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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: NDA 204-442

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Indication(s): Maintenance Treatment of Opioid Dependence

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1 EXECUTIVE SUMMARY

In 2012 Titan Pharmaceuticals, Inc. submitted a New Drug Application (NDA) for Probuphine (buprenorphine hydrochloride/ethylene vinyl acetate) implants for the maintenance treatment of opioid dependence. This application was given a complete response in April 2013. It was recommended that the Applicant explore higher doses. Subsequently, the Applicant proposed restricting the indication to treatment of patients stabilized on sublingual buprenorphine at doses of 8 mg or less. The Agency stated that an additional clinical study would be required for this indication. Since there was a high likelihood that the stability of these subjects would be jeopardized if their buprenorphine treatment was entirely discontinued and replaced with placebo the Agency agreed, an active-controlled, non-inferiority study would be acceptable.

This additional double-blind, double-dummy active controlled, non-inferiority study, PRO-814, was conducted from June 2014 until July 2015 and is the focus of this review. The population for this study was restricted to subjects who were on buprenorphine treatment for at least six consecutive months and were on a stable dose of no more than 8 mg of buprenorphine for at least three months prior to randomization. The Applicant's primary endpoint for this study was the responder rate where a responder was defined as a subject with no more than 2 of 6 months with any evidence of illicit opioid use. There were several deficiencies in the Applicant's analysis of this study, including the analysis population, inadequate exploration of the effect of missing data, no exploration of the effect of supplemental buprenorphine. These issues are discussed in detail in this review.

The Psychopharmacologic Drugs Advisory Committee met on January 12, 2016 to discuss this product. Questions raised included the appropriateness of the study population, whether to include supplemental medication in the responder definition, how to include missing data in the responder definition, and which approach to defining a responder is most appropriate. The committee commented that they considered the Applicant's analyses of the results to be overly optimistic. The committee also agreed with the Agency's more conservative approach to missing data considered in this review and several committee members agreed that supplemental medication should be taken into account in the definition of treatment response. Regardless, the committee voted 12 to 5 in favor of approval.

2 INTRODUCTION

2.1 Overview

Probuphine (buprenorphine hydrochloride/ethylene vinyl acetate) is a subdermal implant designed to provide sustained delivery of buprenorphine for up to six months and is being developed for the maintenance treatment of opioid dependence by Titan Pharmaceuticals. Buprenorphine was first approved in 1981 under the trade name Buprenex for the relief of moderate to severe pain. It has since been approved for the treatment of opioid dependence as a sublingual tablet (Subutex) and in combination with naloxone in sublingual tablet (Suboxone, Zubsolv), sublingual film (Suboxone) and buccal film (Bunavail) formulations.

The development program for Probuphine was conducted under IND 70,852. Two randomized, double-blind, placebo-controlled phase 3 studies were conducted prior to the initial New Drug Application (NDA) submission. The NDA for Probuphine was originally submitted in October 2012 and a complete response was issued in April 2013. In the complete response letter dated April 30, 2013, it was recommended that the Applicant explore higher doses of Probuphine. However, in a meeting held on November 19, 2013, rather than exploring a higher dose the Applicant proposed restricting the indication of Probuphine to patients stabilized on sublingual buprenorphine at doses of 8 mg or less. During this meeting, the Agency stated that data from a controlled clinical trial would be required to support approval in this population and that a double-dummy, active-controlled trial comparing Probuphine to sublingual buprenorphine may suffice. In response, Trial PRO-814 was initiated in June 2014 and completed in May 2015. The Applicant resubmitted the NDA in August 2015

2.2 Data Sources

All data was provided electronically by the Applicant as SAS transport files and can be found at the following location in the CDER electronic document room (EDR):

<\\CDSESUB1\evsprod\NDA204442\0030\m5\datasets>

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data submitted by the Applicant was of a sufficient quality to allow a thorough review of the study.

3.2 Evaluation of Efficacy

My review focused on study PRO-814 submitted to support the indication of maintenance treatment of opioid dependence. The reader is referred to the previous statistical review by David Petullo for a review of the two trials included in the original submission.

3.2.1 PRO-814

3.2.1.1 Study Design and Endpoints

This study was a randomized, double-blind, double-dummy, active-controlled, multicenter, non-inferiority study conducted to evaluate the safety and efficacy of four 80 mg Probuphine

implants in adult outpatients with opioid dependence who were clinically stabilized on no more than 8 mg of sublingual buprenorphine.

The primary objective for this study was to demonstrate maintenance of treatment efficacy when transferring adult outpatients with opioid dependence that were clinically stabilized on 8 mg or less of sublingual buprenorphine to 4 Probuphine implants compared to treatment as usual with sublingual buprenorphine.

This study consisted of three phases: a Screening Phase (Weeks -2 to -1), a 24-week Maintenance Phase, and a 2-week Follow-Up Phase. In order to be eligible for the study, subjects were required to be male or female, between 18 and 65 years of age, have a primary diagnosis of opioid dependence (Diagnostic and Statistical Manual – 4th Edition – Text Revision [DSM-IV-TR]), and be considered clinically stable by their treating healthcare provider. Subjects were also required to meet the following criteria:

- a) Had been on sublingual buprenorphine treatment for at least 6 months.
- b) Had been on a sublingual buprenorphine dose of no more than 8 mg/day for at least the last 90 days.
- c) Had no positive urine toxicology results for illicit opioids in the last 90 days.

Eligible subjects were scheduled for the baseline/randomization visit no more than two weeks after the screening visit.

During the baseline/randomization visit, a subject's eligibility was confirmed by the investigator. Subjects confirmed to be eligible were randomized equally to the following two treatment groups:

- Treatment Group A: Treatment as usual with daily sublingual buprenorphine tables (≤ 8 mg/daily) + four placebo implants.
- Treatment Group B: Four 80 mg Probuphine implants + daily sublingual placebo tablets.

Implants were surgically inserted during this visit. The subject's sublingual buprenorphine/placebo dosage was matched to their prior stable maintenance dose.

Subjects returned for monthly study visits during Week 4, 8, 12, 16, 20, and 24 (End of Treatment Visit). During each of these six visits, subjects were to provide urine toxicology samples. Subjects were also required to provide four random urine toxicology samples throughout the 24-week treatment period. At the end of the study implants were to be removed and subjects were to be transitioned back to their pre-trial care as needed.

The Applicant's primary efficacy endpoint for this study was the proportion of responders for each treatment group, where a responder was defined as a subject with no more than 2 out of 6 months with any evidence of illicit opioid use. Illicit opioid use was defined as either a positive opioid urine toxicology result or self-reported illicit opioid use.

3.2.1.2 Statistical Methodologies

Since this was an active-controlled study the Applicant conducted a test of non-inferiority for the rate of responders between the two treatment arms utilizing a non-inferiority margin of 20%. If π_c and π_t equal the proportion of responders for the control arm and the experimental treatment arm, respectively, then the null hypothesis of inferiority can be stated as:

$$H_0: \pi_t \leq \pi_c - 0.20.$$

The alternative hypothesis of non-inferiority can then be stated as:

$$H_A: \pi_t > \pi_c - 0.20.$$

The hypothesis of non-inferiority will be concluded if the null hypothesis can be rejected at the 5% level. In order to test this hypothesis the Applicant computed the standard Wald confidence interval for the risk difference. If the lower bound of the 95% confidence interval for the difference between Probuphine and sublingual buprenorphine was greater than -0.20 then non-inferiority would be established.

The Applicant provided the following rationale for the 20% non-inferiority margin:

- Previous studies with patients on longer term buprenorphine or methadone treatment found that 18 to 31% of patients remained abstinent following treatment discontinuation.
- The Applicant also conducted a survey of addiction experts and reported that they expected a median of 25% of clinically stabilized patients to remain abstinent if their stable dose were discontinued.

Based on the results of these studies and the assumption that all subjects remaining on sublingual buprenorphine would continue to be stable, a non-inferiority margin of 20% was selected as it would preserve greater than 70% of the estimated effect size. This was considered clinically significant by the Applicant.

The Applicant stated that since this was an active-controlled study, bias would be introduced if all missing values were replaced with extreme values (i.e., either all replaced with “negative” or all replaced with “positive”). For example, if all missing values are replaced with “positive” then the results will be biased in favor of the group with the smaller dropout rate. Therefore the Applicant proposed imputing missing urines using the average of the within-subject proportion of opioid positive samples. The Applicant made the primary analysis more conservative by applying a 20% relative penalty to the higher of the two positive rates to impute missing data in the Probuphine treatment arm. For example, if the imputation for sublingual buprenorphine used a 15% positive rate then the rate for Probuphine would be 18%.

The Applicant provided two different definitions for the primary analysis population. The study protocol defined the Intent-to-Treat (ITT) population as all randomized subjects who received study medication. The statistical analysis plan and final study report defined this population as

all randomized subjects who received study medication and provided some efficacy data. The safety population was consistently defined as all subjects who received study medication.

The Applicant defined several secondary efficacy endpoints in the protocol as follows:

- Measures of desire/need to use:
 - Desire to Use VAS.
 - Need to Use VAS.
- Measures of withdrawal
 - Clinical Opiate Withdrawal Scale (COWS).
 - Subjective Opioid Withdrawal Scale (SOWS).

However, since no adjustments for multiplicity were considered these endpoints will not be discussed further in this review.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

Study PRO-814 was conducted from June 2014 to May 2015 at a total of 21 sites within the United States. A total of 177 subjects were randomized into the study. The disposition for all subjects randomized into the study is shown in Table 1.

Table 1: Subject Disposition

Category	SL BPN	Probuphine	Total
Randomized	90	87	177
Safety Population (N)	89	87	176
Completed, n (%)	84 (94.4)	81 (93.1)	165 (93.8)
Discontinued, n (%)	5 (5.6)	6 (6.9)	11 (6.3)
Reason for discontinuation, n (%)			
Adverse event	0	1 (1.1)	1 (0.6)
Request of sponsor or regulatory agency	1 (1.1)	0	1 (0.6)
Lost to follow-up	2 (2.2)	4 (4.6)	6 (3.4)
Other ^a	0	1 (1.1)	1 (0.6)
Subject request	2 (2.2)	0	2 (1.1)

Abbreviations: SL BPN, sublingual buprenorphine

^a Subject was incarcerated and not able to complete the study visits.

Source: Table 4 from Applicant's clinical study report

The Applicant's analysis populations are shown in Table 2. The Applicant excluded four randomized subjects from the Intent-to-Treat (ITT) population used for the primary analysis. One subject in the sublingual buprenorphine treatment group revealed after randomization but before receiving any study drug that they were scheduled for surgery the week following the baseline visit and so they were removed from the study. In the Probuphine treatment group one

subject was incarcerated and two subjects were lost to follow-up immediately after being randomized and receiving the implants. These subjects did not provide any post-baseline assessments and so were excluded from the SAP and Study Report definitions of the ITT population by the Applicant. These subjects would have been included if the Applicant had used the definition of the ITT population specified in the study protocol.

Table 2: Applicant's Analysis Populations

Category	SL BPN	Probuphine	Total
Randomized (N)	90	87	177
Safety population, n (%)	89 (98.9)	87 (100.0)	176 (99.4)
ITT population, n (%)	89 (98.9)	84 (96.6)	173 (97.7)
PP population, n (%)	72 (80.0)	67 (77.0)	139 (78.5)

Abbreviations: ITT, intent-to-treat; PP, per-protocol; SL BPN, sublingual buprenorphine

Source: Table 6 from Applicant's clinical study report

The Baseline demographics for the safety population are shown in Table 3. The study population was approximately 60% male, 95% white and entirely under the age of 65. See Section 4.1 for an analysis of efficacy by gender.

Table 3: Demographics (Safety Population)

Category	SL BPN N=89	Probuphine N=87	Total N=176
Age (years)			
Mean (SD)	39 (10.8)	38 (11.2)	39 (11.0)
Min, max	22, 64.0	21, 63.0	21, 64.0
Gender, n (%)			
Male	52 (58.4)	52 (59.8)	104 (59.1)
Female	37 (41.6)	35 (40.2)	72 (40.9)
Race, n (%)			
White	85 (95.5)	82 (94.3)	167 (94.9)
Black or African American	2 (2.2)	3 (3.4)	5 (2.8)
Asian	0	1 (1.1)	1 (0.6)
American Indian or Alaska native	1 (1.1)	1 (1.1)	2 (1.1)
Other	1 (1.1)	0	1 (0.6)
Ethnicity, n (%)			
Hispanic or Latino	3 (3.4)	3 (3.4)	6 (3.4)
Not Hispanic or Latino	86 (96.6)	84 (96.6)	170 (96.6)
BMI (kg/m²)			
Mean (SD)	27 (5.92)	28 (6.94)	28 (6.47)
Min, max	19, 50.6	14, 46.4	14, 50.6

Abbreviations: BMI, body mass index; SD, standard deviation; SL BPN, sublingual buprenorphine
Source: Table 7 from Applicant's clinical study report

3.2.1.4 Results and Conclusions

The results of the Applicant's primary analysis are shown in Table 4. The Applicant found that the lower bound of the 95% confidence interval of the difference in the proportion of responders was greater than -0.20 and hence concluded that Probuphine was non-inferior to sublingual buprenorphine. The Applicant also found a p-value for superiority of 0.03 and so concluded that Probuphine was superior to sublingual buprenorphine. However, there were several issues with the primary analysis which I will discuss in detail.

Table 4: Applicant's Primary Analysis

Category	Probuphine n (%)	SL BPN n (%)	Proportion Difference (95% CI) Probuphine – SL BPN	Superiority <i>P</i> -Value (2-Sided)
N	84	89		
Responder	81 (96%)	78 (88%)	0.09 (0.01 , 0.17)	0.03
Non-Responder	3 (4%)	11 (12%)		

Source: Applicant's Study Report Table 12

The first concern noted was the exclusion of four subjects who were randomized into the study but excluded from the analysis population (one subject randomized to sublingual buprenorphine and three subjects randomized to Probuphine). The subject that was randomized to sublingual buprenorphine did not receive study medication; therefore, I agree with the Applicant, it is appropriate to exclude this subject from the analysis population. However, the three subjects that were excluded from the Probuphine arm did receive study medication and should not have been excluded from the analysis population. Table 5 shows the results of a re-analysis of the data when these three subjects are included in the study population as non-responders. Although Probuphine is no longer found to be superior to sublingual buprenorphine in this analysis it would still be considered to be non-inferior.

Table 5: Redefined Analysis Population

Category	Probuphine n (%)	SL BPN n (%)	Proportion Difference (95% CI) Probuphine – SL BPN	Superiority <i>P</i> -Value (2-Sided)
N	87	89		
Responder	81 (93%)	78 (88%)	0.055 (-0.03 , 0.14)	0.22
Non-Responder	6 (7%)	11 (12%)		

Source: Reviewer

I noted three issues with the Applicant's missing data handling procedure for urine samples that were not collected. First, missing data was only imputed if all samples were missing for a particular month. For example, if a random sample was scheduled and missed for a particular month and the sample collected during their monthly visit was found to be negative then no imputation was performed. Second, illicit opioid usage was assumed to be equally likely for missing and observed data. This assumption should also be explored in sensitivity analyses in order to determine the sensitivity of the study's findings. Third, as designed the Applicant's missing data imputation scheme has a small probability of classifying a subject who provided absolutely no efficacy data in the study as a responder. For example, the primary analysis used a positive rate of approximately 13% which gives a 97% probability that someone who provided absolutely no efficacy data would be classified as a responder. I do not think this approach is acceptable in the current clinical setting.

Additionally, there were a number of issues with inconclusive urine samples that the Applicant made no attempt to explore in their original efficacy analysis. The unresolved issues with the inconclusive urine samples fell into one of several categories. First, other compounds in the sample frequently interfered with the analysis of one of the opioid metabolites, norfentanyl. The

Applicant stated that it was not possible to rule out tampering to conceal use at this time. Second, the study sites provided a number of samples to the study laboratory after the defined stability cutoff for creatinine. Approximately half these samples were also provided to the laboratory after the defined stability cutoffs for the majority of the opioids.

A summary of the overall results of the analysis of the urine samples is presented in Table 6. There were approximately twice as many positive samples provided by subjects in the sublingual buprenorphine treatment as for those in the Probuphine treatment arm. There were however, approximately twice as many samples that were either missed or were not conclusively analyzed for Probuphine compared to sublingual buprenorphine.

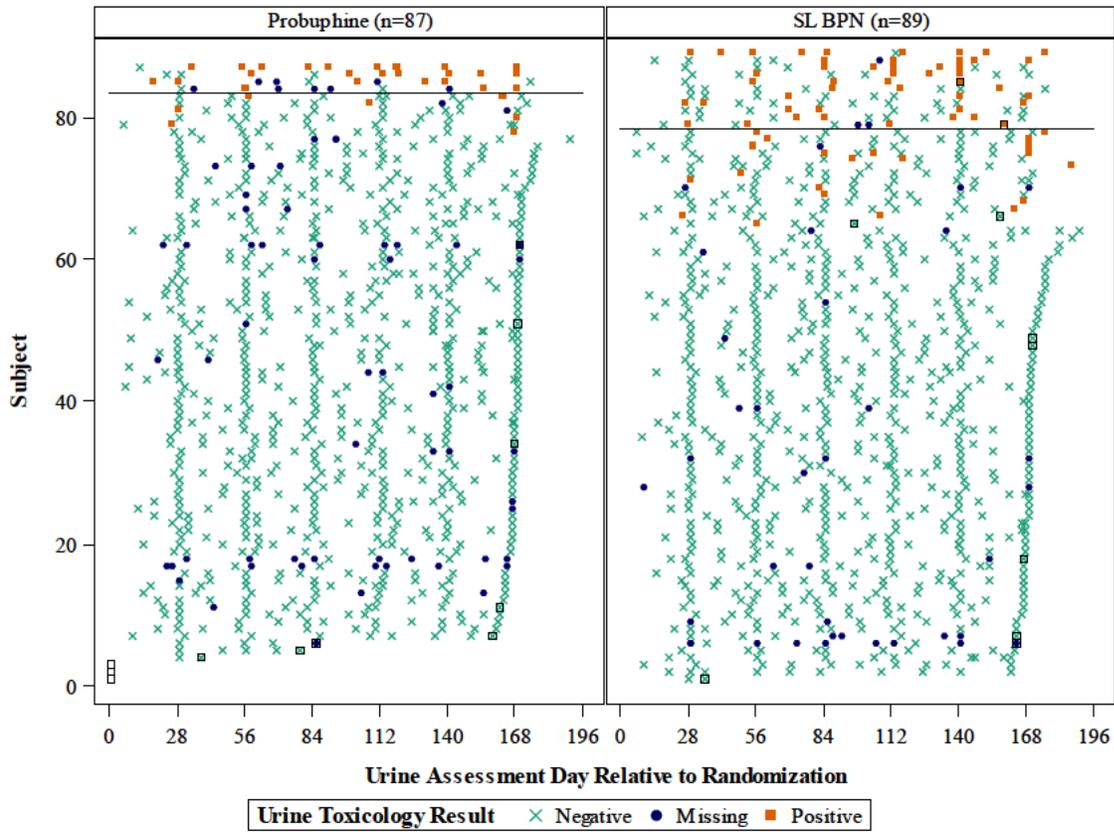
Table 6: Results of the Analysis of Urine Samples

Treatment Group	Negative n (%)	Positive n (%)	Incomplete Result n (%)	Missing Sample n (%)	Total
SL BPN (n=89)	765 (86.0%)	64 (7.2%)	34 (3.8%)	27 (3.0%)	890
Probuphine (n=87)	725 (83.3%)	31 (3.6%)	60 (6.9%)	54 (6.2%)	870

Source: Reviewer

These results are illustrated in Figure 1. Each row in the figure shows the results for a single subject. The green crosses represent negative tests, the orange squares represent positive tests, and the blue circles represent either samples that were not provided or were not completely analyzable. Subjects above the black horizontal line provided at least three positive samples and would be considered responders in the Applicant’s primary analysis.

Figure 1: Urine Toxicology Test Results for Subjects in Study PRO-814



Source: Reviewer

Note: Black squares mark the final visit for subjects marked as non-completers by the Applicant.

Table 7 shows a summary of the percentage of the subjects in the study with and without specific issues with urine toxicology samples. Approximately half of the randomized subjects completed the study and provided ten negative urine samples.

Table 7: Summary of Urine Toxicology Samples

Issue	Probuphine n (%)	SL BPN n (%)	Total n (%)
N	87	89	176
No Issues	46 (53%)	49 (55%)	95 (54%)
Missing Data	31 (36%)	22 (25%)	53 (30%)
Missed Sample	11 (13%)	11 (12%)	22 (13%)
Incomplete Result	22 (25%)	16 (18%)	38 (22%)
Rescue Use	15 (17%)	13 (15%)	28 (16%)
Positive Test	10 (12%)	25 (28%)	35 (20%)

Source: Reviewer

In order to evaluate the effect of the missing data on the analysis of responder rates, two additional sensitivity analyses were conducted. The results of these analyses are shown in Table 8. In the first analysis any missed urine sample was imputed as positive. In the second analysis, any sample that was not completely analyzed was also considered to be positive. Non-inferiority was still concluded for both of these analyses.

Table 8: Sensitivity Analyses to Evaluate Impact of Missing Data

Imputation Scheme	Category	Probuphine n (%)	SL BPN n (%)	Proportion Difference (95% CI) Probuphine – SL BPN
Missing Urine Samples Imputed as Positive	N	87	89	
	Responder	78 (90%)	76 (85%)	0.04 (-0.06, 0.140)
	Non-Responder	9 (10%)	13 (15%)	
Incomplete and Missing Urine Samples Imputed as Positive	N	87	89	
	Responder	73 (84%)	70 (79%)	0.05 (-0.06, 0.17)
	Non-Responder	14 (16%)	19 (21%)	

Source: Reviewer

It was anticipated that since the subjects who were to be enrolled in this study were clinically stable and on a stable dose of sublingual buprenorphine with no dose adjustments for at least the last three months prior to randomization the need for supplemental buprenorphine would be minimal. However, as shown in Table 9, supplemental buprenorphine was required by approximately 16% of the subjects in the study. Similar numbers of subjects in both treatment arms received supplemental buprenorphine. However, when considering number of tablets dispensed, subjects in the Probuphine arm were dispensed approximately 70% more supplemental tablets during the study than subjects in the sublingual buprenorphine arm.

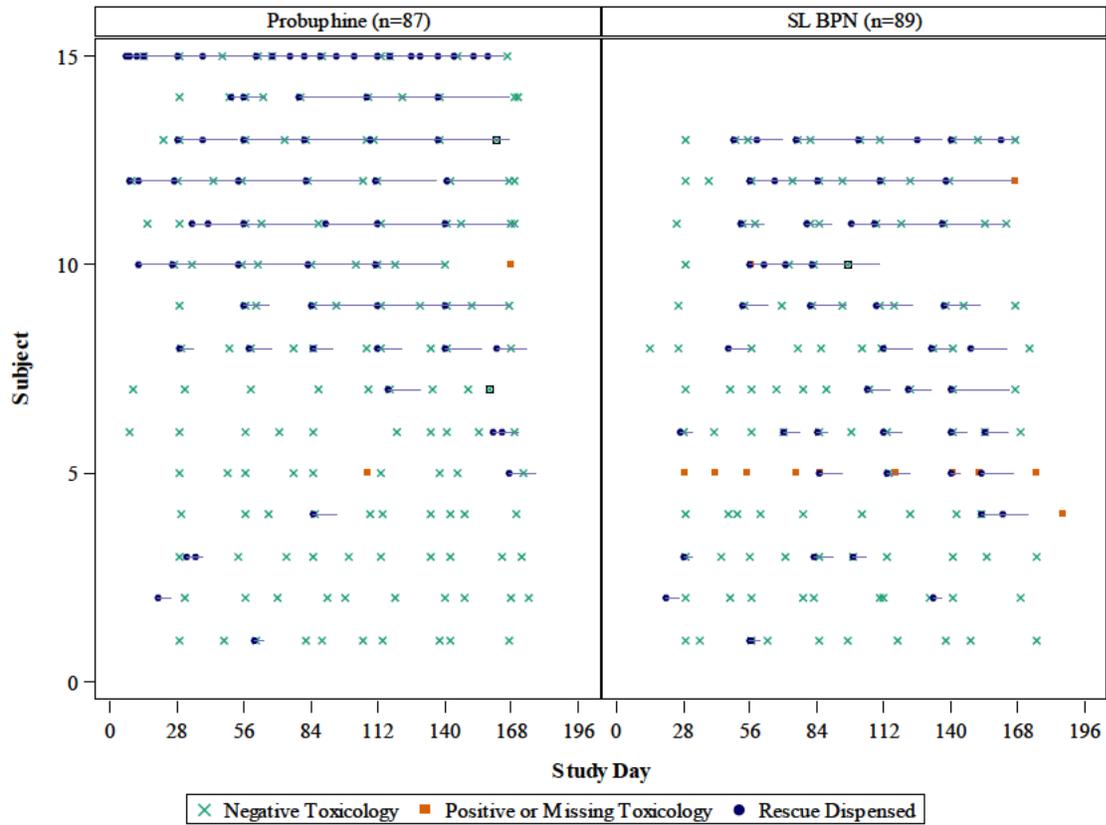
Table 9: Summary of Supplemental Sublingual Buprenorphine Usage

	Probuphine (N=87)	SL BPN (N=89)	Total (N=176)
Number of Subjects who required supplemental SL BPN, n (%)	15 (17%)	13 (15%)	28 (16%)
Average Number of Tablets Dispensed and not Returned Per Subject Requiring Supplemental Medication	43	25	35

Source: Reviewer

The frequency and duration of use for the subjects who required supplemental medication is shown in Figure 2. The blue circles represent days when supplemental medication was dispensed. The length of the line or duration was calculated by assuming that a subject required a single additional sublingual buprenorphine tablet per day unless otherwise specified.

Figure 2: Supplemental Buprenorphine Use



Note: Black squares indicate subjects who did not provide all ten urine samples.

Source: Reviewer

Figure 2 shows that there were a number of subjects who received supplemental medication for the majority of the study. As discussed previously, this level of use was not anticipated and hence was not considered by the Applicant in their definition of a responder. Additional analyses were conducted where subjects who required any supplemental medication were considered to be non-responders. The missing and incomplete urines samples were considered positive as presented in Table 8. Results are presented in Table 10.

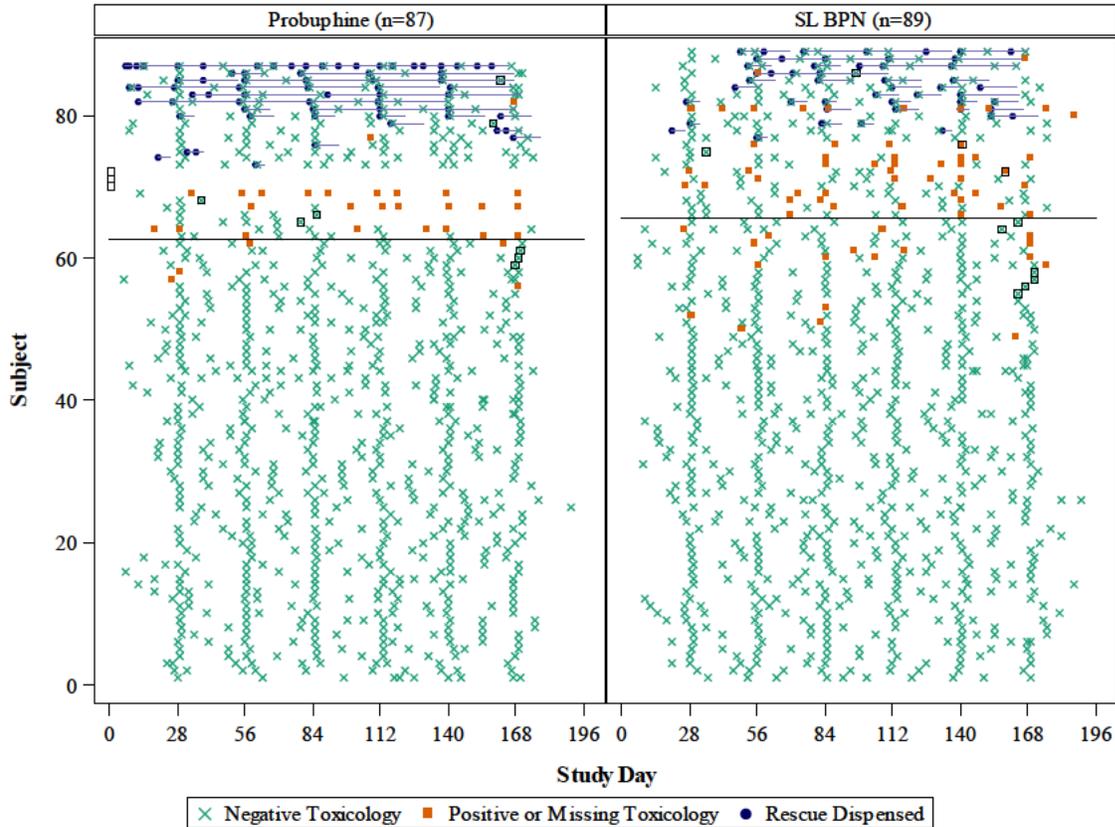
Table 10: Analyses of Responder Rates Considering Use of Supplemental Buprenorphine

Imputation Scheme	Category	Probuphine n (%)	SL BPN n (%)	Proportion Difference (95% CI) Probuphine – SL BPN
Missing urines imputed as positive, supplemental use considered as non- responders	N	87	89	
	Responder	63 (72%)	65 (73%)	-0.01 (- 0.14 , 0.13)
	Non-Responder	24 (28%)	24 (27%)	
Incomplete and missing urines imputed as positive, supplemental use considered as non- responders	N	87	89	
	Responder	58 (67%)	59 (66%)	0.00 (- 0.14 , 0.14)
	Non-Responder	29 (33%)	30 (34%)	

Source: Reviewer

The results of the first analysis from Table 10 are presented graphically in Figure 3. Missing urines samples are imputed as positive and subjects that used supplemental medication as counted as non-responders.

Figure 3: Missing Urine Tests Imputed as Positive and Use of Rescue Considered Non-Response

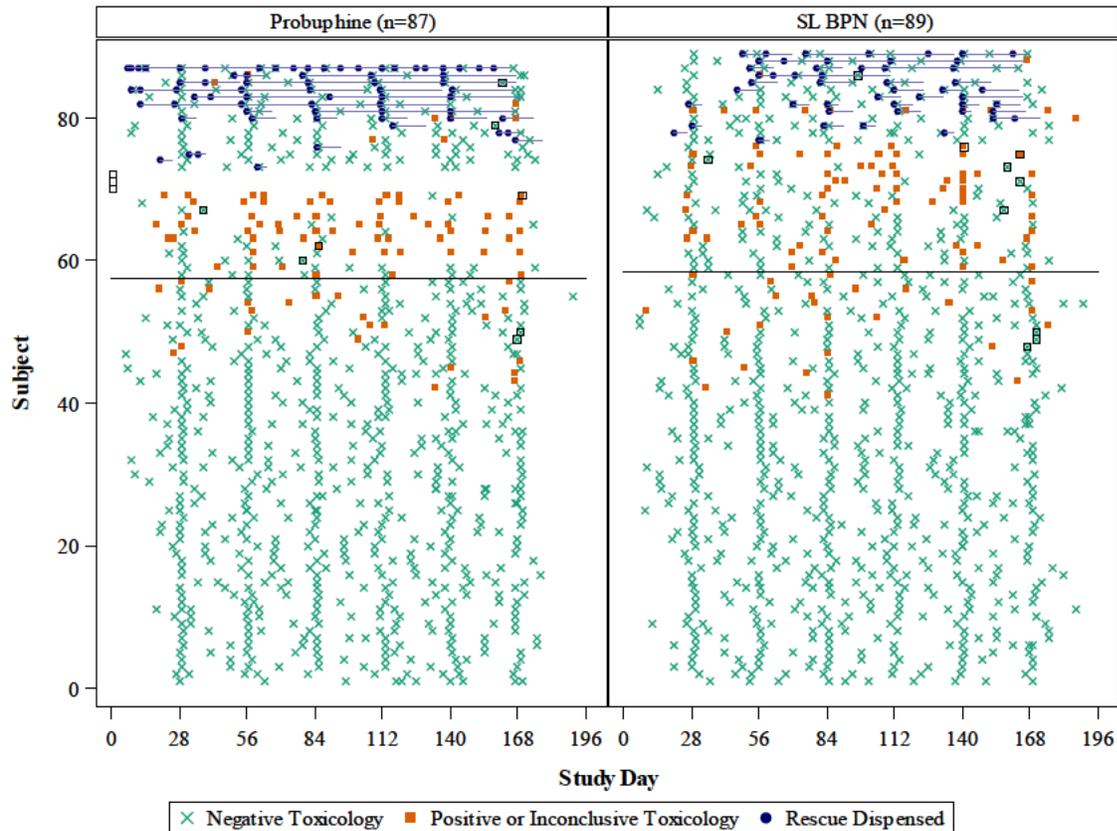


Note: Black squares indicate subjects who did not provide all ten urine samples

Source: Reviewer

The results of the second analysis from Table 9 are presented graphically in Figure 4. Missing and incomplete urines samples are imputed as positive and subjects that used supplemental medication as counted as non-responders.

Figure 4: Missing or Incomplete Urine Tests imputed as Positive and Use of Supplemental Medication Considered to be Non-Response

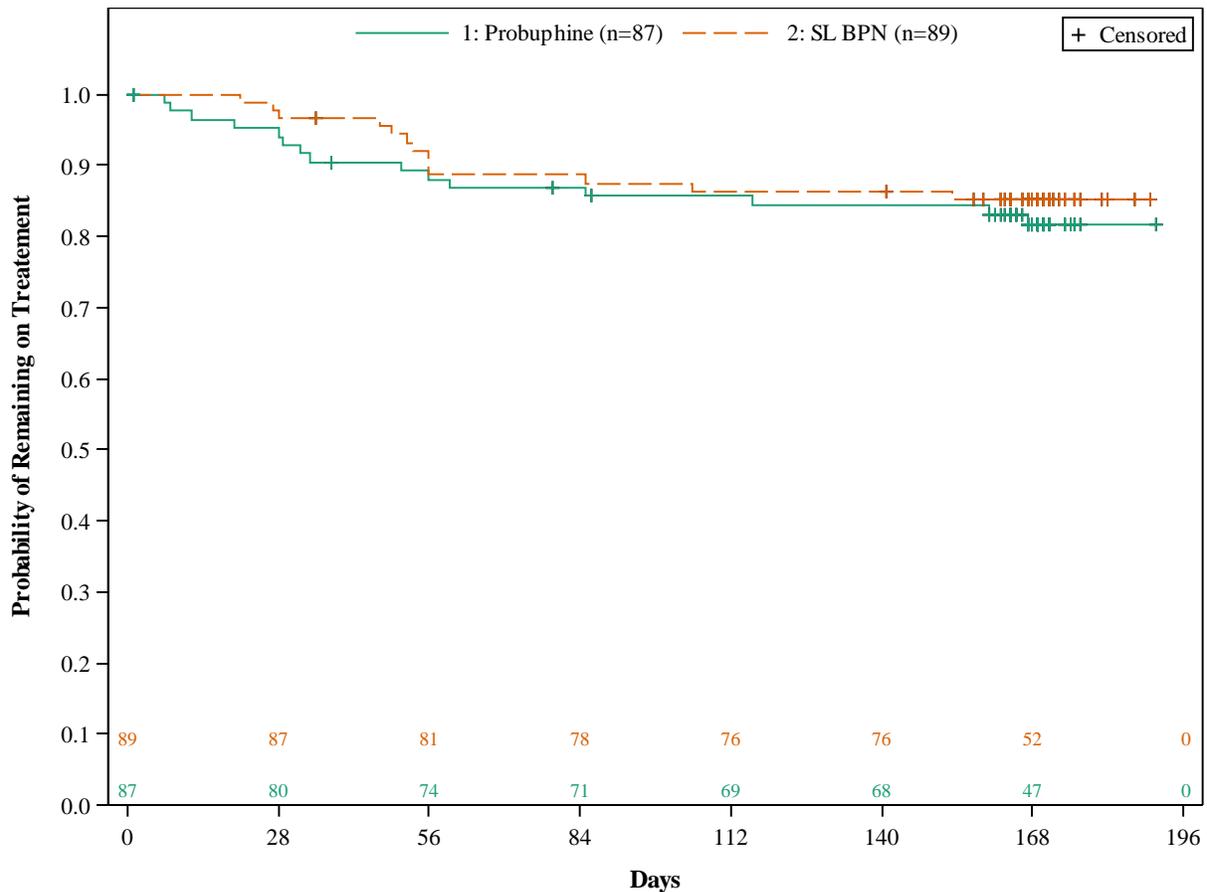


Note: Black squares indicate subjects who did not provide all ten urine samples.

Source: Reviewer

I also considered time to first use of supplemental medication using survival analysis techniques. Subjects who discontinued from the study were censored at the time of their last clinic visit. Figure 5 shows the Kaplan-Meier curves of the time to first use of supplemental medication. The majority of supplemental medication use was initiated during the first two months of the study for both treatment arms. There was no significant difference between the two treatment arms.

Figure 5: Time to First Use of Supplemental Medication



Source: Reviewer

According to the Applicant, one of the main advantages of Probuphine is that it has the potential to reduce the opportunity for theft, accidental loss, diversion, abuse and risk of accidental exposure seen with sublingual buprenorphine. However, if subjects require additional sublingual buprenorphine in order to remain stable, these advantages are reduced or eliminated. For subjects receiving sublingual buprenorphine however, supplemental doses would represent the need for a dose adjustment which would be part of the usual standard of care.

In order to examine this difference in use of supplemental sublingual buprenorphine I conducted two additional analyses. In the first analysis any subject in the Probuphine arm who required supplemental medication was considered to be a non-responder. Subjects in the sublingual buprenorphine arm were allowed supplemental medication. In this analysis the lower bound of the confidence interval of the difference in response rates was below -0.20 so the null hypothesis of inferiority would not be rejected. Further, the two sided p-value was < 0.05 indicating that sublingual buprenorphine would be considered to be superior to Probuphine. Results are presented in Table 11.

This analysis may however be overly strict as it considers subjects in the Probuphine arm with any use of supplemental medication as a non-responder. Consequently, a second analysis was conducted where the subjects were considered to be non-responders only if they required supplemental medication outside of the first and last months of the study. The results of this second analysis with the modified responder definition are also shown in Table 11. In this more realistic setting, Probuphine was again non-inferior to sublingual buprenorphine. Superiority was not evident.

Table 11: Exploration of Differences in Use of Supplemental Buprenorphine

Use of Rescue	Category	Probuphine n (%)	SL BPN n (%)	Proportion Difference (95% CI) Probuphine – SL BPN	Superiority P-Value (2-Sided)
Not allowed	N	87	89		
	Responder	63 (72%)	76 (85%)	-0.13(- 0.25 , -0.01)	0.04
	Non-Responder	24 (28%)	13 (15%)		
Allowed during months 1 and 6 for Probuphine	N	87	89		
	Responder	66 (76%)	76 (85%)	-0.10 (- 0.21 , 0.02)	0.11
	Non-Responder	21 (24%)	13 (15%)		

Source: Reviewer

The Applicant defined a responder as any subject with no more than 2 out of 6 months with any evidence of illicit opioid use. Since subjects were required to have had no positive urine toxicology results for at least 90 days prior to enrollment, another responder definition of clinical interest was a subject with no evidence of opioid use during the study. Two additional analyses were conducted using this definition of a responder. Results are shown in Table 12. For the first analysis use of supplemental medication is not allowed outside of Months 1 and 6 for subjects in either arm. For the second analysis, supplemental medication is allowed for subjects in the sublingual buprenorphine arm but only during Months 1 and 6 for the subjects in the Probuphine arm.

Table 12: Exploration of the Responder Definition

Responder Definition	Category	Probuphine n (%)	SL BPN n (%)	Proportion Difference (95% CI) Probuphine – SL BPN
No Positive or Missed Samples Allowed	N Responder	87 57 (66%)	89 48 (54%)	0.12 (-0.03, 0.26)
Suppl. BPN During Months 1 & 6 Only for Either Group	Non- Responder	30 (34%)	41 (46%)	
No Positive or Missed Samples Allowed	N Responder	87 57 (66%)	89 57 (64%)	0.01 (-0.13, 0.16)
Suppl. BPN During Months 1 & 6 Only for Probuphine Subjects	Non- Responder	30 (34%)	32 (36%)	

Source: Reviewer

I also conducted tipping point analyses to explore the assumptions regarding missing data in the 2nd analysis presented in Table 12. For this analysis rather than assuming all missed urine samples were positive the opioid usage status was randomly imputed. Only in the most extreme case where all missed urine samples for Probuphine were assumed to be positive and the missed samples for sublingual buprenorphine were assumed to be negative did the overall conclusion change.

In this review I conducted a number of analyses to explore the effects of several versions of the missing data handling and responder definitions on the relative response rates in this study. The results of all the analyses conducted are displayed in Table 13. All but one of these analyses found Probuphine to be non-inferior to sublingual buprenorphine with the Applicant’s pre-specified margin of -20%. Superiority of Probuphine to sublingual buprenorphine was not demonstrated.

Table 13: Results of Additional Analyses

Analysis Population	Number of Allowed Positive Months	Value Imputed for Missing Data	Value Imputed for Incomplete Samples	Rescue Use Permitted		PRO n (%)	SL BPN n (%)	Lower Bound (95% CI)
				PRO	SL BPN			
Applicant's	2	Applicant's	Negative	Yes	Yes	81 (96%)	78 (88%)	0.01
Revised	2	Applicant's	Negative	Yes	Yes	81 (93%)	78 (88%)	-0.03
Revised	2	Positive	Negative	Yes	Yes	78 (90%)	76 (85%)	-0.06
Revised	2	Positive	Positive	Yes	Yes	73 (84%)	70 (79%)	-0.06
Revised	2	Positive	Negative	No	No	63 (72%)	65 (73%)	-0.14
Revised	2	Positive	Positive	No	No	58 (67%)	59 (66%)	-0.14
Revised	2	Positive	Negative	No	Yes	63 (72%)	76 (85%)	-0.25
Revised	2	Positive	Negative	Month 1 & 6	Yes	66 (76%)	76 (85%)	-0.21
Revised	0	Positive	Negative	Month 1 & 6	Month 1 & 6	57 (66%)	48 (54%)	-0.03
Revised	0	Positive	Negative	Month 1 & 6	Yes	57 (66%)	57 (64%)	-0.13

Abbreviations: PRO, Probuphine

Source: Reviewer

The analysis preferred by the clinical team is shown in the last row of Table 14. This analysis considers a responder as having no positive urines. Missing and incomplete urines samples are imputed as positive and subjects in the Probuphine arm that used supplemental sublingual buprenorphine during months 2 thru 5 were considered non-responders. All other use of supplemental buprenorphine was allowed.

3.3 Evaluation of Safety

The reader is referred to the Medical Review by Dr. Rachel Skeete for an evaluation of the safety of Probuphine.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The Applicant did not conduct subgroup analyses based on race and age because most of the subjects in the study were white, and all were below 65 years of age. See Table 3 in Section 3.2.1.3 for a summary of the baseline demographics for Study PRO-814. The results of the analysis by gender are shown in the following section.

4.1 Gender

The results of the analysis by gender are shown in Table 14. Response rates were similar regardless of gender.

Table 14: Analysis by Gender

Gender	Category	Probuphine n (%)	SL BPN n (%)
Female	N	35	37
	Responder	23 (66%)	26 (70%)
	Non-Responder	12 (34%)	11 (30%)
Male	N	52	52
	Responder	34 (65%)	31 (60%)
	Non-Responder	18 (35%)	21 (40%)

Source: Reviewer

4.2 Prior Dose

In order to be enrolled in this study subjects were supposed to have been using buprenorphine for at least the last six months. Subjects were also supposed to have been on a specific dose of 8 mg or less with no dose adjustments for at least the last three months. Table 15 summarizes the doses that subjects were receiving prior to being enrolled in the study. Approximately 75% of subjects were receiving a dose of 8 mg or equivalent.

Table 15: Summary of Subjects by Prior Dose

Dose of Buprenorphine at Study Entry (mg/day) n (%)	Probuphine N=87	SL BPN N=89	Total N=176
2	3 (3%)	6 (7%)	9 (5%)
4	15 (17%)	12 (14%)	27 (15%)
6	4 (4%)	8 (9%)	12 (7%)
8	67 (75%)	61 (70%)	128 (73%)

Source: Applicant's Study Report Table 9

To examine the impact of prior dose response rates were computed for two dosage groups; those receiving 8 mg prior to being enrolled in the study, and those receiving less than 8 mg. Results are displayed in Table 16. Subjects previously receiving 8 mg of sublingual buprenorphine had a lower response rate overall compared to those receiving a lower dose. The response rates are comparable between the two treatment groups for both dosage groups.

Table 16: Analysis by Prior Dose

Prior Dose	Category	Probuphine n (%)	SL BPN n (%)
Received 8 mg	N	61	67
	Responder	38 (62%)	40 (60%)
	Non-Responder	23 (38%)	27 (40%)
Received less than 8 mg	N	26	22
	Responder	19 (73%)	17 (77%)
	Non-Responder	7 (27%)	5 (23%)

Source: Reviewer

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were several statistical concerns with the Applicant's analysis for this study. First, their choice of analysis population was not appropriate because it excluded several subjects who received study medication. Second, their missing data imputation scheme was overly optimistic and the sensitivity analyses conducted were inadequate. Third, the Applicant made no attempt to analyze the effect of supplemental medication on the responder rate.

The first concern was addressed by including all the subjects who received study medication in the analyses. To address the second and third concern additional sensitivity analyses were conducted which are discussed in Section 3.2.1.4.

An additional concern raised by the Advisory Committee held on January 12, 2016 was that the 20% absolute non-inferiority margin selected by the Applicant was too large. The selection of the margin was based on two key assumptions made by the Applicant; first, they assumed a placebo response rate of 25%, and second, they assumed an effect size for sublingual buprenorphine of 75%.

The placebo response rate was based on literature and a survey of addiction specialists conducted by the Applicant. The applicability of the placebo response rate noted in the literature review is questionable since the studies reported subjects were not restricted to subject's clinical stable on a relatively low dose of buprenorphine. Consequently, the estimates presented in the literature may underestimate the expected response rate for the current study.

The results of the survey of addictions specialists conducted by the Applicant are shown in the Appendix (Table A1). The survey estimated that a median of 25% (mean of 30%) of subjects discontinued from their stable dose of buprenorphine would not relapse after six months.

The primary assumption for the effect size noted by the Applicant is that all subjects randomized to sublingual buprenorphine would continue to be clinically stable throughout the study. As I have shown this was not the case in the current study. In fact the actual effect observed could be as low 20%-25% depending on the analysis considered and the placebo response rate assumed.

Using this information, the Applicant estimated that a non-inferiority margin of 20% would preserve at least 70% of the active control’s effect and should be considered clinically acceptable. As discussed the effect noted in the current study was much lower 75% and as such, a 20% absolute non-inferiority margin may no longer be justified as it would preserve less than 70% of the effect size noted for sublingual buprenorphine. In Table 17 a range of assumed placebo response rates and sublingual buprenorphine response rates are presented. The sublingual buprenorphine response rates used were based on the analyses presented in Table 12. In each case I present the non-inferiority margin that would be required to preserve at least 70% of the effect for sublingual buprenorphine.

Table 17: Selection of the Non-Inferiority Margin

Placebo Response Rate	Sublingual Buprenorphine Response Rate			
	55%		65%	
	SL BPN Effect	Non-Inferiority Margin	SL BPN Effect	Non-Inferiority Margin
25%	30%	9%	40%	12%
30%	25%	7.5%	35%	10.5%
35%	20%	6%	30%	9%

Source: Reviewer

The analysis preferred by the clinical team is shown in Table 12 (final row). In this analysis the lower bound of the 95% confidence interval was 12.6% which is larger than any of the margins shown in Table 17. Therefore, if preservation of 70% is of clinical importance, non-inferiority would no longer be concluded with this stricter margin.

As stated previously, the main justification for the 20% non-inferiority margin was that it would preserve 70% of the estimated effect of sublingual buprenorphine. However, according to my analysis approximately 58-69% of the sublingual buprenorphine’s effect was preserved depending on the assumed placebo response rate. As the responder definition used for this analysis was stricter than originally proposed by the sponsor it may be appropriate to assume a lower placebo response rate which would allow for a NI margin of approximately 12%. It is important to note that when the supplemental medication restrictions, which are applied only to Probuphine in the preferred analysis, are applied to both arms (Table 12 first row) the lower bound of the confidence interval was -0.03. In this case non-inferiority would be concluded.

5.2 Collective Evidence

The previous efficacy studies, PRO-805 and PRO-806, are not relevant as they were studied for a different indication than is currently sought and so only the newly submitted study, PRO-814, will be considered for the proposed indication.

5.3 Conclusions and Recommendations

Based on my review of Study PRO-814, I can conclude that while the rate of response for the subjects receiving Probuphine is similar to that observed for subjects receiving sublingual buprenorphine for the clinical team’s preferred analysis, non-inferiority cannot be concluded for

the more conservative margin presented in Section 5.1. Even though the Applicant's original non-inferiority margin is met, I do not believe that this margin is appropriate given the differences between the assumed and observed response rates for sublingual buprenorphine.

This conclusion is based on the Applicant's requirement that at least 70% of the effect of the sublingual buprenorphine be maintained. If this requirement were relaxed to around 60% then non-inferiority could be concluded, however, this will require clinical judgment.

5.4 Labeling Recommendations (as applicable)

I recommend the following changes to Section 14 of the label submitted on Aug 27, 2015:

- When reporting responder rates, the Applicant should use a clinically relevant definition of a responder. This definition should consider use of supplemental buprenorphine and appropriately account for missing data.
- The details [REDACTED] (b) (4) should be removed [REDACTED] (b) (4)
- Information [REDACTED] (b) (4) should be removed [REDACTED] (b) (4)
- The inclusion criteria for the study should be described in greater detail.

APPENDICES

Table A1: Summary of Survey Results from Addiction Specialists

PI #	% Negative UDS Over 6 MThs*	% Negative UDS Over Next 6 MThs*	% Relapse upon BPN Discontinuation (Over 6 MThs)	Maximum Reasonable Change in % UDS Positive	% of Patients
1	100	83	85	0	85
2	75	80	75	17	65
3	NNR	DNAQ	NNR	33	55
4	NNR	90	35	17	10
5	75	91.5	70	17	60
6	NNR	NNR	NNR	17	55
7	99	95	90	17	95
8	80	95	80	17	20
9	95	95	80	8.5	80
10	NNR	65	75	33	60
11	83	90	75	17	66
12	100	80	95	0	85
13	100	100	60	0	10
14	100	90	30	0	90
15	91.5	90	75	17	60
16	91.5	90	50	17	80
17	100	90	90	17	90
18	100	100	60	8.5	NNR
Mean (Median)	92 (97)	89 (90)	70 (75)	14 (17)	63 (65)
Range	75-100	65-100	30-95	0-33	10-95

NOTES: DNAQ =response given did not match question asked and is not useful for the averages;

NNR =no numerical response; UDS=Urine Opioid toxicology

* Some answered as % positive some as % negative, for ease, results have been converted to % negative.

- If range was given; the average of the range has been entered here (i.e., 30-40% = 35% for purposes of these calculations)
- If answer given as < or > , response was entered as the numeric value
- "X of 6 responses were calculated as: 0 of 6 = 0%; 1 of 6 = 17%; 2 of 6 = 33%; 3 of 6 = 50%; 4 of 6 = 67%; 5 of 6 = 83%; 6 of 6 = 100%

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/s/

JAMES E TRAVIS
02/03/2016

DAVID M PETULLO
02/03/2016
I concur.



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 # 204-442

Drug Name: Probuphine[®] (buprenorphine)

Indication(s): Treatment of opioid dependence

Applicant: Titan Pharmaceuticals, Inc.

Date(s): Received: October 31, 2012
PDUFA: April 30, 2013

Review Priority: Priority – 6 month

Biometrics Division: Division of Biometrics II

Statistical Reviewer: David Petullo, M.S.

Concurring Reviewers: Dionne Price, Ph.D.

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

Clinical Team: Medical Officer: Rachael Skeete, M.D.
Medical Team Leader: Celia Winchell, M.D.
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Project Manager: Lisa Basham

Keywords: clinical studies, NDA review, double-blind, active control

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1. EXECUTIVE SUMMARY

Titan Pharmaceuticals, Inc. has submitted a 505(b)(2) application for Probuphine (buprenorphine hydrochloride/ethylene vinyl acetate) to support an indication for the maintenance treatment of opioid dependence following induction with sublingual buprenorphine. This product is intended to be used in combination with counseling and psychosocial support and will be marketed as a 6-month transdermal implant. The applicant requested and received a priority review as they claim a surgical implant would be more difficult to divert than sublingual formulations of buprenorphine. Of note, in the studies submitted, there were no cases of the implants being intentionally removed. However, this was a controlled clinical trial setting where subjects had frequent clinic visits and may not represent a real life setting.

Two Phase 3 studies, PRO-805 and PRO-806, were submitted. These were randomized, double-blind, placebo-controlled studies conducted in the United States. Both studies demonstrated a statistically significant difference with respect to the primary endpoint, the cumulative distribution or response profile of negative urine screens for Weeks 1-24. The data was also examined in several different ways to explore the treatment effect when incorporating grace periods, the percentage of patients with none or almost no positive urine samples, and the use of supplemental sublingual buprenorphine. The results from these exploratory analyses were supportive of a treatment effect with Probuphine.

The Psychopharmacologic Drugs Advisory Committee met on March 21, 2013 to discuss this product. Questions posed to the committee pertained to efficacy, the overall safety of implants, and the proposed Risk Evaluation and Mitigation Strategy (REMS). Several members of the committee stated that the company had not adequately characterized the product with regards to the dose, and they suggested that additional work was needed on the proposed REMS. Overall, the committee concluded there were no specific safety concerns that would preclude approval.

2. INTRODUCTION

2.1 Overview

Buprenorphine was approved in 1981 for the treatment of pain, and two sublingual tablet formulations were approved in 2002 for the treatment of opioid dependence. A sublingual film formulation was approved in 2010. According to the applicant, Probuphine will provide sustained delivery of a therapeutic level of buprenorphine for up to six months when 4 to 5 rods are implanted subdermally. Probuphine is intended as a maintenance treatment for opioid-dependent patients who have been initially titrated to a target dose using sublingual buprenorphine.

The clinical development program for Probuphine was reviewed under IND 70,852. The applicant was advised that two randomized, double-blind, placebo-controlled, adequate and well controlled studies would be required. A non-inferiority design would not be acceptable as there was no consensus on necessary aspects of such a study. The choice of a primary efficacy measurement was discussed extensively. The applicant was advised not to focus on group means

such as mean percent of weeks abstinent since this would not reflect the efficacy of individual patients who might range from complete responders to complete non-responders. Definitions for a treatment responder were discussed, but no consensus was reached. The applicant agreed to evaluate the full range of response definitions based on the percentage of negative urines. This analysis was referred to by Titan as the cumulative distribution function. Recognizing that patients might require some time for engagement in treatment, Titan was encouraged to perform analyses incorporating a “grace period” during which use of illicit opioids early in treatment would not be counted in the assessment of response.

2.2 Data Sources

All data was supplied electronically by the applicant as SAS transport files and can be found at the following location in the CDER electronic document room (EDR):

<\\cdsesub1\evsprod\NDA204442\0000\m5\datasets>

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The electronic data submitted by the applicant for the two Phase 3 studies was of sufficient quality to allow a thorough review of the data. I was able to derive the primary endpoint for each study, and my results were consistent with those of the applicant.

A preliminary report from the Office of Scientific Investigations revealed no significant findings.

3.2 Evaluation of Efficacy

My review focused on the two Phase 3 studies, PRO-805 and PRO-806, submitted to support the efficacy of Probuphine to treat opioid dependence. These were randomized, double-blind, parallel-group, multi-center studies. Study PRO-806 also included a treatment group in which patients were treated with open-label sublingual buprenorphine (SL BPN). The data from the open-label SL BPN arm will be presented to explore the number of positive urine samples present with an approved product. However, no statistical comparisons will be performed either to placebo or to Probuphine. Even though Study PRO-805 was 6-months in duration, the applicant evaluated efficacy at 4 months. Since this product is to be marketed as a 6-month implant, my review will focus on efficacy at 6 months.

As the studies were essentially identical in design with the exception of the open-label BPN arm, the study design and results will be presented and discussed jointly. I present the primary efficacy results first followed by my exploratory analyses. The results of the urine toxicology data for the open label SL BPN arm will be presented graphically following the results of my exploratory analyses.

Study Design and Endpoints

Studies PRO-805 and PRO-806 consisted of three phases: induction, treatment, and an open-label extension phase. Eligible patients were 18-65 years of age and met the Diagnostic and Statistical Manual of Mental Disorders criteria for opioid dependence. Patients were ineligible to participate if they had received treatment for opioid dependence in the previous 90 days, required opioid treatment for a current chronic pain condition, were considered candidates for short-term detoxification only, met criteria for dependence on other psychoactive substances (nicotine dependence permitted), or used illicit benzodiazepines.

Patients were to undergo initiation of buprenorphine treatment (induction) using sublingual tablets. In order to be randomized to treatment, patients had to meet the following criteria after the induction phase:

- Completed induction with sublingual buprenorphine to a dose of 12–16 mg/day as clinically appropriate within 10 days. Patients requiring < 12 mg/day or > 16 mg/day were ineligible.
- No significant withdrawal symptoms (defined as a score \leq 12 on the Clinical Opiate Withdrawal Scale [COWS])
- No significant cravings for opioids (defined as a score \leq 20-mm on the 100-mm Opioid Craving Visual Analog Scale [VAS])

Eligible subjects were randomized in a 2:1 ratio to either Probuphine or placebo. Randomization in both studies was stratified by gender and pooled site. The starting dose for Probuphine was four implants and occurred within 12 to 24 hours after the last dose of sublingual buprenorphine. If within the first two weeks, a subject required supplemental SL BPN dosing on 3 or more days per week for 2 consecutive weeks or on 8 or more days total over 4 consecutive weeks, the subject received a fifth implant.

During the 24-week treatment period, there were 16 study site visits and 72 urine collection visits. Urine samples were taken three times per week and tested for illicit drugs and opioids. Positive urine samples underwent confirmatory testing. Assessments of safety (extent of exposure, adverse events [AEs], laboratory evaluations, vital signs, physical examination, electrocardiography [ECG]), concomitant medications) and efficacy (urine toxicology screening, quality of life, withdrawal symptoms and cravings, clinical global impressions [CGI]) were taken at each visit. Subjects were also asked about the use and duration of illicit drugs since the last visit.

Subjects were allowed to request supplemental SL BPN during the study. Each dose of was obtained by patients at their clinic or pharmacy. However, take-home sublingual buprenorphine was allowed for weekends, holidays, or other circumstances at the discretion of the investigator. Subjects were deemed treatment failures and discontinued from the study if they required three or more days of supplemental SL BPN for two consecutive weeks or eight or more days for four consecutive weeks after receiving a fifth implant.

Patient Disposition, Demographic and Baseline Characteristics

Study PRO-805

This study randomized 163 opioid-dependent subjects to either placebo or Probuphine. Demographics for these patients are shown in Table 1.

Table 1. Patient demographics for Study PRO-805

Characteristic	Placebo	Probuphine
Number of Patients , n	55	108
Age in years		
Mean (SD)	39 (12)	36 (11)
[range]	[20, 61]	[19, 62]
Gender, n (%)		
Female	15 (27)	40 (33)
Male	40 (73)	72 (67)
Race, n (%)		
Caucasian	40 (73)	82 (76)
Black	6 (11)	14 (13)
Asian	1 (2)	0 (0)
Other	8 (15)	12 (11)

Source: Reviewer

Of the randomized subjects that received study drug, 17 placebo subjects (31%) and 71 Probuphine (66%) completed the study. The number of subjects discontinuing and the reasons for discontinuations are shown in Table 2.

Table 2. Disposition of patients that discontinued in Study PRO-805

	Placebo, n (%)	Probuphine, n (%)
Randomized	55	108
Completed	17 (31)	71 (66)
Discontinued	38 (69)	37 (34)
Reason for discontinuation		
Subject request	9 (16)	8 (7)
Non-compliance	7 (13)	12 (11)
Treatment failure	17 (31)	0 (0)
Adverse event	0 (0)	4 (4)
Lost to follow-up	4 (7)	10 (9)
Other	1 (2)	3 (3)

Source: Reviewer

Study PRO-806

This study randomized 168 subjects to either placebo or Probuphine. There were an additional 119 subjects that were randomized to the open-label SL BPN arm that were not included in my review of efficacy. The demographics for all randomized and treated patients are shown in Table 3.

Table 3. Patient demographics for Study PRO-806

Characteristic	Placebo	Probuphine
Number of Patients, n	54	114
Age in years		
Mean (SD)	35 (10)	36 (11)
[range]	[19, 59]	[19, 60]
Gender, n (%)		
Female	23 (43)	42 (37)
Male	31 (57)	72 (63)
Race, n (%)		
Caucasian	45 (83)	95 (83)
Black	7 (13)	14 (12)
Asian	1 (2)	0 (0)
Other	1 (2)	5 (5)

Source: Reviewer

A total of 87 patients completed Study PRO-806, 14 (26%) in the placebo arm and 73 (64%) in the Probuphine arm. The number of subjects discontinuing and the reasons for discontinuation are shown in Table 4.

Table 4. Disposition of patients that discontinued in Study PRO-806

	Placebo, n (%)	Probuphine, n (%)
Randomized	54	114
Completed Study	14 (26)	73 (64)
Discontinued	40 (74)	41 (36)
Reason for discontinuation		
Subject request	9 (17)	5 (4)
Non-compliance	9 (17)	10 (9)
Treatment failure	9 (17)	6 (5)
Adverse event	0 (0)	0 (0)
Lost to follow-up	3 (5)	9 (8)
Other	10 (18)	11 (10)

Source: Reviewer

There were no discontinuations due to adverse events in either treatment arm. As in Study PRO-805, there were more treatment failures in the placebo arm than in Probuphine; 17% versus 5%.

Statistical Methodologies

The primary efficacy analysis compared the cumulative distribution function (CDF) of the percentage of urine samples negative for opioids in the two treatment groups. The distributions were compared using a rank-based test (Wilcoxon rank-sum) that included pooled site and gender as stratification variables.

The primary analysis for both studies was conducted on the intent-to-treat population, defined as all randomized patients who received treatment. The percentage of negative urines was derived for each patient by summing the total number of negative urine samples and dividing by all possible samples. For Weeks 1-24, the denominator was 72. For some patients, the denominator was greater as they had unscheduled urine test results. Missing samples were considered positive. The following describes how missing samples were treated in the applicant's analysis.

1. If a subject was withdrawn from the study, urine samples from that point onward were considered positive.
2. If a valid urine sample was not provided by a subject, the sample was considered missing and therefore positive.
3. If a valid urine sample was obtained from the subject but was deemed non-missing and non-analyzable, then the sample was removed from the analysis.
4. If urine sample data were missing for any other reason, the urine sample was considered positive.

Non-missing and non-analyzable samples were coded as container received empty, no specimen received, quantity not sufficient, and specimen received beyond stability. In my analyses, samples that the applicant deemed non-missing and non-analyzable were included and considered positive.

Self-reported use of illicit opioids was also accounted for in the analyses. In Study PRO-805, analyses incorporating self-report data were conducted post-hoc following advice from the division. In Study PRO-806, the pre-specified analyses incorporated self-report data. I handled self-reported use of illicit opioids slightly different than the applicant. In addition to asking a subject "have you used illicit opioids?" a subject was asked "what was the duration of use?" If a subject reported opioid use for the past two weeks, I considered any negative urine tests to be positive for those two weeks. It appears the applicant only considered the day of report.

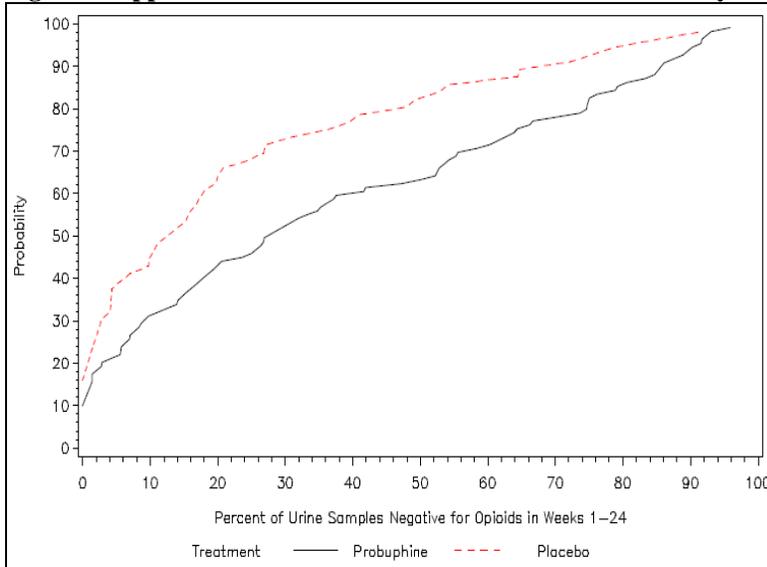
Since some patients require time to engage in treatment but ultimately attain and sustain abstinence from use of illicit opioids, the data were examined using various grace periods. In these analyses, drug use during the initial grace period was not included in the calculation of percent negative urines. Patients who attained and sustained abstinence by the end of the grace period were represented as fully abstinent. I also examined the number of patients with all or almost all of their urines positive and the use of supplemental SL BPN. Note, these were all exploratory analyses, and no formal statistical comparisons were performed.

The statistical analysis plan for both studies proposed a sequential testing strategy for various secondary endpoints such as mean percent of negative urines, proportion of study completers, mean number of weeks abstinent, mean maximum period of continuous abstinence, the subjective opioid scale (SOWS), the COWS, and VAS. These secondary endpoints either have little or no clinical interpretation or are not derived using validated clinical tools.

Results and Conclusions

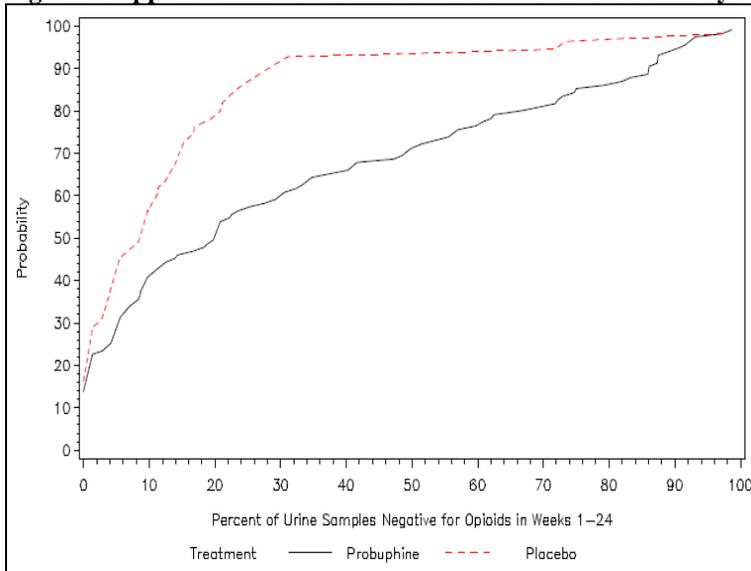
Primary Efficacy Outcome: The applicant's CDFs for the percentage of negative urines samples for Weeks 1-24 are shown in Figures 1 and 2. The CDFs were formulated incorporating self-report data, and missing urine samples were considered positive. The applicant reported statistically significant differences between placebo and Probuphine for both studies, p-values of 0.01 and <0.0001 for studies PRO-805 and PRO806, respectively.

Figure 1. Applicant's cumulative distribution function for Study PRO-805



Source: Figure 7.1.3 from Applicant's ISE

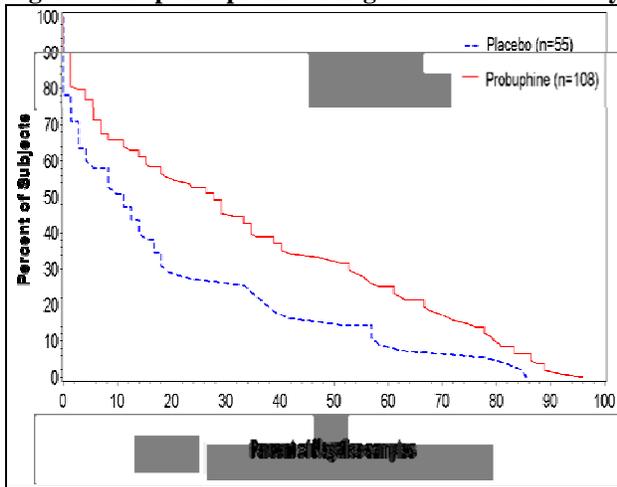
Figure 2. Applicant's cumulative distribution function for Study PRO-806.



Source: Figure 7.1.4 from Applicant's ISE

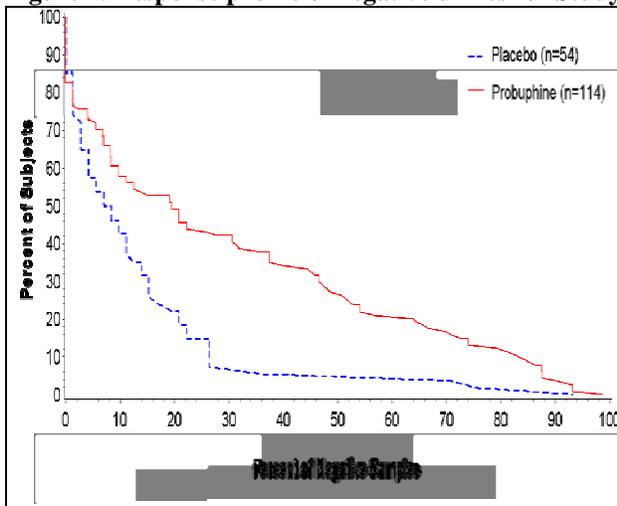
The CDFs shown in Figures 1 and 2 depict the percentage of subjects that submitted at most a certain percentage of negative urine samples. For example, all subjects had 100% or less negative urines. To provide a more intuitive presentation of the results, I graphed the data to illustrate the proportion of patients who submitted a particular percentage of negative urine samples or better. I refer to these as the response profiles of negative urine samples. These are shown in Figures 3 and 4.

Figure 3. Response profile of negative urines for Study PRO-805



Source: Reviewer

Figure 4. Response profile of negative urines for Study PRO-806



Source: Reviewer

A significant difference was noted between the response profile for placebo and Probuphine for Study PRO-805 and PRO-806, 0.01 and 0.0003, respectively. The response profiles are also presented in tabular format in Tables 5 and 6.

Table 5. Percentage of negative urines for subjects in Study PRO-805

% Negative Samples	% Subjects	
	Placebo	Probuphine
≥ 30	27	45
≥ 50	16	32
≥ 75	7	15
≥ 80	5	10
≥ 85	2	6
≥ 90	0	2
≥ 95	0	1
100	0	0

Source: Reviewer

Table 6. Percentage of negative urines for subjects in Study PRO-806

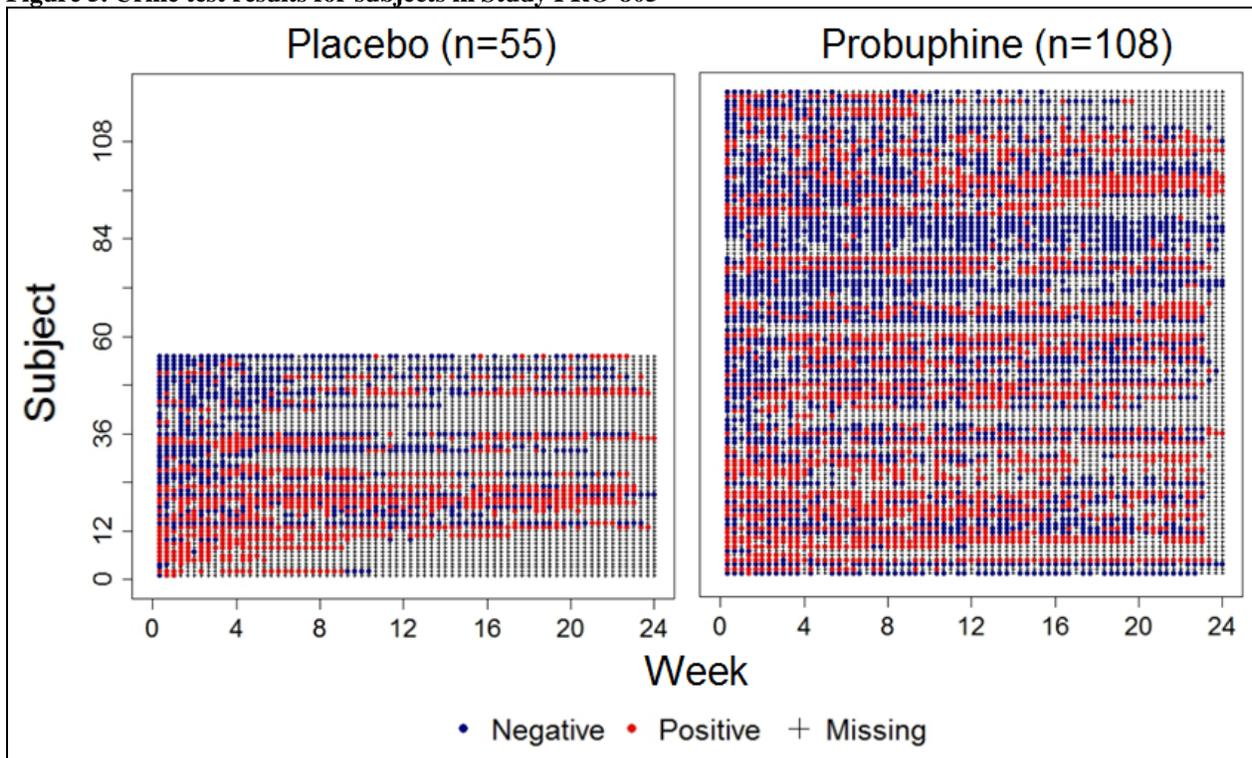
% Negative Samples	% Subjects	
	Placebo	Probuphine
≥ 30	7	42
≥ 50	6	27
≥ 75	4	13
≥ 80	2	12
≥ 85	2	9
≥ 90	2	4
≥ 95	0	1
100	0	0

Source: Reviewer

Although no subjects were able to achieve complete abstinence, there were a higher percentage of subjects in the Probuphine arm versus placebo that had negative urine samples across the range of response definitions.

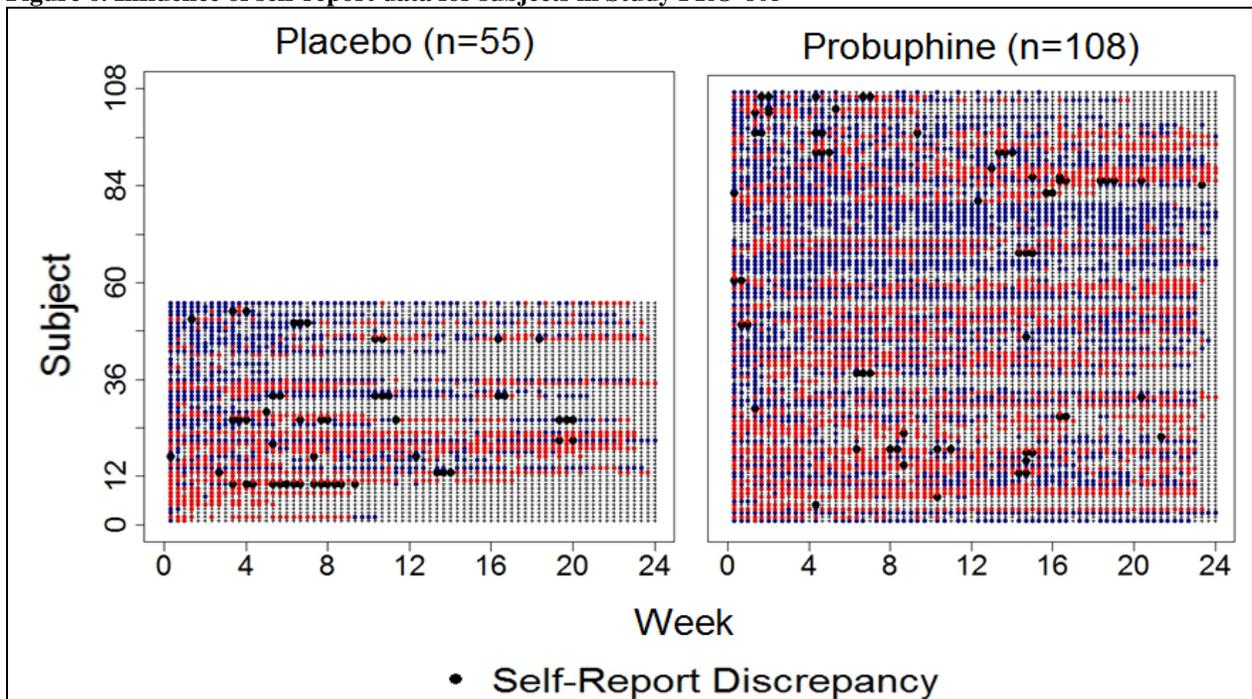
To examine the influence of self-report data and missing urine samples on the derivation of the response profiles, I created graphical displays of subject-level urine toxicology data. In Figures 5-8, each row represents the urine test results for that subject. A blue dot indicates a negative sample, a red dot indicates a positive sample, and a black dot indicates a urine sample that was not collected. There are more rows for the Probuphine arm because of the 2:1 randomization.

Figure 5. Urine test results for subjects in Study PRO-805



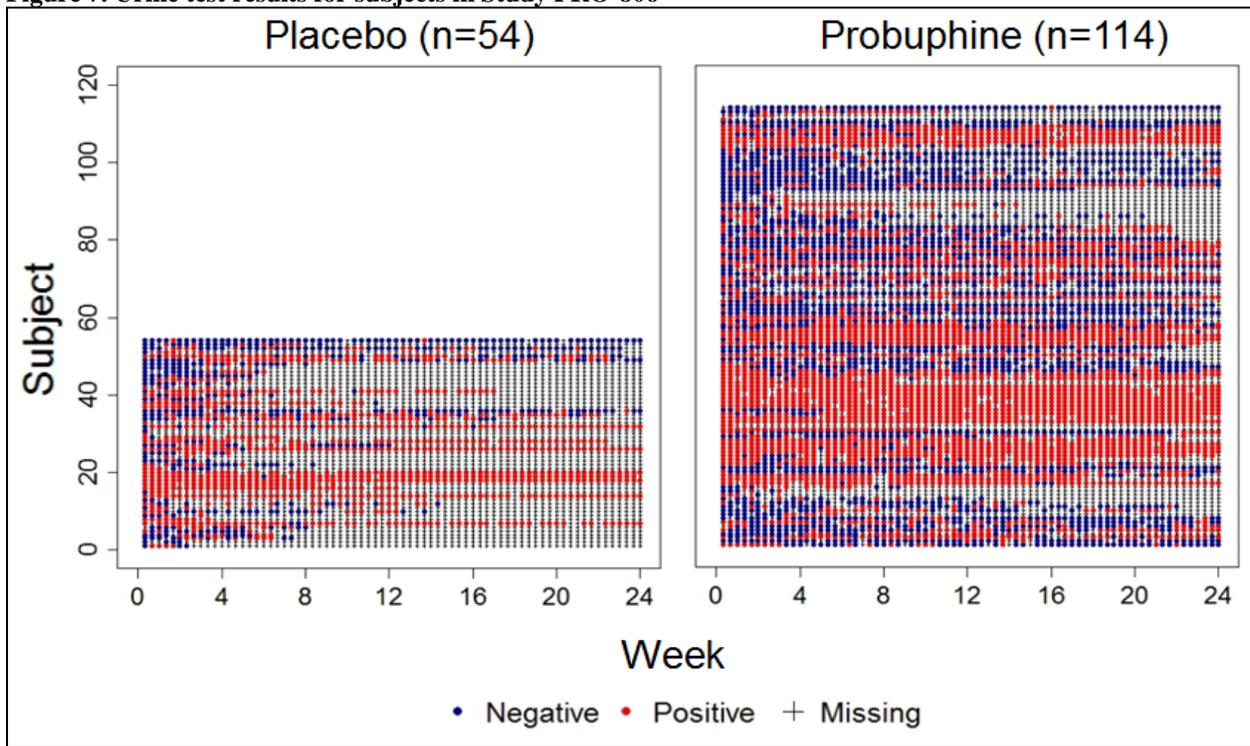
Source: Reviewer

Figure 6. Influence of self-report data for subjects in Study PRO-805



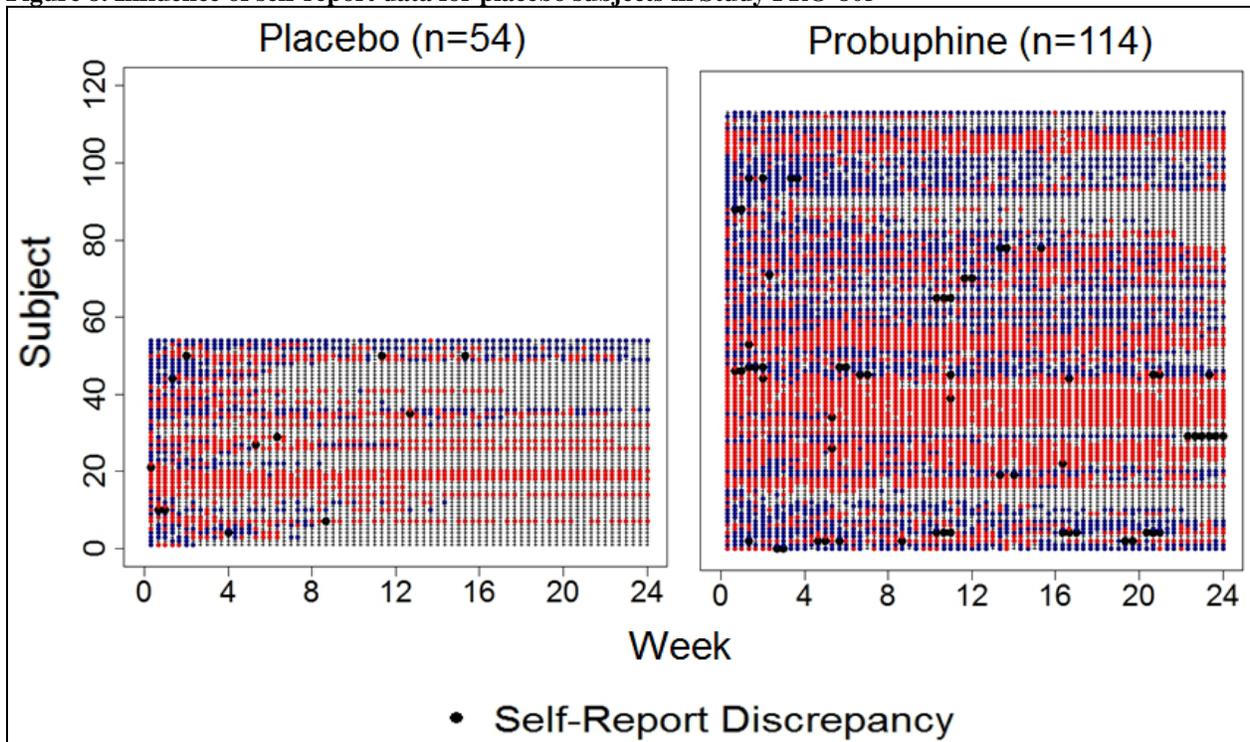
Source: Reviewer

Figure 7. Urine test results for subjects in Study PRO-806



Source: Reviewer

Figure 8. Influence of self-report data for placebo subjects in Study PRO-805



Source: Reviewer

In the above figures, the substantial number of positive urines or red dots indicates continued usage of illicit opioids throughout the study regardless of treatment. There were more missing urines in the placebo group versus the Probuphine group. This was expected as the discontinuation rate in the placebo group for both studies was approximately twice that of the Probuphine group, 70% versus 30%, respectively.

Since missing urine samples were considered positive in the primary analysis, I explored alternative approaches to examine the impact of this imputation. I considered a conservative analysis where missing urine samples for the placebo arm were considered negative, and missing urines for the Probuphine arm were considered positive. However, this scenario was not clinically relevant since it is doubtful that placebo subjects would discontinue due to improvement in their drug use behavior. In contrast, it may be clinically relevant to consider missing urines for the placebo group to be positive and missing urines for the Probuphine group to be negative, but this could give an unsubstantiated advantage to the Probuphine group. I decided the approach used in the review was acceptable.

Exploratory Analysis: In these studies, there were subjects with numerous positive urines samples. I conducted an analysis evaluating the percentage of subjects with all positive urines. The analysis considered missing urines to be positive and included self-report data. Results are presented in Table 7.

Table 7. Percentage of subjects with all positive urine samples

Study	Placebo	Probuphine
PRO-805	22%	8%
PRO-806	15%	18%

Source: Reviewer

In Study PRO-805, there were more placebo patients having all positive urine samples than Probuphine-treated patients. This was not observed in Study PRO-806 where the percentages were more similar. The similar percentages may represent subjects who would not have responded regardless of the treatment received.

I further explored the data by investigating subjects that had almost all of the urines positive. I arbitrarily chose 95% to represent almost all positive urine samples. Results are shown in Table 8.

Table 8. Percentage of subjects with 95% positive urine samples

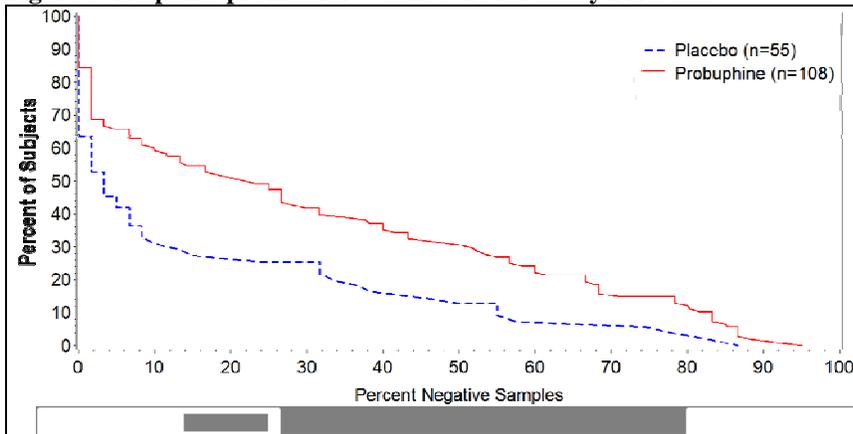
Study	Placebo	Probuphine
PRO-805	40%	21%
PRO-806	43%	27%

Source: Reviewer

In both studies, more subjects in the placebo arm had 95% or more of their urine samples positive versus Probuphine-treated subjects.

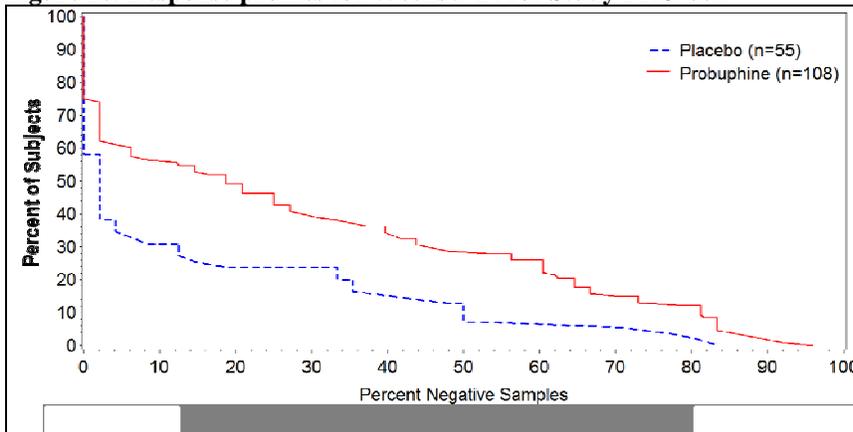
Theoretically, some subjects who do not respond to treatment initially may abstain from using illicit opioids at some later time. To examine this possible scenario, I examined response profiles excluding urine test results from the first 4, 8, and 16 weeks of treatment. Results are presented in Figures 9-14.

Figure 9. Response profiles for Weeks 5-24 for Study PRO-805



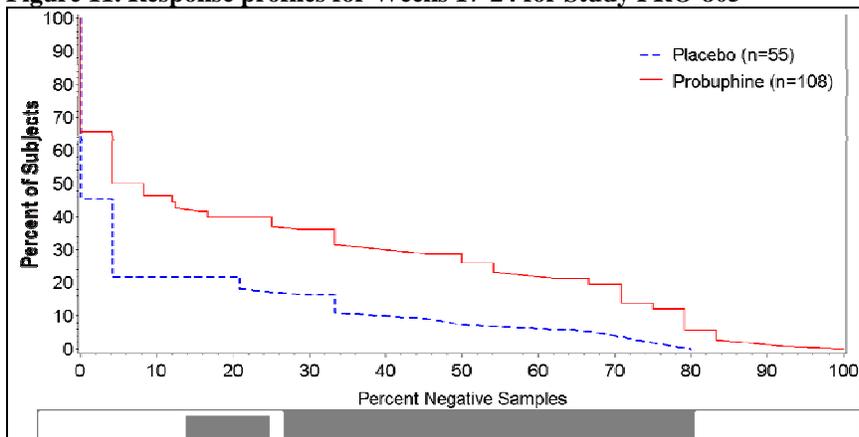
Source: Reviewer

Figure 10. Response profiles for Weeks 9-24 for Study PRO-805



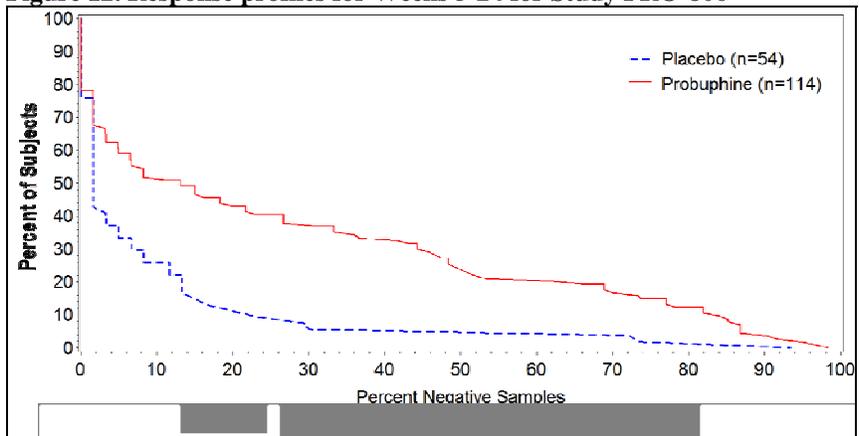
Source: Reviewer

Figure 11. Response profiles for Weeks 17-24 for Study PRO-805



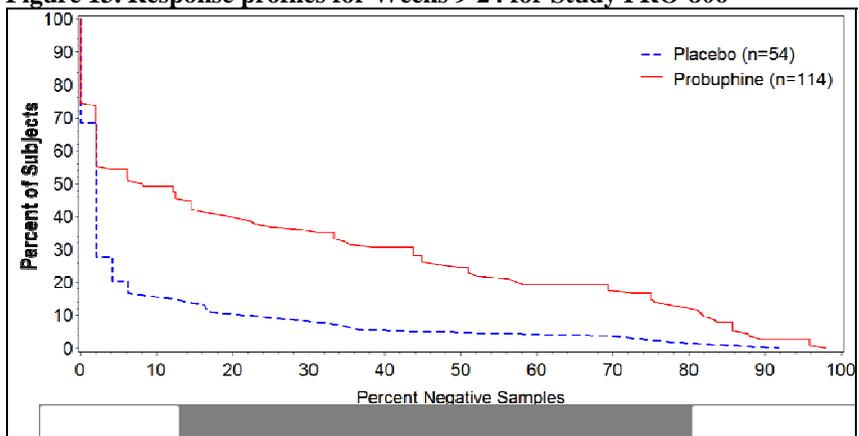
Source: Reviewer

Figure 12. Response profiles for Weeks 5-24 for Study PRO-806



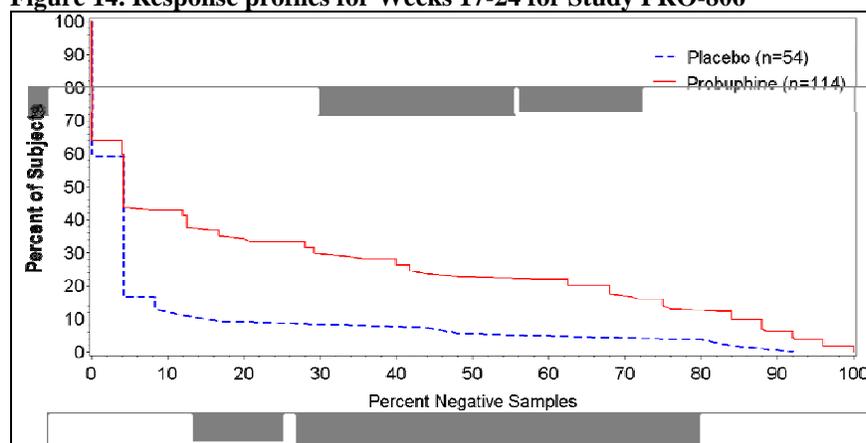
Source: Reviewer

Figure 13. Response profiles for Weeks 9-24 for Study PRO-806



Source: Reviewer

Figure 14. Response profiles for Weeks 17-24 for Study PRO-806



Source: Reviewer

In both studies, the response profiles excluding the first 4, 8, and 16 weeks of treatment were similar to the response profiles observed for Weeks 1-24 and did not suggest that given a grace period, the treatment effect was different.

The review team also considered the possibility that three times a week urine testing may have been too burdensome on subjects. To explore this, I reanalyzed the data to determine the percentage of subjects who had negative results for all urine samples collected during each of the last 8 weeks of treatment. For the reanalysis, I incorporated self-report data but did not account for missing urine samples. For example, if a subject provided a negative urine sample during Visit 1 but missed Visits 2 and 3 of the same week, the subject was considered opioid-free for that week. Results are presented in Table 9.

Table 9. Impact of frequent clinic visits

Study	% Subjects	
	Placebo	Probuphine
PRO-805	0	6
PRO-806	2	4

Source: Reviewer

Even though there was a higher percentage of subjects in the Probuphine arm in both studies that had at least one negative urine sample during the last 8-weeks, the results were not impressive.

Subjects were allowed to use SL BPN as rescue medication in these studies. I examined the percentage of subjects that required rescue medication and created graphical displays of the subject level data for use of supplemental SL BPN. I present the Kaplan-Meier survival curves for time to first use and median survival times for both studies. The percentage of subjects requiring use of SL BPN is shown in Table 10.

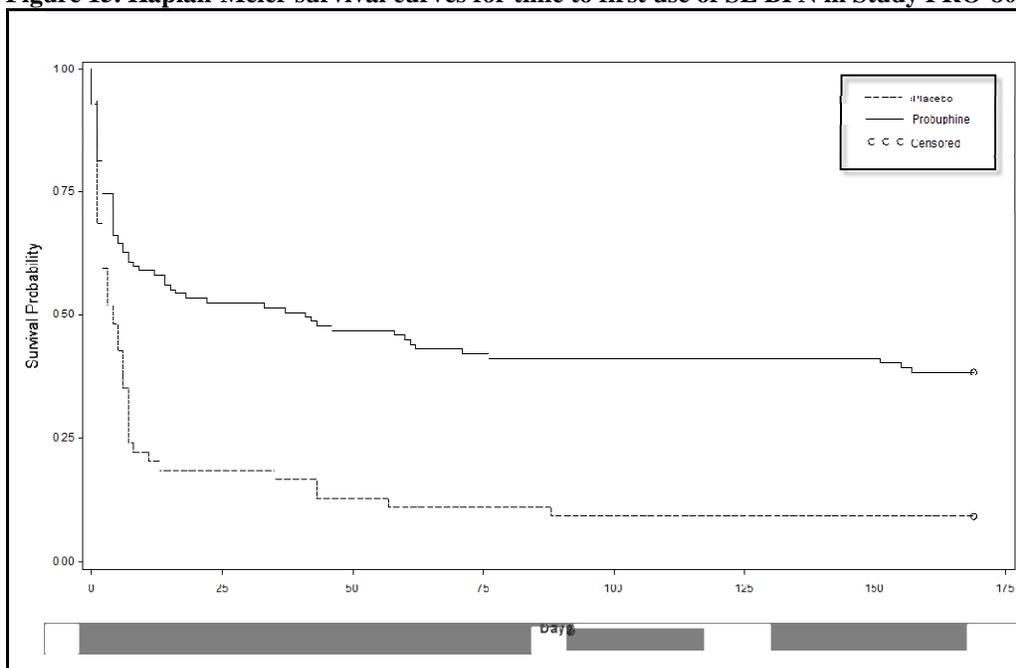
Table 10. Percentage of subjects requiring rescue medication

Study	% Subjects	
	Placebo	Probuphine
PRO-805	91	64
PRO-806	67	39

Source: Reviewer

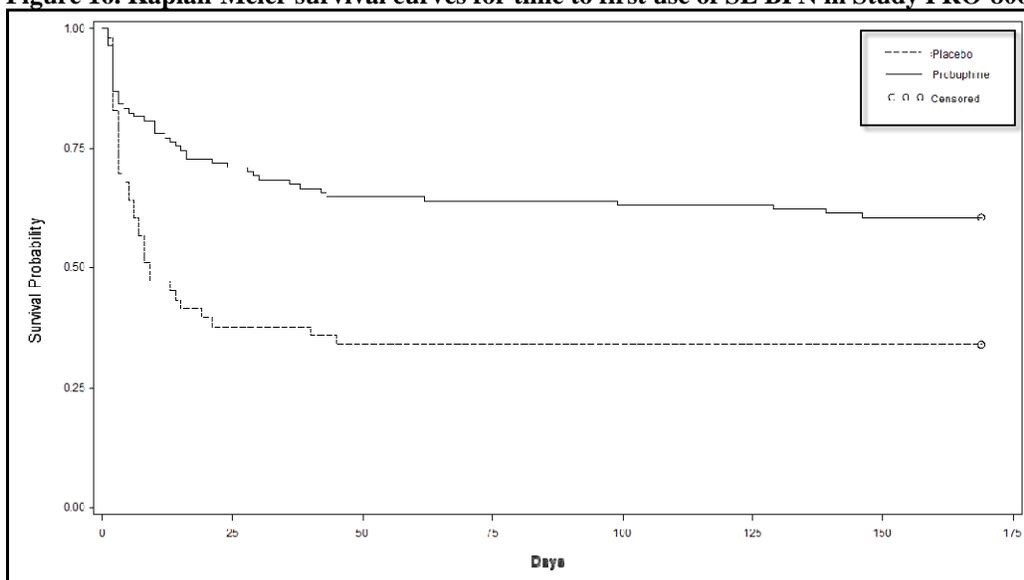
More placebo subjects used rescue medication than did subjects on Probuphine. However, there were considerable subjects in the Probuphine arm in both studies that used supplemental buprenorphine, 64% in Study 805 and 39% in Study 806. The Kaplan-Meier curves depicting the time to first use of SL BPN are presented in Figures 15 and 16.

Figure 15. Kaplan-Meier survival curves for time to first use of SL BPN in Study PRO-805



Source: Reviewer

Figure 16. Kaplan-Meier survival curves for time to first use of SL BPN in Study PRO-806



Source: Reviewer

Median times (in days) to first use of SL BPN are shown in Table 11. This is the time when half of the subjects first used rescue medication. Since 50% of the subjects randomized to Probuphine in Study PRO-806 did not use rescue medication, a median survival time was not presented.

Table 11. Median survival times for time to first use of SL BPN

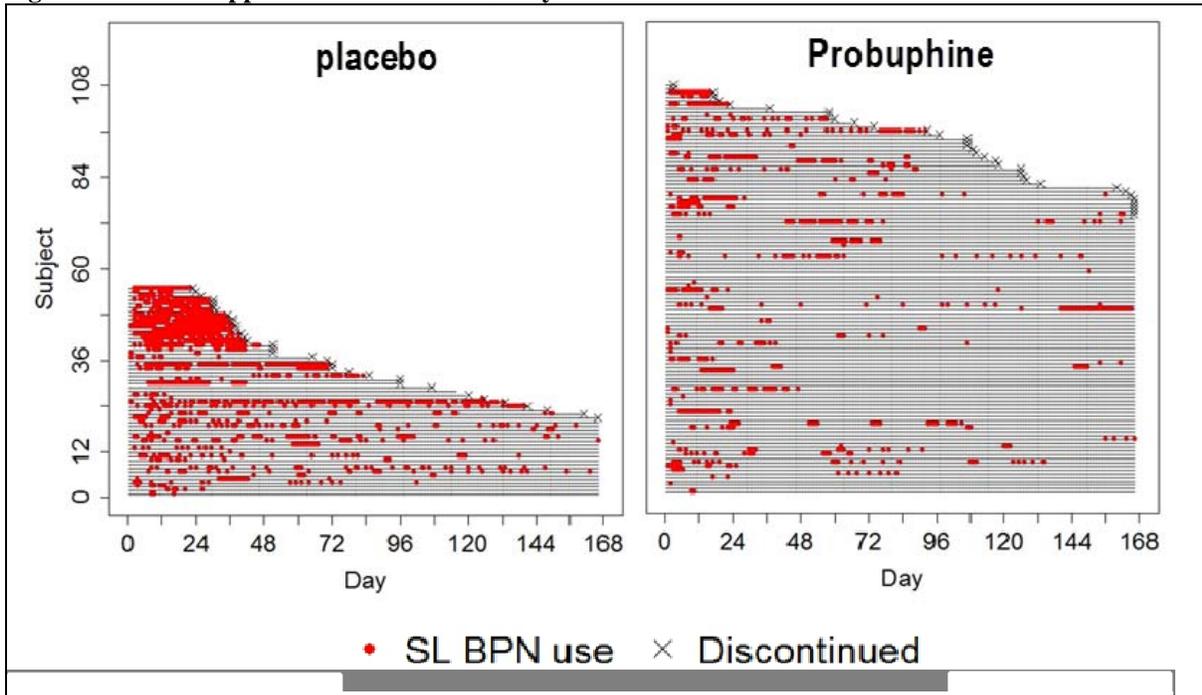
Study	Time in days	
	Placebo	Probuphine
PRO-805	4	41
PRO-806	9	-

Source: Reviewer

As seen in Figures 15 and 16 and Tables 10 and 11, more placebo subjects used rescue medication, and they used it earlier in the study than subjects randomized to Probuphine.

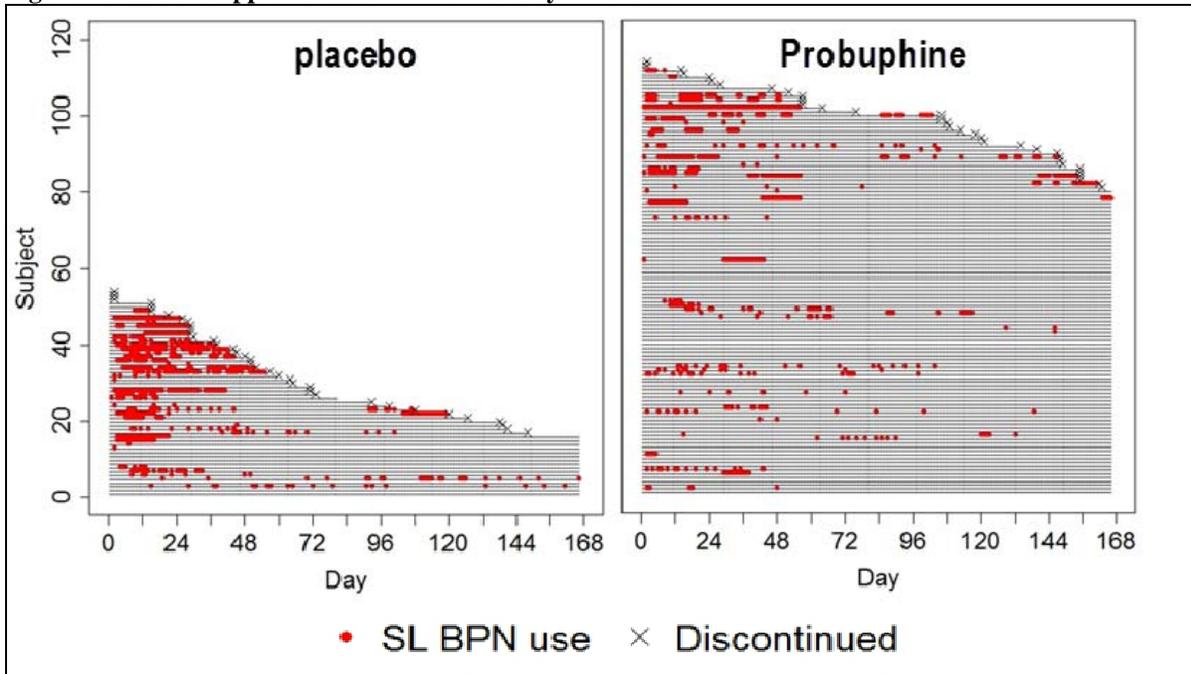
Figures 17 and 18 depict the days an individual subject used rescue medication. The x-axis denotes day, and each row represents an individual subject. A red dot indicates a day of use, a black dash indicates a day when a subject did not use, and the x indicates the day the subject withdrew from the study.

Figure 17. Use of supplemental SL BPN in Study PRO-805



Source: Reviewer

Figure 18. Use of Supplemental SL BPN in Study PRO-806



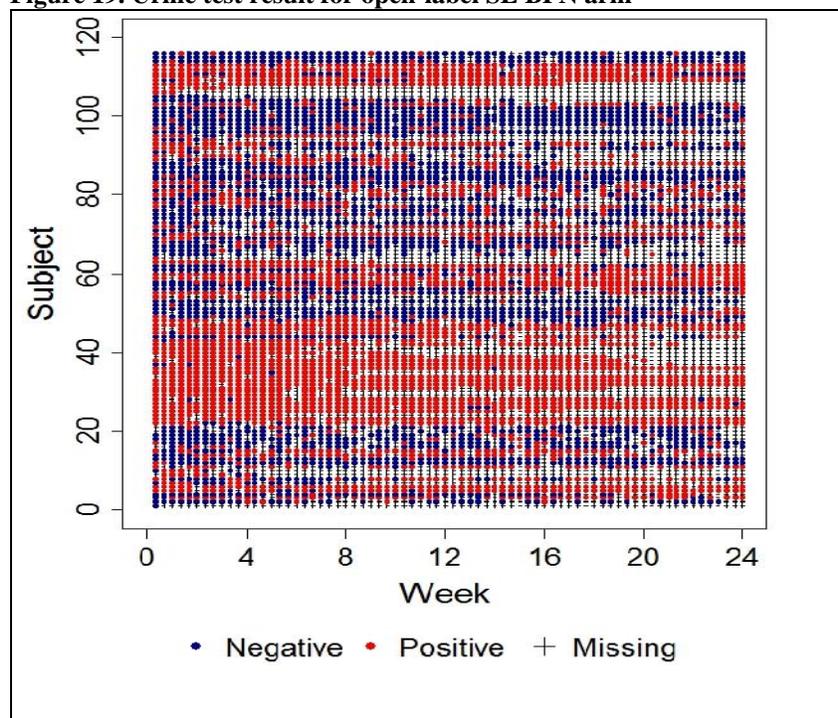
Source: reviewer

The figures show that placebo subjects used rescue medication more frequently early on and then discontinued. Probuphine subjects used SL BPN more sporadically and stayed in the study longer.

Finally, since the Wilcoxon rank sum test is more sensitive to differences in the left-hand side of the response profiles, I compared the results using the log-rank test which has been shown to be more sensitive to differences in the right-hand side of the response profiles. The far right-hand side of the response profile is where abstinence would be observed. The separation in the curves was statistically significantly different for both studies when compared using the log-rank test, p-values < 0.05.

Open-label SL BPN arm in Study PRO-806: Buprenorphine is the active ingredient in Probuphine and is an approved product used to treat opioid dependence. To examine the use of illicit opioids as indicated by positive urine in subjects receiving an approved product, I graphed the urine test results for each individual subject. I excluded the data from five subjects that were missing all urines. Results are shown in Figure 19.

Figure 19. Urine test result for open-label SL BPN arm



Source: Reviewer

Even with an approved product, subjects continued to use illicit opioids as indicated by the positive urine samples.

3.3 Evaluation of Safety

The Agency's previous experience with surgically implanted products, specifically contraceptive implants, was used to identify potential concerns that could arise in the use of Probuphine. The

applicant has described a model of care in which physicians who may or may not have surgical backgrounds would undergo a one-time training program to instruct them on the insertion and removal of the Probuphine rods. However, they note that perhaps one-third of patients would be treated under a divided care model, in which a physician who had undergone the training program would perform the implantation procedure but would not take responsibility for the patient's addiction treatment. The patient would then be followed by a different physician qualified to provide buprenorphine treatment of addiction but who had not received the training on how to implant or remove the product and potentially had no surgical background. In this scenario, follow-up care and management of potential complications would be provided by a physician who may not be equipped to manage them.

Drug utilization data indicate that 32% of prescriptions for buprenorphine/naloxone sublingual tablets are written by physicians whose specialty is identified as General Practitioner/Family Medicine/Doctor of Osteopathy. While some of these individuals may perform minor surgical procedures, others may not be prepared to do so. Twenty-two percent of prescriptions are written by psychiatrists whose training likely includes little in the way of surgical procedures and whose office environments may be unsuitable for managing an implantation-site complication. Internists write 16% of prescriptions, while only a very small proportion of prescriptions are written by physicians whose specialties involve surgical training.

The advisory committee voted almost unanimously that there were no safety issues that would preclude the approval of this product. However, they commented that the applicant's REMS proposal would need significant modifications.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

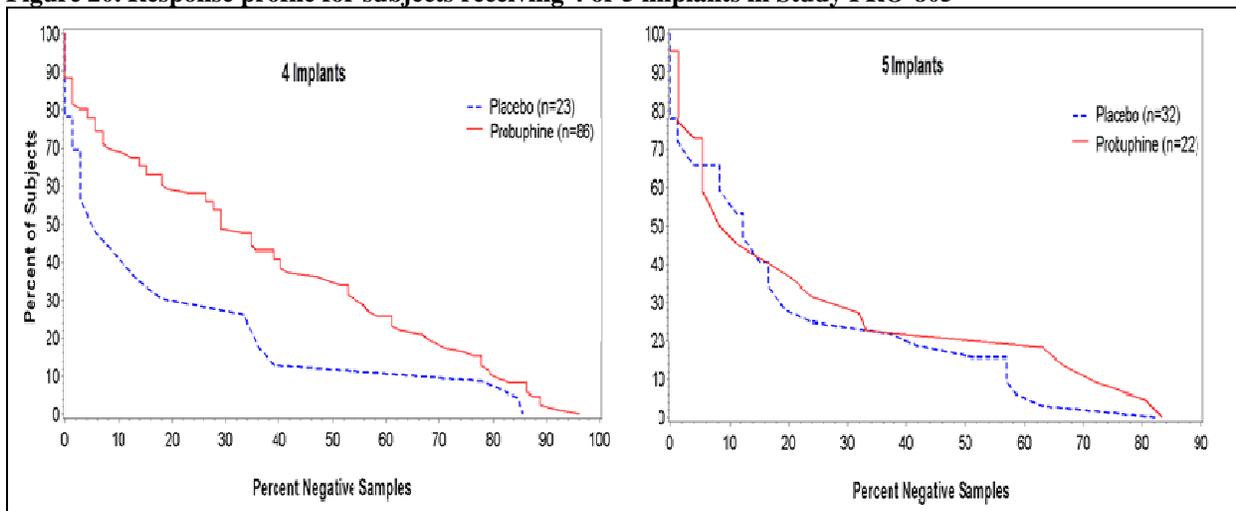
The primary efficacy endpoint, response profile of negative urines, was examined for any differences due to study sites, racial subgroups, gender, and age. I classified racial subgroups as Caucasian or not Caucasian and age as 35 years of age or younger and older than 35 years. As these studies were conducted in the United States, I did not examine geographic region.

To explore any potential differences in the treatment effect by subgroups, I utilized an ANOVA model with a treatment interaction for each subgroup. In both studies, the effect of the treatment was consistent for age, gender, and racial subgroups.

4.2 Other Special/Subgroup Populations

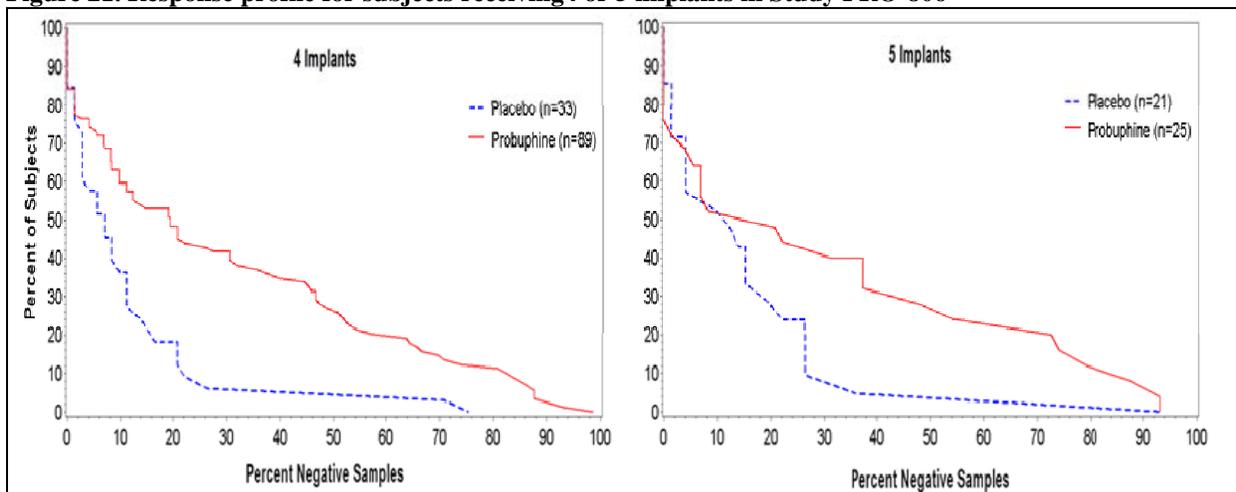
The treatment effect was examined in subjects receiving 4 implants versus 5 implants. The response profiles are presented in Figures 20 and 21.

Figure 20. Response profile for subjects receiving 4 or 5 implants in Study PRO-805



Source: Reviewer

Figure 21. Response profile for subjects receiving 4 or 5 implants in Study PRO-806



Source: Reviewer

In Study PRO-806, the response profiles for subjects receiving 5 implants were similar to the response profiles observed in subjects receiving 4 implants, i.e. the response profile for Probuphine subjects was better than that of placebo. However, for Study PRO-805 in subjects receiving 5 implants, the response profile for placebo subjects was similar to the response profile for Probuphine subjects.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

I reviewed two Phase 3 clinical trials to evaluate the efficacy of Probuphine for maintenance treatment of opioid addiction. The pre-defined primary endpoint in both studies was statistically significant when compared to placebo. Based on my evaluation of the data, I concluded that the

applicant adequately addressed self-report data and missing urines samples in their primary analysis. However, there were no patients regardless of treatment that refrained from using illicit opioids during this study and the use of supplemental SL BPN seemed widespread in both studies. Each study is discussed separately below.

The pre-defined primary endpoint in Study PRO-805 was the response profile of negative urines for Weeks 1-16. There was a statistically significant difference in the response profiles when comparing Probuphine to placebo. However, the clinical review team requested that I evaluate the response profile of negative urines from Weeks 1-24 since Probuphine is intended for marketing as a six-month implant. Further, the preliminary results presented by the applicant prior to the NDA submission indicated a discrepancy between a subject's self-reported use and the urine test results, i.e., a subject reported using illicit opioids but had a negative urine screen. Thus, a post-hoc analysis of the response profiles of negative urines for Weeks 1-24 incorporating self-report data was conducted and demonstrated a statistically significant difference in favor of Probuphine. My exploratory analyses further support the efficacy of Probuphine.

Study PRO-806 utilized the preferred 24-week primary endpoint and incorporated self-report data. The results of primary analysis yielded a statistically significant treatment effect in favor of Probuphine. My exploratory analyses also provided support of the efficacy of Probuphine.

5.2 Conclusions and Recommendations

Based on my analyses, subjects treated with Probuphine provided an overall higher percentage of negative urine samples compared to placebo patients. However, the inability of subjects to achieve complete abstinence from illicit opioid use was of concern to the review team. The clinical relevance of the findings was discussed at a meeting of the Psychopharmacologic Drugs Advisory Committee. Members of the panel commented that positive urine samples and the need for supplemental SL BPN merely suggest a need for a dose adjustment or some other modification to treatment. After consideration of the trial results and the discussions that took place at the Advisory Committee meeting, I conclude that Probuphine may offer clinical benefit to some subjects by limiting their use of illicit opioids when combined with counseling and psychosocial support. The safety concerns regarding the surgical implantation procedures do not seem to negate this potential clinical benefit.

5.3 Label Review

The following was presented in Section 14 of the applicant's proposed label. My comments and suggestions follow the Applicant's proposed wording and are italicized.

(b) (4)

The above statement is consistent with the study reports.

(b) (4)

Refer to this as (b) (4)

(b) (4)

The above is consistent with the study report.

(b) (4)

(b) (4) *if appropriate may be included on the label.*

(b) (4)

While this statement is supported by the data, this type of information is usually not included in the label as it has little meaning to a practicing clinician. .

(b) (4)

(b) (4) *I recommend deleting the paragraph above and replacing it with text describing the response profiles.* (b) (4)

(b) (4)

(b) (4)



(b) (4)

To provide a more intuitive presentation of the study results, present the data to illustrate the proportion of patients who submitted a particular percentage of negative tests or better such as Figure 3 in my review.



(b) (4)

Since this product is to be marketed as 6-month implant, this statement should not be included in the label.



This (b) (4) *should not be included in the label.*



[Redacted] (b) (4)

[Redacted] (b) (4), they [Redacted] (b) (4)
should not be included in the label.

[Redacted] (b) (4)

These [Redacted] (b) (4) should not be reported in the label.

[Redacted] (b) (4)

Refer to this as [Redacted] (b) (4)

[Redacted] (b) (4)

The above is consistent with the study report.

[Redacted] (b) (4)

[Redacted] (b) (4) *if appropriate, may be included in the label.*

[Redacted] (b) (4)

[Redacted] (b) (4)

This [Redacted] (b) (4) may be included in the label. However, [Redacted] (b) (4) should not be included.

[Redacted] (b) (4)

[Redacted] (b) (4)
To provide a more intuitive presentation of the study results, present the data to illustrate the proportion of patients who submitted a particular percentage of negative tests or better such as Figure 4 in my review.

[Redacted] (b) (4)

[Redacted] (b) (4)
it has little clinical interest and should not be included in the label.

[Redacted] (b) (4)

(b) (4)



These (b) (4) *should not be reported in the label.*

(b) (4)



(b) (4)



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

/s/

DAVID M PETULLO
04/05/2013

DIONNE L PRICE
04/05/2013
concur