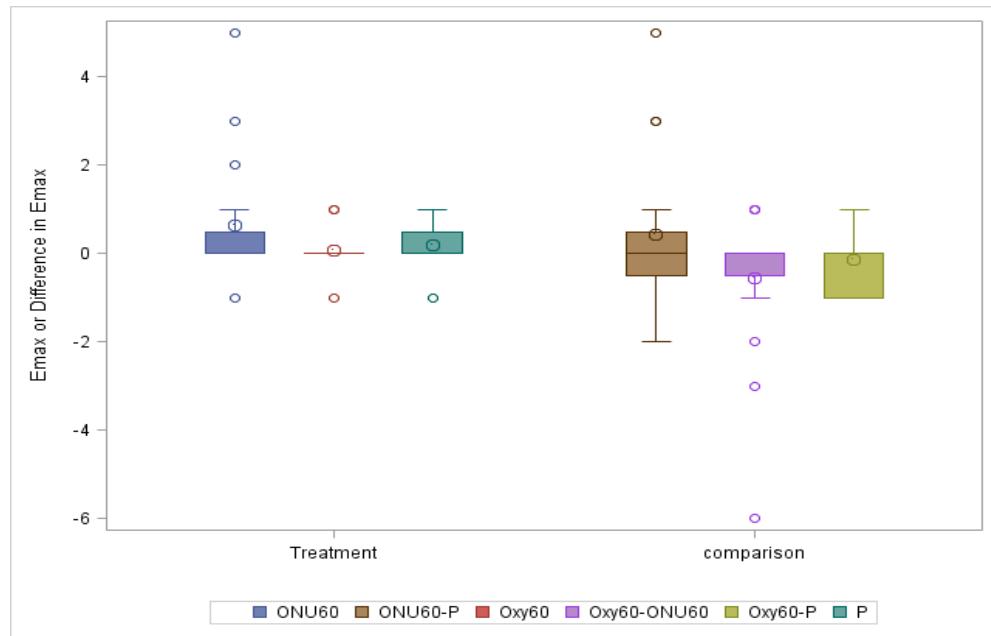
**Figure 11: Boxplots of OOWS by Time for Treatment Session 2**

Note: The black line and blue line are overlapped.

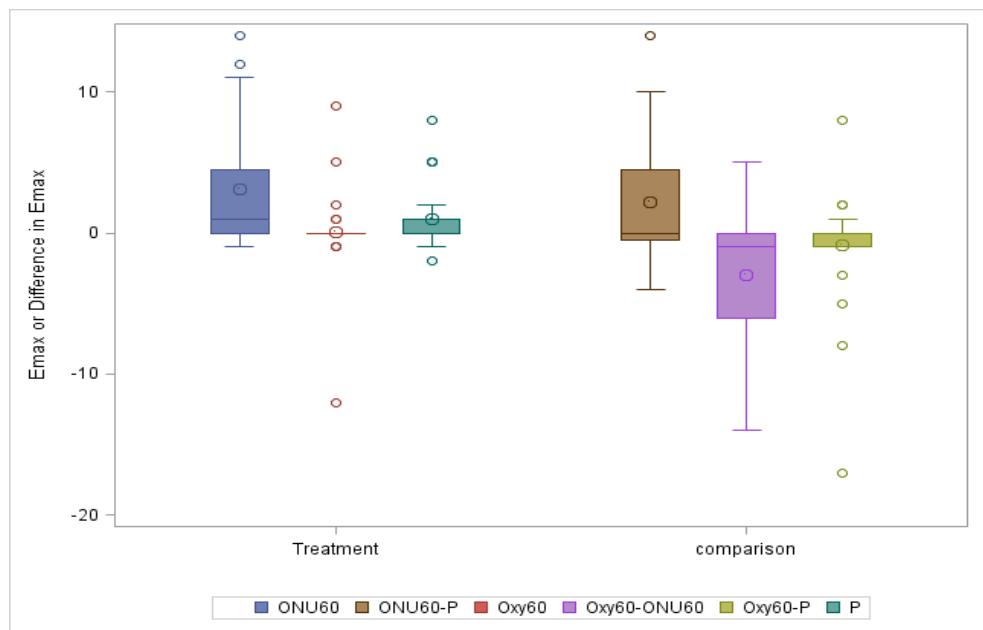


**Figure 12: Boxplots of SOWS by Time for Treatment Session 2**

Figures 13 and 14 are boxplots for treatments and difference between treatments for Emax of OOWS and Emax of SOWS, respectively. The line in each box denotes the median and the big circle in each boxplot is for the mean. Notice that the scales of these two measures are different. OOWS is ranged from 0 to 13 and SOWS is ranged from 0 to 64.



**Figure 13: Boxplot for each treatment and each treatment comparison for Emax of OOWS in Treatment Session 2**



**Figure 14: Boxplot for each treatment and each treatment comparison for Emax of SOWS in Treatment Session 2**

### 3.3.2.2 Statistical testing

The same statistical methodologies used for Treatment Session 1 were used for Treatment Session 2 (See [2.3.1.2 Inferential Statistics](#)).

Tables 11 and 12 show the statistical testing results in Treatment Session 2. The results show that:

- There was no significant difference among Oxy API 60 mg, chewed ONU 60/30 mg and placebo on OOWS.
- There was no significant difference between Oxy API 60 mg and placebo on SOWS.
- Chewed ONU 60/30 mg had significantly larger mean than placebo and Oxy API 60 mg on SOWS.

**Table 11: Analysis Results for Emax of OOWS in Treatment Section 2**

Treatment Session 2 (N=16)	Total OOWS Score (Emax)		
	Mean /Median diff	StdErr/IQR	p-Value
<b>Pairwise comparisons</b>			
Oxy API 60 mg - Placebo*	-1	(-2, 0)	0.146
ONU 60/30 mg - Placebo	0.44	0.45	0.3432
ONU 60/30 mg - Oxy API 60 mg	0.56	0.45	0.2274

**Table 12: Analysis Results for Emax of SOWS in Treatment Section 2**

Measure	Treatment	ONU 60/30 mg	Oxy API 60 mg	P
	N	16	16	16
SOWS	LS mean	5.63	0.37	1.83
	95% CI	(3.57, 7.69)	(-1.70, 2.44)	(-0.23, 3.89 )
	Diff vs Oxy60/pval	5.26 /0.0006		
	95% CI	(2.16, 8.35)		
	Diff vs P/pval	3.80/0.0129	-1.46/0.4833	
	95% CI	(0.72, 6.88)	(-4.54, 1.65)	

Note: W-test for the residual of the model is not significant ( $p=0.2412$ ) for SOWS in Treatment Session 2. Thus, least square mean and confidence interval for each treatment is presented for each treatment.

### 3.4 Conclusion

The reviewer is not able to assess the abuse potential of ONU in this study because there was no significant difference between ONU and Oxy API for Drug Liking VAS, and some other positive subjective measures. The results from the assessment of OOWS and SOWS show that a few subjects had mild or moderate withdrawn syndrome. Chewed ONU 60/30 mg had significantly larger mean than both placebo and Oxy API 60 mg on SOWS. The least square means were 5.26, 0.37 and 1.83 for ONU60/30

mg, Oxy API 60 mg and placebo, respectively. The 95% confidence intervals of the mean difference in Emax were (0.72, 6.88) and (2.16, 8.35) when comparing ONU 60/30 mg to placebo and to Oxy API 60 mg, respectively. Note that SOWS is ranged from 0 to 64. The CSS may comment on the clinical significance of these differences on SOWS.

**Appendix I: Summary statistics for abuse potential measures other than Drug Liking VAS in Study ONU 1003**

**Table 13: Summary statistics for other abuse potential measures in group 1 (N=14)**

Abuse Potential Measures	TRT	Mean	StdErr	Min	Q1	Med	Q3	Max
High VAS	ONU 40/20 mg*	85.64	7.33	0	81.75	99.5	100	100
	Oxy 40 mg**	96.93	2.39	67	99.75	100	100	100
	Placebo	19.64	9.07	0	0	0	51	100
	Oxy-P	77.29	10.73	-33	49	100	100	100
	Oxy-ONU	11.29	5.43	-8	0	0	18	67
	ONU-P	66.00	14.35	-100	47.5	86	100	100
ARCI MBG	ONU 40/20 mg	8.50	1.63	0	1.75	10.5	14	16
	Oxy 40 mg	9.86	1.54	-1	5.5	13	14	14
	Placebo	1.43	0.99	0	0	0	1.25	14
	Oxy-P	8.43	1.84	-3	-1	12	14	14
	Oxy-ONU	1.36	1.03	-3	-0.25	0	2.75	12
	ONU-P	7.07	2.27	-13	-0.25	10	14	16
Good Effects VAS	ONU 40/20 mg	90.57	4.21	60	73	100	100	100
	Oxy 40 mg	93.43	3.11	66	85.5	100	100	100
	Placebo	30.00	9.93	0	0	8	51	100
	Oxy-P	63.43	11.88	-34	26.5	86	100	100
	Oxy-ONU	2.86	3.89	-22	0	0	3	36
	ONU-P	60.57	11.46	-40	42.5	67	99.25	100
Bad Effects VAS	ONU 40/20 mg	30.57	9.92	0	0	12	52.5	100
	Oxy 40 mg	32.50	9.65	0	0	26	51	100
	Placebo	11.14	5.77	0	0	0	14.25	51
	Oxy-P	21.36	11.15	-51	0	0	50	100
	Oxy-ONU	1.93	2.68	-14	-0.25	0	0.25	27
	ONU-P	19.43	11.09	-51	0	0.5	46.75	100
Overall Drug Liking VAS	ONU 40/20 mg	83.00	4.46	51	68	86	100	100
	Oxy 40 mg	85.57	4.99	51	69	97	100	100
	Placebo	52.07	1.39	50	50	51	51	70
	Oxy-P	33.50	5.81	-13	17.75	46.5	50	50
	Oxy-ONU	2.57	3.55	-16	-8.5	0	9	32
	ONU-P	30.93	5.38	-19	16.75	35.5	49	50
Take Drug Again VAS	ONU 40/20 mg	84.71	5.05	51	67	100	100	100
	Oxy 40 mg	89.79	4.60	50	78	100	100	100
	Placebo	32.57	8.50	0	0	50	51	100
	Oxy-P	57.21	11.52	-40	37	50	100	100
	Oxy-ONU	5.07	4.06	-20	0	0	13.5	32
	ONU-P	52.14	11.62	-49	16.25	50	99.25	100

\*: chewed ONU 40/20 mg

\*\*: Oxycodone oral solution 40 mg

**Table 14: Summary statistics for other abuse potential measures in group 2 (N=23)**

Abuse Potential Measures	TRT	Mean	StdErr	Min	Q1	Med	Q3	Max
High VAS	ONU*	36.22	7.44	0	0	47	67	100
	OxyAPI**	92.74	4.52	0	100	100	100	100
	P	8.30	4.91	0	0	0	1	100
	OxyAPI-P	84.43	6.55	0	82	99	100	100
	OxyAPI-ONU	56.52	7.71	0	25	50	100	100
	ONU-P	27.91	9.17	-100	0	16	57	100
ARCI MBG	ONU	2.09	0.96	0	0	0	1	16
	OxyAPI	10.87	1.14	0	7	14	16	16
	P	1.17	0.66	0	0	0	1	14
	OxyAPI-P	9.70	1.18	-1	4	10	14	16
	OxyAPI-ONU	8.78	1.26	-1	3	9	14	16
	ONU-P	0.91	1.04	-13	0	0	1	16
Good Effects VAS	ONU	38.91	7.82	0	0	50	70	100
	OxyAPI	96.61	1.83	67	100	100	100	100
	P	9.09	5.28	0	0	0	0	100
	OxyAPI-P	87.52	6.00	0	96	100	100	100
	OxyAPI-ONU	57.70	7.78	0	29	50	96	100
	ONU-P	29.83	8.66	-50	0	10	70	100
Bad Effects VAS	ONU	26.26	7.34	0	0	2	62	100
	OxyAPI	24.48	6.95	0	0	0	55	100
	P	0.30	0.22	0	0	0	0	5
	OxyAPI-P	24.17	6.97	-1	0	0	54	100
	OxyAPI-ONU	-1.78	7.90	-100	-9	0	11	78
	ONU-P	25.96	7.37	-5	0	1	62	100
Overall Drug Liking VAS	ONU	53.43	3.48	14	50	51	51	100
	OxyAPI	92.91	2.48	63	90	100	100	100
	P	50.26	3.15	0	50	50	51	100
	OxyAPI-P	42.65	3.94	0	38	49	50	98
	OxyAPI-ONU	39.48	4.13	0	31	49	50	77
	ONU-P	3.17	5.35	-49	0	0	1	85
Take Drug Again VAS	ONU	42.61	6.37	0	6	50	56	100
	OxyAPI	93.57	2.31	62	87	100	100	100
	P	30.74	6.09	0	0	50	51	100
	OxyAPI-P	62.83	6.05	0	49	50	99	100
	OxyAPI-ONU	50.96	5.94	0	36	50	74	100
	ONU-P	11.87	8.01	-51	0	0	35	100

\*: finely crushed ONU 40/20 mg

\*\*: Oxy API 40 mg powder.

**Table 15: Summary statistics for other abuse potential measures in group 3 (N=22)**

Abuse Potential Measures	TRT	Mean	StdErr	Min	Q1	Med	Q3	Max
High VAS	ONU*	19.55	7.12	-1	0	0	56.75	100
	Oxy**	92.32	4.97	0	100	100	100	100
	P	2.91	2.49	0	0	0	0.25	55
	Oxy-P	89.41	5.64	0	97	100	100	100
	Oxy-ONU	72.77	10.21	-100	43.25	100	100	100
	ONU-P	16.64	7.85	-55	-0.25	0	56.75	100
ARCI MBG	ONU	1.45	0.62	0	0	0	1.25	12
	Oxy	10.23	1.07	0	5.75	12	14	16
	P	0.36	0.23	0	0	0	0	5
	Oxy-P	9.86	1.05	0	5.5	11.5	14	16
	Oxy-ONU	8.77	1.28	-7	4	10.5	14	16
	ONU-P	1.09	0.64	-4	0	0	1.25	11
Bad Effects VAS	ONU	7.45	4.52	0	0	0	1	76
	Oxy	11.45	4.77	0	0	0	15.75	75
	P	2.86	2.63	0	0	0	0	58
	Oxy-P	8.59	5.68	-58	0	0	15.75	75
	Oxy-ONU	4.00	2.79	-18	-0.25	0	0	43
	ONU-P	4.59	5.42	-58	0	0	0.25	76
Good Effects VAS	ONU	20.00	7.44	0	0	0	53	100
	Oxy	94.00	4.52	0	95.75	100	100	100
	P	2.73	2.50	0	0	0	0	55
	Oxy-P	91.27	5.13	0	95.75	100	100	100
	Oxy-ONU	74.00	10.44	-100	46.25	100	100	100
	ONU-P	17.27	8.16	-54	0	0	53	100
Overall Drug Liking VAS	ONU	49.50	3.94	0	50	50	51	100
	Oxy	79.50	5.68	0	56	92	100	100
	P	45.95	3.19	0	50	50	51	58
	Oxy-P	33.55	5.53	-5	5.25	42	50	100
	Oxy-ONU	30.00	7.95	-100	14.25	41	50	100
	ONU-P	3.55	6.23	-51	-0.25	0	1	100
Take Drug Again VAS	ONU	36.95	6.18	0	0	50	51	100
	Oxy	82.00	6.05	0	60.5	99	100	100
	P	34.50	5.15	0	0	50	50.25	55
	Oxy-P	47.50	7.60	-18	30	49.5	67.25	100
	Oxy-ONU	45.05	9.91	-100	31.25	50	72.25	100
	ONU-P	2.45	7.78	-51	-2	0	6.25	100

\*: oxycodone 0.07 mg/kg/naloxone 0.035 mg/kg

\*\*: oxycodone 0.07 mg/kg

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/s/

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LING CHEN  
02/11/2014

YI TSONG  
02/11/2014

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 205777

Applicant: Purdue Pharma L.P.

Stamp Date: September 23, 2013

Drug Name: Targiniq

NDA/BLA Type: NDA

On initial overview of the NDA/BLA application for RTF:

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

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			Also refer to clinical review.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	See clinical review.
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

## Information request to the Sponsor:

It appears that for some subjects in Study ONU3701 the actual treatment received in the double-blind period was different from the randomized (planned) treatment. In addition, the study report mentioned that some subjects might be randomized twice. Provide an explanation or clarification along with the relevant documentations for the above randomization issues.

## **STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA**

Feng Li	November 18, 2013
Reviewing Statistician	Date
Janice Derr	November 18, 2013
Supervisor/Team Leader	Date

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/s/

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FENG LI  
11/18/2013

JANICE A DERR  
11/18/2013