

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204442Orig1s000

NON-CLINICAL REVIEW(S)



FOOD AND DRUG ADMINISTRATION
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Pharmacology Toxicology Memo to File

TO: NDA 204442

FROM: R. Daniel Mellon, PhD
Pharmacology Toxicology Supervisor
DAAAP

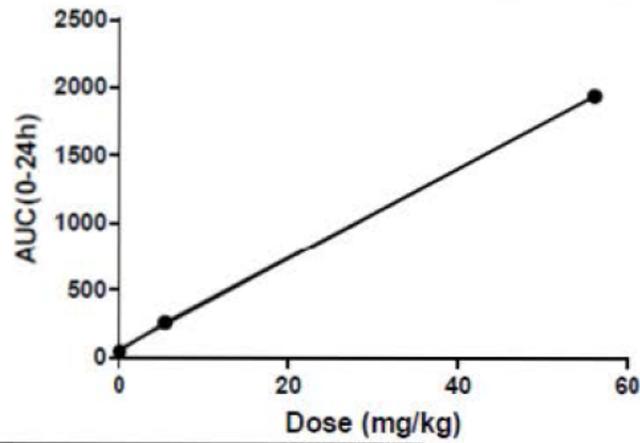
SUBJECT: Probuphine Labeling Recommendations

SOURCE DOCUMENT: SDN 31 (August 27, 2015)

Dr. Gary Bond completed the primary review of NDA 204442 and recommended that NDA 204442 may be approved from a nonclinical pharmacology toxicology perspective. Dr. Jay Chang and I have concurred with this recommendation.

In Dr. Bond's NDA review, the nonclinical team recommended labeling for fertility with exposure margins based on body surface area as there were no exposure data following an oral dose of 47 mg/kg in the rat. However, upon further review, we have revised the exposure margins presented in the labeling based on a linear extrapolation of the exposure data from the submitted rat 28-day oral toxicity study. Based on this extrapolation, the dose of 47 mg/kg is predicted to result in an AUC_{0-24h} of 1638.593 ng•h/mL. As the maximum human exposure over the course of the treatment period results in an AUC_{0-24h} of 75 ng•h/mL, the appropriate exposure margin for Sections 8.3 and 13.1 is 22 ($1638.593/75 = 21.9$) based on AUC. The details of the linear extrapolation are depicted below (GraphPad Prism).

Probuphine NDA 204442 Labeling Extrapolation
Exposure Data Rat 28-day Toxicity



Best-fit values	
Slope	33.67 ± 0.5180
Y-intercept when X=0.0	58.08 ± 16.83
X-intercept when Y=0.0	-1.666
1/slope	0.02970
95% Confidence Intervals	
Slope	27.09 to 40.25
Y-intercept when X=0.0	-157.7 to 269.9
X-intercept when Y=0.0	-9.295 to 4.201
Goodness of Fit	
R square	0.9998
Sy.x	22.60
Is slope significantly non-zero?	
F	4225
DFn, DFd	1,000, 1,000
P value	0.0098
Deviation from zero?	
Significant	
Data	
Number of X values	3
Maximum number of Y replicates	1
Total number of values	3
Number of missing values	1

	Dose (mg/kg)	
	47.000	1638.593

**Dose in fertility study:
AUC 1638.593 / 75 =
21.9-times**

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

/s/

RICHARD D MELLON
05/03/2016

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 204442
Supporting document/s: 31 (NDA) & 104 (IND)
Applicant's letter date: August 27, 2015; October 6, 2015 for PPSR for IND 70852
CDER stamp date: August 27, 2015; October 7, 2015
Product: Probuphine® (Buprenorphine HCL) implant for subdermal administration
Indication: Maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing product (no more than 8 mg/day of Subutex or Suboxone sublingual tablet or generic equivalent).
Applicant: Titan Pharmaceuticals c/o Braeburn Pharmaceuticals
Review Division: Division of Anesthesia, Analgesia, and Addiction Products
Reviewer: Gary P. Bond, PhD
Team Leader: Jay H. Chang, PhD
Supervisor: R. Daniel Mellon, PhD
Division Director: Sharon Hertz, MD
Project Manager: Swati Patwardhan, MS

Disclaimer

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1 Executive Summary

1.1 Introduction and Regulatory History

Probuphine® is a buprenorphine containing subdermally implantable formulation. The active pharmacological ingredient, buprenorphine hydrochloride (buprenorphine), is a partial opioid agonist administered in a solid matrix of ethylene vinyl acetate polymer (EVA). Probuphine is intended to provide sustained delivery of buprenorphine for up to 6 months for the maintenance treatment of opioid dependence. As the drug product is implanted, the Applicant claims that this product will have less abuse and diversion liability and result in greater compliance. Each implant contains 74.2 mg buprenorphine (equivalent to 80 mg buprenorphine hydrochloride (HCl)) and (b) (4) mg of EVA. The maximum proposed dose is 4 implants totaling 320 mg buprenorphine HCl. The drug product formulation was developed under IND 70852.

NDA 204442 for marketing application for Probuphine was originally submitted on October 31, 2012 via the 505(b)(2) pathway with reference to the Agency's previous determination of safety and efficacy for Suboxone (buprenorphine and naloxone) sublingual film and Subutex (buprenorphine) sublingual tablet. Dr. Gary Bond completed the primary pharmacology toxicology review and Dr. Adam Wasserman completed the secondary review. A recommendation was made to approve the NDA from the nonclinical perspective. However, the NDA was ultimately not approved and the Division issued a complete response letter (CRL) on April 30, 2013 that indicated several outstanding clinical deficiencies/issues. Nonclinical comments were also included in the letter recommending that additional information or studies be submitted to justify exposure margins, which are based on animal data derived from the listed drug label compared to the human exposures to Probuphine at the maximum recommended daily dose that would go into the Probuphine label (see CRL for specific comments).

In the minutes from the November 19, 2013 post-action meeting, the Division provided the following comments:

- For Developmental Toxicity, SC doses of 0.1, 1, & 5 mg/kg/day in rats and 5 mg/kg/day in rabbits as you propose and as listed in the reference NDA label are acceptable. It is assumed you mean that the toxicokinetic samples will be taken on the first day of dosing (Day 6 of gestation) and then 14 days later (Day 20 of gestation). If so, this is acceptable. In order to account for potentially extended elimination half-lives of buprenorphine, additional time points should be considered for sampling, particularly after the last dose.
- For the Carcinogenicity section of the label, we do not believe (b) (4) . In order to provide a more meaningful description of labeled studies, conduct bridging studies targeting dietary doses of 0.6, 5.5, and 56 mg/kg/day in rats and 100 mg/kg/day

in mice as listed in the reference NDA label. The duration of daily dosing and toxicokinetic sampling should be appropriate so as to adequately define steady state for daily dosing with a long enough sampling time, most notably after the last dose.

- For the Impairment of Fertility section of the label, you will need to provide bridging TK data for the SC dose of 5 mg/kg/day in rats as described in the reference NDA label. The duration of daily dosing and toxicokinetic sampling should be appropriate so as to adequately define steady state with a long enough sampling time, most notably after the last dose.
- If the exposure data obtained in the SC bridging TK study would provide for a safety margin for human exposure to be expressed in the label, the inclusion of nonclinical findings from the other exposure routes is unnecessary. However, if the SC dosing data indicates that exposure does not adequately cover human exposure then study findings utilizing non-SC routes may be of greater relevance and must be included and addressed in the label.

The Applicant submitted a resubmission of the NDA on August 27, 2015 that included newly proposed nonclinical labeling based on the requested nonclinical toxicokinetic data.

- a. A 28 Day Pharmacokinetic Study of Buprenorphine in Sprague-Dawley Rats – Study Number 2335-001.
- b. A 28 Day Pharmacokinetic Study of Buprenorphine in CD1 Mice – Study Number 2335-002.
- c. A 12 to 14-Day Pharmacokinetic Study of Buprenorphine in Gravid and Non-Gravid Sprague-Dawley Rats – Study Number 2335-003.
- d. A 12-Day Pharmacokinetic Study of Buprenorphine in Gravid New Zealand White Rabbits– Study Number 2335-004.5.

(b) (4)



(b) (4)

Dr. Gary Bond completed the primary review of the submitted PK studies. Drs. Bond, Jay Chang, Elizabeth Bolan, and R. Daniel Mellon collectively discussed the labeling recommendations presented in this review. The labeling recommendations are intended to comply with the final Pregnancy and Lactation Labeling Rule (PLLR).

1.2 Brief Discussion of Nonclinical Findings

This review is in response to the Applicant's newly proposed product labeling related to the nonclinical Toxicokinetic (TK) Bridging Plan, supported by nonclinical TK studies designed for converting reference NDA label human to nonclinical dose ratios (mg/m² body surface area basis) into values that allow blood level comparisons (AUC basis) for the proposed drug product Probuphine (buprenorphine HCl). As a brief background, the labels of the listed drugs (LDs) Suboxone (buprenorphine and naloxone) sublingual film and Subutex (buprenorphine) sublingual tablet each describe virtually identical nonclinical findings from reproductive and developmental toxicology studies, carcinogenicity studies, and mutagenicity studies conducted with buprenorphine. The Suboxone label also describes findings from nonclinical studies conducted with buprenorphine and naloxone. Notably, the nonclinical information described in Section 8.1 *Pregnancy* of these labels describe findings derived from reproductive and developmental toxicology studies performed in animals using a variety of routes of administration including oral, intravenous, intramuscular, and subcutaneous. Also of note, the carcinogenicity information described Section 13.1 *Carcinogenesis, Mutagenesis, Impairment of Fertility* in those labels were derived from rodent feeding studies. As such, the Sponsor conducted and submitted nonclinical TK studies employing the subcutaneous route, which is the clinically relevant route for Probuphine, to bridge to the reproductive and developmental information in the LD labels and studies employing dietary administration of buprenorphine to bridge to the carcinogenesis information. As noted above in the introductory remarks of this NDA review, we informed the Applicant that if the exposure data obtained in the SC bridging TK study provides adequate safety margins to be expressed in the label, the inclusion of nonclinical findings from the other exposure routes (e.g., oral, IV, IM) would be unnecessary. However, if the SC dosing data indicated that nonclinical exposures do not adequately cover human exposure then study findings utilizing non-SC routes may be of greater relevance and must be included and addressed in the label.

The reviewer-generated table below summarizes the exposure margins established by comparing the AUC exposure to buprenorphine observed in nonclinical TK bridging studies with the AUC exposure observed in human subjects administered the maximum recommended dose of Probuphine at 320 mg buprenorphine HCl (4 rods). Note that

was used to calculate exposure margins for the doses related to the nonclinical embryofetal development studies

In contrast, steady state human AUC_{0-24h} levels were considered appropriate for the doses related to the nonclinical carcinogenesis (e.g., feeding) studies since this endpoint is most likely influence by the concentration at steady state, which is fairly constant over the 6 month period of implantation. The table notes a difference between the Applicant’s proposed exposure margins and this reviewer’s calculated margins. For the embryofetal studies, this appears to be due to the fact that the Agency used the mean values obtained in the animal PK bridging studies and the Applicant apparently used . The Agency uses the mean values when making exposure comparisons for labeling purposes, as the overall toxicology findings are based on the totality of the data, rather than

In contrast, the differences in exposure margins between the Agency and the Applicant noted for the 28-day feeding study is because the Applicant used whereas we consider the steady state level to be more appropriate for a carcinogenicity endpoint. For labeling purposes, the exposure margin values can be rounded to the nearest single digit.

Table 1: Summary of Exposure Margins based on Pharmacokinetic Data

Dose Ratios for Animal to Human Doses Comparing Animal AUC doses in Nonclinical Studies to Human AUC Values at Maximum Recommend Human Dose of 320 mg Buprenorphine HCL contained in 4 Probuphine Rods					
Study	Species	Dose route	Dose (mg/kg)	AUC _{0-24h} ^a (ng * hr/mL)	Dose Ratio ^b nonclinical:clinical (Applicant’s value)
28-day feeding	Male and female rat	oral	0.6	43	2 ^{(b) (4)} b
			5.5	258	13 ^{(b) (4)} b
			56	1940	99 ^{(b) (4)} b
	Male and female mouse	oral	100	1045	53 ^{(b) (4)} b
Embryo-fetal	Female rat (gravid)	sc ^d	0.1	72	1 ^{(b) (4)} c
			1	359	5 ^{(b) (4)} c
			5	1355	18 ^{(b) (4)} c
	Female	sc	5	1575	21 ^{(b) (4)} c

	rabbit				
	(gravid)				
14-day repeat dose	Male and female rat	sc	5	1995	27 (b) (4) c

a – average of last 2 sampling periods (at steady state)

b – based on steady state human AUC for 4 Probuphine rods from clinical study PRO-810 ($AUC_{0-24h} = 19.6$ ng*h/mL on Day 28 following implantation)

c – based on (b) (4)

(b) (4)

d – subcutaneous

Refer to the Applicant's proposed labeling and FDA's recommended changes in Section 1.3.3 of this review. The above exposure margins have been incorporated into the draft Probuphine label where appropriate.

1.3 Recommendations

1.3.1 Approvability

Consistent with the previous recommendation after the first review cycle, from the nonclinical perspective, the NDA may still be approved. Note that adequate nonclinical data were submitted with the original NDA submission that provided evidence for human safety for the expected systemic exposure to buprenorphine and characterized the potential local toxicity from Probuphine implants.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The table below contains the draft labeling proposed by the Applicant, changes suggested by this reviewer, and the rationale for this reviewer's changes. Of note, as per the meeting minutes from the post-action meeting held on November 19, 2013, the Agency stated the following:

If the exposure data obtained in the SC bridging TK study would provide for a safety margin for human exposure to be expressed in the label, the inclusion of nonclinical findings from the other exposure routes is unnecessary. However, if the SC dosing data indicates that exposure does not adequately cover human exposure then study findings utilizing non-SC routes may be of greater relevance and must be included and addressed in the label.

However, upon formal review of the submitted PK data and the referenced drug product labels, the review team is not comfortable including only the data derived from SC dosing studies, as the toxicological characterization of buprenorphine is based on the

entirety of the data from the referenced product labels. Removal of the studies that were not completed by the SC route of administration minimizes the overall risk summary message and there is no reason to believe that this drug product is any safer than the other buprenorphine drug products that would be used by the patients who are stabilized on not more than 8 mg of buprenorphine via the sublingual route. As such, we recommend that the referenced product labels' animal data sections be reproduced in the Probuphine labeling with the exposure margins updated to reflect actual exposure data, where available. The risk summary should also be reproduced from the referenced Subutex labeling with the statements regarding human exposure relevance updated based on the limited new PK data. Ideally, exposure data would have been provided for all of the studies, to put the findings into context, since the limited exposure data submitted suggest a larger safety margin than predicted by the body surface area comparison in the referenced product labeling. However, since we do not have AUC data for all of these studies, the label can only reflect the data we have and the relative risk suggested by the data in the referenced product labels. The PLLR labeling recommendations also cannot be updated to include information regarding maternal toxicity in this label, as we do not have access to the original study reports to support this 505(b)(2) application.

The labeling recommendations below reflect the collective discussions of the nonclinical review team and have not yet been discussed with the Applicant and the entire review team. As such, the reader is referred to the action letter for final labeling for this drug product formulation.

Applicant's Proposed Label (nonclinical relevant sections)	Reviewer's recommended changes to Applicant's proposed label	Rationale for Reviewer's edits
<p>HIGHLIGHTS OF PRESCRIBING INFORMATION</p> <p>-----INDICATIONS AND USAGE----- -----</p> <p> (b) (4)</p> <p>----USE IN SPECIFIC POPULATIONS-----</p> <ul style="list-style-type: none"> Proposed statement not included 	<p>HIGHLIGHTS OF PRESCRIBING INFORMATION</p> <p>-----INDICATIONS AND USAGE----- -----</p> <p>PROBUPHINE contains buprenorphine, a partial opioid agonist. PROBUPHINE is indicated for the maintenance treatment of opioid dependence. Prescription use of this product is limited under the Drug Addiction Treatment Act. (1)</p> <p>----USE IN SPECIFIC POPULATIONS-----</p> <ul style="list-style-type: none"> Pregnancy: May cause fetal harm. (8.1) 	<p>Added buprenorphine and FDA Established Pharmacologic Class for this compound.</p> <p>Modified from Suboxone label to current listing in consultation with Maternal Health Team</p>

<p>8. Use in Specific Populations 8.1 Pregnancy</p> <p>Risk Summary</p> <p>(b) (4)</p>	<p>8. Use in Specific Populations 8.1 Pregnancy</p> <p>Risk Summary</p> <p>Reproductive and developmental studies in rats and rabbits identified adverse events at clinically relevant and higher doses. Embryofetal death was observed in both rats and rabbits administered buprenorphine daily during organogenesis at doses approximately 12 and 0.5 times, respectively, the maximum recommended human dose (MRHD) of Probuphine. Pre-and postnatal development studies in rats demonstrated increased neonatal deaths at a dose approximately equivalent to the MRHD and dystocia at approximately 6-times the MRHD. No clear teratogenic effects were seen with a range of doses equivalent to or greater than the MRHD. However, increases in skeletal abnormalities were noted in rats administered buprenorphine daily during organogenesis at a dose approximately 5 times the MRHD and in rabbits at approximately 12 times the MRHD. In a few studies, some events such as acephalus and omphalocele were also observed but these findings were not clearly treatment-related.</p>	<p>The risk summary statement from the referenced products labeling was reproduced and edited to adjust for exposure margins, since some of these margins are now based on AUC while others are still based on BSA.</p> <p>The adverse effects were reported first, as these findings are considered to be the most important for the prescriber.</p> <p>As per PLLR recommendations, the route of administration for the studies is omitted from the Risk Summary. The Animal Data sections include these details.</p> <p>The referenced product labeling included developmental delays from the pre- and post-natal studies, however, as these effects were noted at ~99 times the human dose, they can be omitted from the risk summary.</p> <p>As in the referenced product labeling, the unusual findings of acephalus and omphalocele are included as neural tube defects have occasionally also been reported with high doses of other opioids in nonclinical studies.</p>
<p>Data</p> <p>Animal Data</p> <p>(b) (4)</p>	<p>Data</p> <p>Animal Data</p> <p>Buprenorphine was not teratogenic in rats and rabbits after subcutaneous (SC) of up to 5 mg/kg/day (approximately 18 and 21 times, respectively, the highest daily exposure from the maximum recommended human dose (MRHD) of Probuphine on an AUC basis), after intramuscular (IM) doses of up to 5 mg/kg/day (approximately 6 and 12 times, respectively, the human daily sublingual (SL) dose of 8 mg buprenorphine on a mg/m²</p>	<p>When no PK data were submitted, the exposure ratios must be based on body surface area comparisons. In contrast to Subutex, which can be dosed higher than this drug product, the referenced daily dose chosen was based on an 8 mg/day dose, since Probuphine is only indicated for individuals who were maintained on 8 mg/day, is designed to deliver relatively the same plasma levels as 8 mg/day sublingual, and cannot be dosed higher.</p>

<p>(b) (4)</p>	<p>basis), after IV doses up to 0.8 mg/kg/day (approximately 1 and 2 times, respectively, the human daily SL dose of 8 mg buprenorphine on a mg/m² basis), or after oral doses up to 160 mg/kg/day in rats (approximately 190 times the human daily SL dose of 8 mg buprenorphine on a mg/m² basis) and 25 mg/kg/day in rabbits (approximately 60 times the human daily SL dose of 8 mg buprenorphine on a mg/m² basis). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (approximately 5 times the highest daily exposure from the MRHD of Probuphine on an AUC basis), but were not observed at oral doses up to 160 mg/kg/day (approximately 194 times the human daily SL dose of 8 mg on a mg/m² basis). Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (approximately 12 times the human daily SL dose of 8 mg on a mg/m² basis) or oral administration of 1 mg/kg/day or greater (approximately 2 times the human daily SL dose of 8 mg on a mg/m² basis) were not statistically significant.</p> <p>In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater (approximately 2 times the human daily SL dose of 8 mg on a mg/m² basis) and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure was approximately 0.5 times the human daily SL dose of 8 mg on a mg/m² basis).</p> <p>Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine 5 mg/kg/day (approximately 6 times the human daily SL dose of 8 mg on a mg/m² basis). Fertility/pre- and post-natal</p>	
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	<p>development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately equivalent to the human daily SL dose of 8 mg on a mg/m² basis), after IM doses of 0.5 mg/kg/day and up (approximately 0.6 times the human daily SL dose of 8 mg on a mg/m² basis), and after SC doses of 0.1 mg/kg/day and up (approximately equivalent to the highest daily exposure from the MRHD of Probuphine on an AUC basis). An apparent lack of milk production during these studies likely contributed to the decreased pup viability and lactation indices. Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 97 times the human daily SL dose of 8 mg on a mg/m² basis).</p>	
<p>8.3 Females and Males of Reproductive Potential</p> <p>Infertility: Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure approximately (b) (4)) produced a reduction in fertility demonstrated by reduced female conception rates (13.1)]</p>	<p>8.3 Females and Males of Reproductive Potential</p> <p><i>Infertility</i> Females</p> <p>Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure approximately (b) (4)) produced a reduction in fertility demonstrated by reduced female conception rates (13.1)</p>	<p>New PLLR section</p> <p>PK data for 47 mg/kg were not provided. Exposure ratio was adjusted for the maximum dose 8 mg equivalents.</p>
<p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p><i>Carcinogenicity:</i></p> <p>Carcinogenicity data on PROBUPHINE are not available.</p>	<p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p><i>Carcinogenicity:</i></p> <p>Carcinogenicity data on PROBUPHINE are not available.</p>	<p>The exposure margins listed in this reviewer’s recommended language are based on AUC comparison</p>

<p>Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at equivalent doses of 0.6, 5.5, and 56 mg/kg (b)(4)/day (approximately (b)(4)).</p> <p>A statistically significant dose-related increases in Leydig cell tumors occurred. In an 86-week study in CD-1 mice, buprenorphine was not carcinogenic when administered in the diet at equivalent doses up to 100 mg/kg (b)(4)/day (b)(4).</p>	<p>Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at equivalent doses of 0.6, 5.5, and 56 mg/kg/day for 27 months (approximately 2, 13, and 99 times the steady state exposure from the recommended dose of Probuphine on an AUC basis). Statistically significant dose-related increases in Leydig's cell tumors occurred. In an 86-week study in CD-1 mice, buprenorphine was not carcinogenic at (b)(4) doses up to 100 mg/kg/day (approximately 53 times the steady state exposure from the recommended dose of Probuphine on an AUC basis).</p>	<p>using data from TK bridging studies conducted by the Applicant in rats and mice to mimic dosing described in listed drug label to the steady state AUC human exposure observed in subjects receiving maximum recommended human dose of 320 mg buprenorphine HCl from Probuphine (Clinical Study PRO-810 Day 28 AUC_{0-24h}=19.6 ng.h/mL).</p>
<p>Mutagenicity:</p> <p>Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (<i>Saccharomyces cerevisiae</i>) for recombinant, gene convertant, or forward mutations; negative in <i>Bacillus subtilis</i> "rec" assay; negative for clastogenicity in Chinese hamster ovary, bone marrow, and spermatogonia cells; and negative in the mouse lymphoma L5178Y assay.</p> <p>Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5 mg/plate) in a third study.</p>	<p>Mutagenicity:</p> <p>Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (<i>Saccharomyces cerevisiae</i>) for recombinant, gene convertant, or forward mutations; negative in <i>Bacillus subtilis</i> "rec" assay; negative for clastogenicity in Chinese hamster ovary, bone marrow, and spermatogonia cells; and negative in the mouse lymphoma L5178Y assay.</p> <p>Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5 mg/plate) in a third study. Results were positive in the Green-Tweets (<i>E. coli</i>) survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both in vivo and in vitro incorporation of [³H]thymidine, and positive in unscheduled DNA synthesis test using testicular cells from mice.</p>	<p>No changes to Applicant's proposed language.</p> <p>This information is excerpted from the Suboxone label</p> <p>The Applicant omitted details of positive genotox studies that are included in the Suboxone and Subutex labels. We recommend including this information in the Probuphine label.</p>

<p>Impairment of Fertility:</p> <p>Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure approximately (b) (4) times (b) (4) on a mg/m² basis) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure approximately (b) (4) (b) (4) had no adverse effect on fertility.</p>	<p>Impairment of Fertility:</p> <p>Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; approximately (b) (4) times the human daily SL dose of 8 mg on a mg/m² basis) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; approximately (b) (4) (b) (4) had no adverse effect on fertility.</p> <p>Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily oral doses up to 80 mg/kg/day (estimated exposure approximately 100 times the human daily SL dose of 8 mg on a mg/m² basis) or up to 5 mg/kg/day IM or SC (estimated exposure was approximately (b) (4) times the human daily SL dose of 8 mg on a mg/m² basis).</p>	
<p>11 Description (b) (4)</p>		
<p>12 Clinical Pharmacology 12.1 Mechanism of Action PROBUPHINE implants contain buprenorphine HCl. (b) (4)</p>	<p>12 Clinical Pharmacology 12.1 Mechanism of Action PROBUPHINE implants contain buprenorphine HCl. Buprenorphine (b) (4) is a partial agonist (b) (4) at the mu (μ)-opioid receptor (b) (4) and an antagonist at the kappa (κ)-opioid receptor (b) (4)</p>	<p>Edited to reflect the mechanism described in the Subutex and Suboxone labeling. (b) (4)</p>

(b) (4)	(b) (4)	
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2 Drug Information

2.1 Drug

CAS Registry Number – 53152-21-9

Generic Name – buprenorphine hydrochloride

Code Name - buprenorphine implant

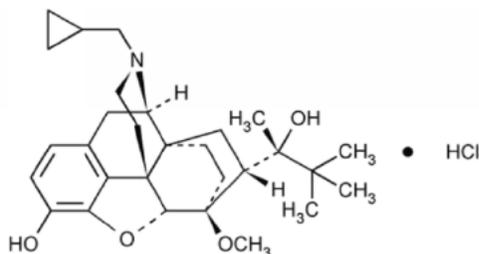
Chemical Name

- 21-Cyclopropyl-7 α -[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-endoethano-6,7,8,14-tetrahydrooripavine hydrochloride

Molecular Formula/Molecular Weight

- C₂₉H₄₁NO₄•HCl/504.1068

Structure or Biochemical Description



Pharmacologic Class

- partial opioid agonist (FDA EPC)

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA#	Drug Name	Div	Strength (route)	Marketing Status	AP Date	Indication	Company
20733	Suboxone (buprenorphine and naloxone)	DAAAP	2/0.5 & 8/2 mg (sublingual tablets)	Approved	10/8/2002	Maintenance of Opioid Dependence	Indivior
20732	Subutex (buprenorphine)	DAAAP	2 & 8 mg (sublingual tablets)	Approved	10/8/2002	Induction and Maintenance of Opioid Dependence	Indivior

IND#	Drug	Status	Division	Indication	Stamp Date	Sponsor
70852	Probuphine (buprenorphine/ethylene vinyl acetate)	Active	DAAAP	Treatment of opioid dependence	12/21/2004	Titan Pharmaceuticals

2.3 Drug Formulation

Refer to NDA 204442 Pharmacology Toxicology review dated 4/5/2013 for details regarding the clinical formulation of Probuphine. No new issues have been identified with this NDA resubmission.

2.4 Comments on Novel Excipients

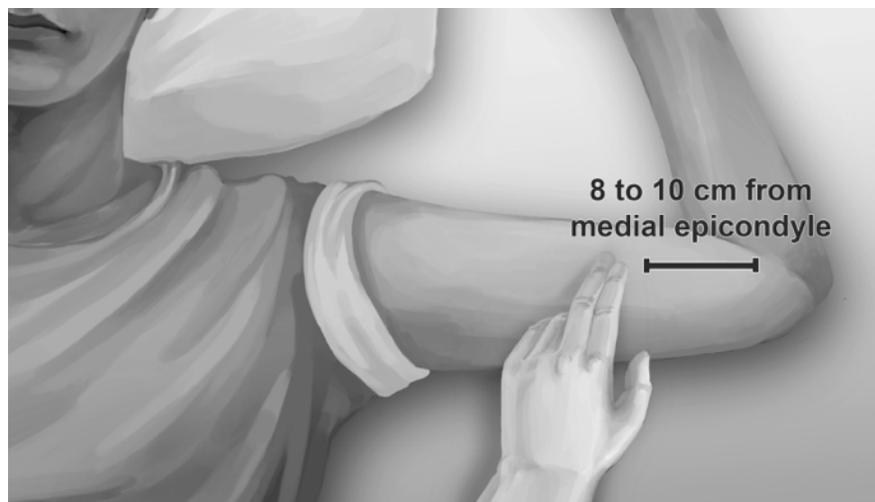
Refer to NDA 204442 Pharmacology Toxicology review dated 4/5/2013 for details regarding the clinical formulation of Probuphine. No new issues have been identified with this NDA resubmission.

2.5 Comments on Impurities/Degradants of Concern

Refer to NDA 204442 Pharmacology Toxicology review dated 4/5/2013 for details regarding the clinical formulation of Probuphine. No new issues have been identified with this NDA resubmission.

2.6 Proposed Clinical Population and Dosing Regimen

Subjects who are dependent on opioids are the proposed clinical population. The proposed dosing regimen is 4 Probuphine rods inserted subdermally at the “inner side of the upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus in the sulcus between the biceps and triceps muscle” for 6 months and then removed with insertion of an additional 4 rods under the skin, preferably on the opposite “inner side of the upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus in the sulcus between the biceps and triceps muscle” as per the instructions in the labeling. The figure below was reproduced from the proposed labeling:



2.7 Regulatory Background

Buprenorphine has been marketed for over 30 years as injectable Buprenex (NDA 18 401). 505(b)(2) reference for buprenorphine is made to the approved Subutex (NDA 20732) and Suboxone (NDA 20733) sublingual tablet labels with the Maximum Recommended Human dose (MRHD) of 16 mg buprenorphine per day.

NDA 204442 was originally submitted on October 31, 2012 via the 505(b)(2) pathway with reference to the Agency's previous determination of safety and efficacy for Suboxone (buprenorphine and naloxone) sublingual tablets and Subutex (buprenorphine) sublingual tablets. A recommendation was made to approve the NDA from the nonclinical perspective. However, the NDA was ultimately not approved and the Division issued a complete response letter (CRL) on April 30, 2013 that indicated several outstanding clinical deficiencies/issues. The Applicant submitted this resubmission of the NDA on August 27, 2015. This review focuses on the submitted nonclinical pharmacokinetic bridging data and the proposed labeling recommendations.

3 Studies Submitted

3.1 Studies Reviewed

- A 28 Day Pharmacokinetic Study of Buprenorphine in Sprague-Dawley Rats – Study Number 2335-001
- A 28 Day Pharmacokinetic Study of Buprenorphine in CD1 Mice – Study Number 2335-002
- A 12 to 14-Day Pharmacokinetic Study of Buprenorphine in Gravid and Non-Gravid Sprague-Dawley Rats – Study Number 2335-003
- A 12-Day Pharmacokinetic Study of Buprenorphine in Gravid New Zealand White Rabbits– Study Number 2335-004.5

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

NDA 204442 Pharmacology Toxicology review dated 4/5/2013

4 Pharmacology

No new pharmacology studies were submitted with this NDA resubmission.

5 Pharmacokinetics/ADME/Toxicokinetics

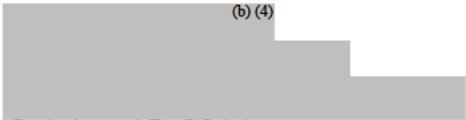
5.1 PK/ADME

No new PK/ADME studies were submitted with this NDA resubmission.

5.2 Toxicokinetics

These nonclinical studies were conducted at doses listed in the current Suboxone label so as to allow animal:human dose ratios to be expressed on an AUC basis instead of the current body surface area (mg/m^2) basis. Doses were selected to match the Suboxone label values for oral carcinogenicity and subcutaneous embryo-fetal toxicity studies.

Study title: A 28 Day Pharmacokinetic Study of Buprenorphine in Sprague-Dawley Rats

Study no.:	2335-001
Study report location:	Global Submit Review
Conducting laboratory and location:	 (b) (4)
Date of study initiation:	October 15, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Buprenorphine HCl, 13-002717, 98.5% Vehicle acetone, 2CJ0255 & T30A480, 99.5%

Key Study Findings

- Male and female Sprague-Dawley rats received daily dietary administration of the buprenorphine HCl in the feed for 28 days at doses of 0.6, 5.5, and 56 mg/kg/day.
- The test article was well tolerated, with males and females demonstrating consistent consumption of the diet by Day 2, gradual weight increases and no adverse clinical findings over the duration of administration.
- Systemic exposure to buprenorphine as measured by $\text{AUC}_{0-24\text{h}}$ was as follows:

Buprenorphine PK Summary Table								
Day	Target Dose (mg/kg)	Mean Actual Dose (mg/kg)	Mean Actual Dose Ratio	AUC _{0-24hr} (hr*ng/mL)	AUC _{0-24hr} Ratio	C _{max} (ng/mL)	C _{max} Ratio	T _{1/2} (hr)
1	0.6	0.528	1	16.4	1	1.52	1	NA
	5.5	2.75	5.2	90.4	5.5	6.83	4.5	NA
	56	23.6	44.7	700	42.7	56.3	37.0	NA
14	0.6	0.618	1	44.7	1	2.95	1	NA
	5.5	5.47	8.9	306	6.8	16.7	5.7	NA
	56	59.0	95.5	2200	49.2	127	43.1	NA
28	0.6	0.595	1	41.8	1	2.28	1	8.04
	5.5	5.22	8.8	208	5.0	10.4	4.6	10.0
	56	52.8	88.7	1680	40.2	87.3	38.3	17.4
NA - Not Applicable								

- **Steady state was achieved by Day 14.** Buprenorphine T_{1/2} could not be determined on Days 1 and 14.

Methods

Doses:

Group Number	Target Dose Level (mg/kg/day)*	Group Assignments	
		Number of Animals	
		Male	Female
1	0.6	9	0
2	5.5	9	0
3	56	9	0
4	0.6	0	9
5	5.5	0	9
6	56	0	9

Frequency of dosing: Daily for 28 days
 Route of administration: Oral feed (*ad libitum*)
 Dose volume: NA
 Formulation/Vehicle: acetone
 Species/Strain: Sprague Dawley
 Number/Sex/Group: 9
 Age: ~9 weeks at receipt
 Weight: 357 to 390 g (males) and 213 to 248 g (females)
 Satellite groups: none
 Unique study design: Study designed to determine blood levels only (i.e., no histology, clinical chemistry, etc.)
 Deviation from study protocol: Nothing significant

Observations and Results

Mortality

All animals were observed for morbidity, mortality, injury, and the availability of food and water twice daily.

No mortality related to treatment.

Clinical Signs

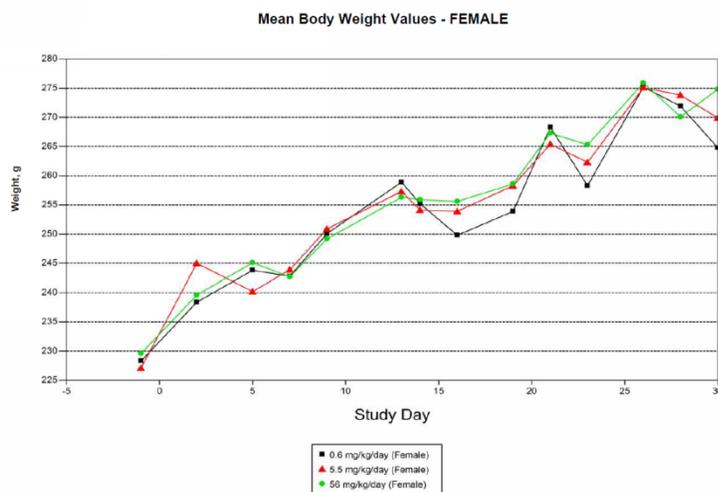
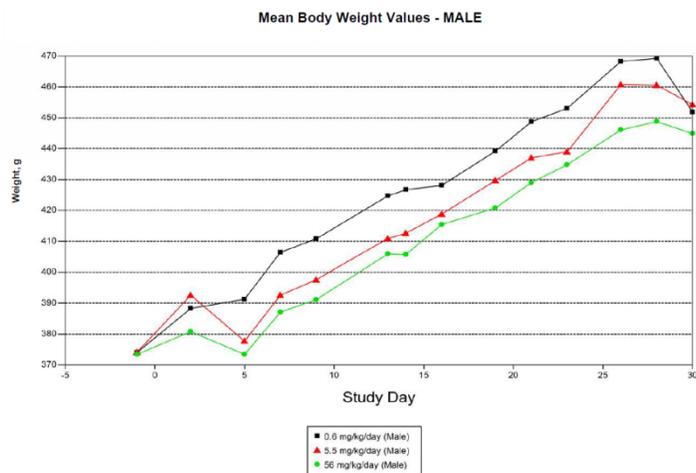
A detailed clinical examination of each animal was performed at least once daily.

No clinical signs related to buprenorphine treatment.

Body Weights

Body weights for all animals were measured and recorded at receipt, prior to randomization, and at least three times weekly during the study. The body weights recorded at receipt are not reported but are maintained in the study file.

Body weights demonstrated an overall gradual increase over the course of the study in both sexes, with no treatment related effects.

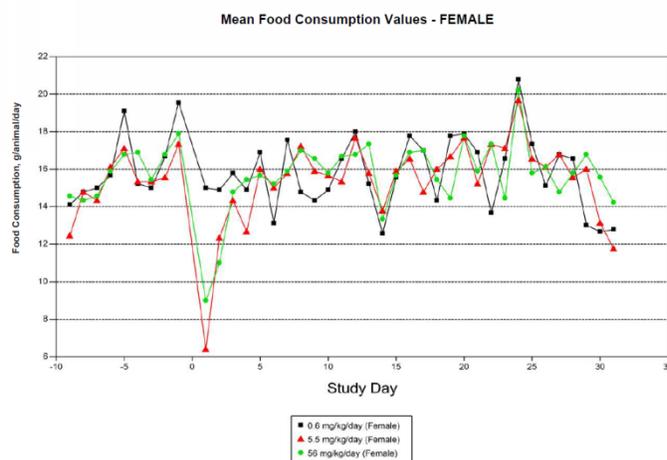
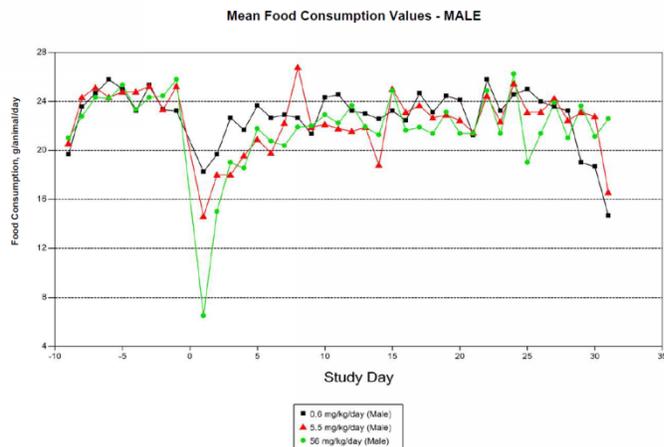


Food Consumption

Food consumption was measured and recorded daily beginning on Day -9 during the study, at the beginning of the dark cycle (± 30 minutes) on each day.

Mean food consumption values showed a slight to moderate decrease in daily consumption following administration of the treated diet compared to pretest food

consumption values (more evident in males than females). Particularly low food consumption values were observed in both sexes on Day 1, the first day of treated diet offering. Mean consumption values for both sexes increased over the next 1-2 days of treated diet administration, and for the remainder of the study duration.



Gross Pathology

Only animals euthanized *in extremis* were evaluated. At study termination, the surviving animals were euthanized by inhalation of carbon dioxide. Euthanasia was confirmed by cervical dislocation and the carcasses were discarded.

There were no buprenorphine treatment-related observations.

Toxicokinetics

Blood samples (0.4 mL) were collected via the lateral tail vein from three cohorts of three animals/group/time point at alternating time points for determination of the plasma concentrations of the test article. Samples were collected at 1, 2, 4, 12, 13, 14, 16, and 24 hours post-dose on Days 1 and 14, and at 1, 2, 4, 12, 13, 16, 24, 40, 56, and 72 hours post-dose on Day 28.

Following daily oral (dietary) administration of buprenorphine HCl, systemic exposure to buprenorphine appeared to be independent of sex; therefore, the values presented below are for males and females combined. Buprenorphine $T_{1/2}$ could not be determined on Days 1 and 14.

Buprenorphine PK Summary Table								
Day	Target Dose (mg/kg)	Mean Actual Dose (mg/kg)	Mean Actual Dose Ratio	AUC _{0-24hr} (hr*ng/mL)	AUC _{0-24hr} Ratio	C _{max} (ng/mL)	C _{max} Ratio	T _{1/2} (hr)
1	0.6	0.528	1	16.4	1	1.52	1	NA
	5.5	2.75	5.2	90.4	5.5	6.83	4.5	NA
	56	23.6	44.7	700	42.7	56.3	37.0	NA
14	0.6	0.618	1	44.7	1	2.95	1	NA
	5.5	5.47	8.9	306	6.8	16.7	5.7	NA
	56	59.0	95.5	2200	49.2	127	43.1	NA
28	0.6	0.595	1	41.8	1	2.28	1	8.04
	5.5	5.22	8.8	208	5.0	10.4	4.6	10.0
	56	52.8	88.7	1680	40.2	87.3	38.3	17.4
NA – Not Applicable								

Dosing Solution Analysis

Documentation of the strength, purity, composition, stability, and other pertinent information for each lot of vehicle component used on study was limited to that information listed on the label of these commercially available products. The Sponsor has provided documentation of the strength, purity, composition, stability, and other pertinent information for the lot of test article used on study. Dosing formulations prepared for the study were evaluated for homogeneity and concentration.

Results of the analysis of dietary dosing formulations indicated that the dietary mixtures were homogenous and prepared at appropriate concentrations, with average calculated concentrations for the lowest and highest concentrations of diet prepared within $\pm 20\%$ of nominal concentration, and precision $\leq 15\%$ relative standard deviation.

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Study title: A 28 Day Pharmacokinetic Study of Buprenorphine in CD1 Mice

Study no.: 2335-02
 Study report location: Global Submit Review
 Conducting laboratory and location: (b) (4)
 Date of study initiation: October 15, 2014
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: Buprenorphine, 13-002717, 98.5%
 Vehicle acetone, 2CJ0255 & T30A480, 99.5%

Key Study Findings

- Male and female CD-1 mice received daily dietary administration of buprenorphine hydrochloride in the feed at a dose of 100 mg/kg/day for 28 days.
- The test article was well tolerated overall, with the majority of animals showing consistent consumption of the test diet, stable body weights and no adverse clinical findings over the duration of administration.
- Systemic exposure to buprenorphine, as measured by AUC_{0-24h} values were as follows:

Buprenorphine TK Summary Table							
Day	Target Dose (mg/kg)	Mean Actual Dose (mg/kg)	AUC _{0-24hr} (hr*ng/mL)	AUC _{0-24hr} /Dose (hr*kg*ng/mL/mg)	C _{max} (ng/mL)	C _{max} /Dose (kg*ng/mL/mg)	T _{1/2} (hr)
1	100	68.6	817	11.9	47.5	0.693	11.1
14	100	80.1	1040	12.9	56.8	0.709	NA
28	100	84.0	1050	12.4	61.3	0.729	5.90
NA - Not Applicable							

- **Steady state was considered achieved by Day 14.** Buprenorphine T_{1/2} could not be determined on Day 14.

Methods

Group Number	Group Assignments		
	Target Dose Level (mg/kg/day)*	Number of Animals	
		Male	Female
1	100	108	0
2	100	0	108

Frequency of dosing: Daily for 28 days
 Route of administration: Oral feed (*ad libitum*)
 Dose volume: NA
 Formulation/Vehicle: Acetone
 Species/Strain: Crl:CD1® (ICR) mice
 Number/Sex/Group: 108
 Age: ~8 weeks
 Weight: 26.3 to 36.4 g (male) and 22.5 to 29.8 g (female)
 Satellite groups: none
 Unique study design: Study designed to determine blood levels only (i.e., no histology, clinical chemistry, etc.)
 Deviation from study protocol: Nothing significant

Observations and Results

Mortality

All animals were observed for morbidity, mortality, injury, and the availability of food and water twice daily.

Five animals were euthanized prior to scheduled sacrifice. Prior to euthanasia, the 3 male and 2 female animals were observed with significantly decreased body weights and decreased food consumption. The cause of death was considered to be related to the loss in body weight.

Clinical Signs

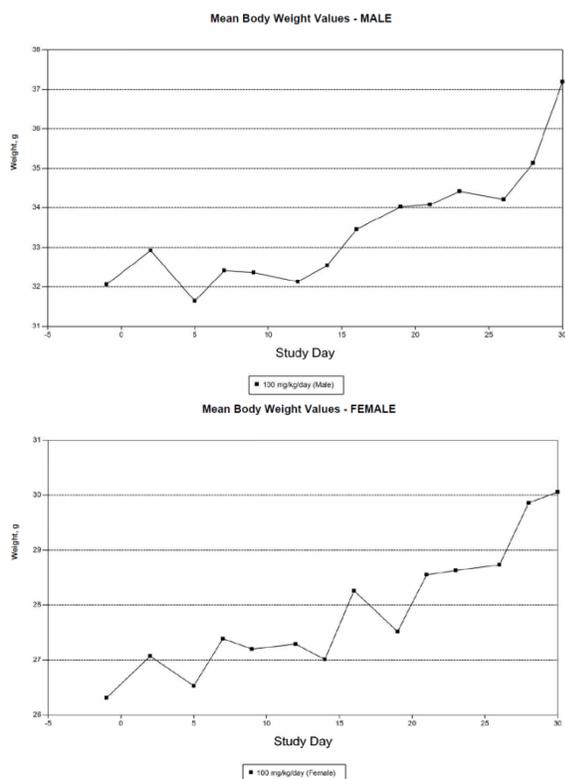
A detailed clinical examination of each animal was performed at least once daily during the study beginning on Day 1.

For the five animals that were euthanized between Days 13 and 16, clinical observations noted in these animals prior to euthanasia included decreased activity, decreased skin turgor, thinness, skin cold to touch, tremors and/or unkempt appearance. These findings are considered secondary to a significant loss in body weight, were limited to animals that became moribund, and were not observed in animals that survived to their scheduled termination.

Body Weights

Body weights for all animals were measured and recorded at receipt, prior to randomization, and at least three times weekly during the study. The body weights recorded at receipt are not reported but are maintained in the study file.

Body weights showed a slight decrease on Day 5 in both sexes, relative to Day 2 values. This correlated with a general decrease in mean food consumption values compared to pretest values upon switching from untreated to treated diet, as discussed below. The mice that were euthanized between Days 13 and 16 all demonstrated a significant loss of body weight in the days preceding euthanasia, which also correlated with decreased to no food consumption in most of the animals. Body weights otherwise generally increased slowly over the duration of study.

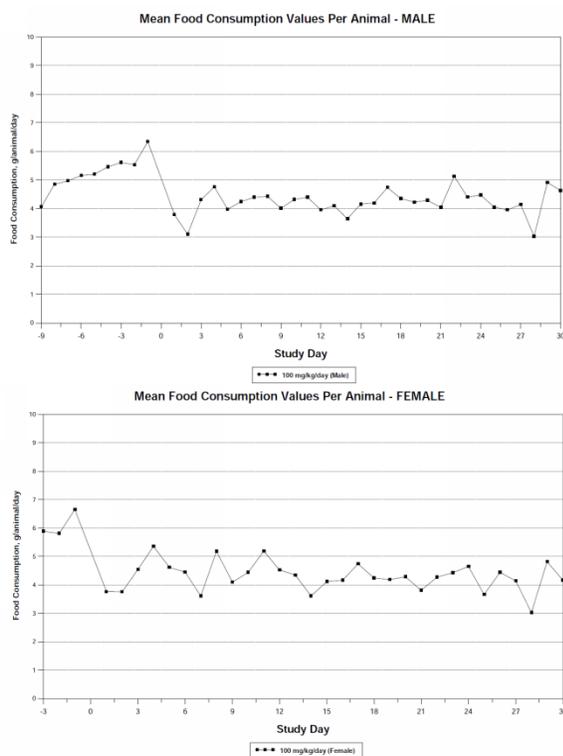


Food Consumption

Food consumption was measured and recorded daily beginning on Day -9 during the study, at the beginning of the dark cycle (± 30 minutes) on each day.

Mean food consumption values showed a slight decrease compared to pretest values upon switching from untreated diet to the diet formulated with test article. The decrease was attributed to an overall decreased palatability of the test diet, however, mean food consumption values remained consistent and within an expected range of variability for the duration of study, demonstrating consistent consumption of the test article in diet. Individual food consumption values for the animals that were euthanized *in extremis* between Days 13 and 16 generally showed a significant decrease in consumption,

relative to both group mean and previous individual values, in the days preceding euthanasia, which correlated with the significant decrease in body weight in these animals as previously discussed. Slight decreases in mean food consumption values were noted on Days 1, 14 and 28, and were affected by the inclusion in the mean of partial-day food consumption values (lower values due to less than 24 hours of diet consumption), as a result of animals that were utilized for terminal PK sample collections occurring prior to 24 hours post the Day 1, 14, and 28 food offering.



Gross Pathology

Only animals euthanized *in extremis* were evaluated. At study termination, the surviving animals were euthanized by inhalation of carbon dioxide. Euthanasia was confirmed by cervical dislocation and the carcasses were discarded.

One female (animal number 363) was observed to have depleted body fat, which correlated with clinical observations of thinness and weight loss in the days preceding euthanasia. No other macroscopic abnormalities were noted in any of the animals submitted for examination due to early termination.

Toxicokinetics

Blood samples (maximum amount obtainable) were collected from four animals/group/time point (where available) via cardiac puncture under carbon dioxide anesthesia for determination of the plasma concentrations of the test article. Samples were collected at 1, 2, 4, 12, 13, 14, 16, and 24 hours post-dose on Days 1 and 14, and

at 1, 2, 4, 12, 13, 14, 16, 24, 40, 56, and 72 hours post-dose on Day 28. Post-dose sample collection intervals were based off the time of initial test article dietary formulation offering/food start on Day 1, and were based off the start of the dark cycle on Days 14 and 28. The animals were not fasted prior to blood collection.

Following daily oral (dietary) administration of buprenorphine HCl, systemic exposure to buprenorphine appeared to be independent of sex; therefore, the values presented in the summary table below are for males and females combined. Buprenorphine $T_{1/2}$ could not be determined on Day 14.

Buprenorphine TK Summary Table							
Day	Target Dose (mg/kg)	Mean Actual Dose (mg/kg)	AUC _{0-24hr} (hr*ng/mL)	AUC _{0-24hr} /Dose (hr*kg*ng/mL/mg)	C _{max} (ng/mL)	C _{max} /Dose (kg*ng/mL/mg)	T _{1/2} (hr)
1	100	68.6	817	11.9	47.5	0.693	11.1
14	100	80.1	1040	12.9	56.8	0.709	NA
28	100	84.0	1050	12.4	61.3	0.729	5.90
NA - Not Applicable							

Dosing Solution Analysis

Documentation of the strength, purity, composition, stability, and other pertinent information for each lot of vehicle component used on study was limited to that information listed on the label of these commercially available products. The Sponsor has provided documentation of the strength, purity, composition, stability, and other pertinent information for the lot of test article used on study. Dosing formulations prepared for the study were evaluated for homogeneity and concentration.

Results of the analysis of dietary dosing formulations indicated that the dietary mixtures were homogenous and prepared at appropriate concentrations, with average calculated concentrations for the lowest and highest concentrations of diet prepared within $\pm 20\%$ of nominal concentration, and precision $\leq 15\%$ relative standard deviation.

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Embryonic Fetal Development**Study title: A 12 to 14-Day Pharmacokinetic Study of Buprenorphine in Gravid and Non-Gravid Sprague-Dawley Rats**

Study no.:	2335-03
Study report location:	Global Submit Review
Conducting laboratory and location:	(b) (4)
Date of study initiation:	January 22, 2015
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Buprenorphine, 13-002717, 98.5% Dextrose, 33-094-JT, 5% Sodium acetate, AM0580646 337, not reported

Key Study Findings

- Male and female gravid and non-gravid Sprague Dawley rats received single daily SC administration of buprenorphine HCl at dose levels of 0.1, 1, & 5 mg/kg/day for 12 consecutive days (GD 6 through GD 17) in gravid females and of 5 mg/kg/day for 14 consecutive days in males and non-gravid females. Blood levels of buprenorphine were the focus of the study with biological indices of dosing such as clinical chemistry and histopathology not being evaluated.
- Buprenorphine was well tolerated. There were no significant or persistent adverse clinical signs or effects on body weights or food consumption noted in any animals over the course of the study.
- Systemic exposure to buprenorphine, as measured by AUC_{0-24h}, was as follows for gravid rats:

Buprenorphine PK Summary Table (Gravid Females)							
Day	Dose (mg/kg)	Dose Ratio	AUC _{0-24hr} (ng*hr/mL)	AUC _{0-24hr} Ratio	C _{max} (ng/mL)	C _{max} Ratio	T _{1/2} (hr)
1	0.1	1	NA	NA	19.8	1	1.47
	1	10	384	1	94.8	4.8	4.93
	5	50	1140	3	229	11.6	9.50
8	0.1	1	77.5	1	24.1	1	2.55
	1	10	367	4.7	70.3	2.9	5.29
	5	50	1420	18.3	197	8.2	11.2
12	0.1	1	66.4	1	24.9	1	2.36
	1	10	351	5.3	63.5	2.6	6.80
	5	50	1290	19.4	171	6.9	30.6
NA – Not Applicable							

- Steady state in gravid females appeared to have been achieved by Day 8.
- Systemic exposure to buprenorphine, as measured by AUC_{0-24h}, was as follows for male and nongravid female rats:

Buprenorphine PK Summary Table (Males and Non-Gravid Females)				
Day	Dose (mg/kg)	AUC _{0-24hr} (ng*hr/mL)	C _{max} (ng/mL)	T _{1/2} (hr)
1	5	1130	245	NA
8	5	1570	241	8.90
14	5	2330	230	39.4
NA – Not Applicable				

Methods

Doses:

Group Number	Dose Level (mg/kg/day)	Dose Volume (mL/kg/day)	Dose Concentration (mg/mL)	Group Assignments		
				Number of Animals		
				Male	Non-Gravid	Gravid
1	0.1	1	0.1	0	0	15
2	1	1	1.0	0	0	15
3	5	2	2.5	0	0	15
4	5	2	2.5	9	9	0

Frequency of dosing: The test article was administered once daily during the study for animals in Groups 1 through 3 for 12 consecutive days (GD 6 through GD 17), and for animals in Group 4 for 14 consecutive days

Dose volume: 0.1-2.5 mL (see table)

Route of administration: subcutaneous

Formulation/Vehicle: 5% dextrose & sodium acetate

Species/Strain: CD® [CrI: CD®(SD)] rats

Number/Sex/Group: 15 gravid females, 9 non-gravid females and males

Satellite groups: none

Study design: Study to determine plasma levels only, no reproduction indices

Deviation from study protocol: Nothing significant

Observations and Results

Mortality

All animals were observed for morbidity, mortality, injury, and the availability of food and water twice daily.

All animals survived to the scheduled study termination.

Clinical Signs

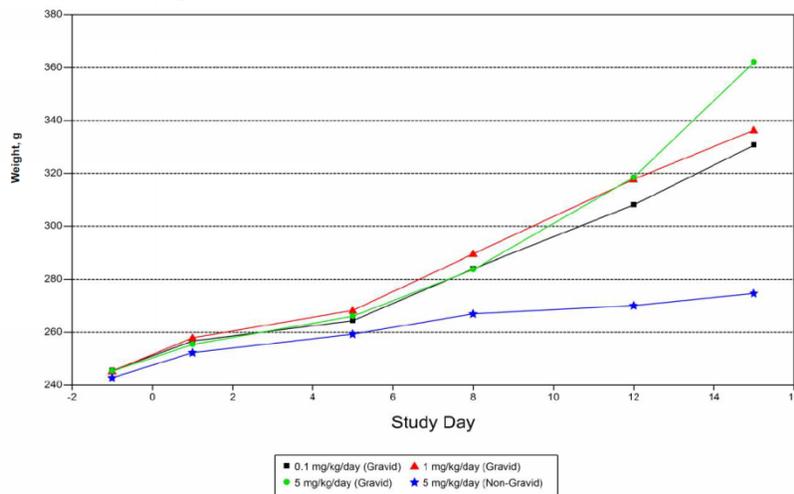
A detailed clinical examination of each animal in Groups 1 through 3 was performed on Days 1 through 15 (GD 6 through GD 20) and was performed on each animal in Group 4 on Days 1 through 17 during the study.

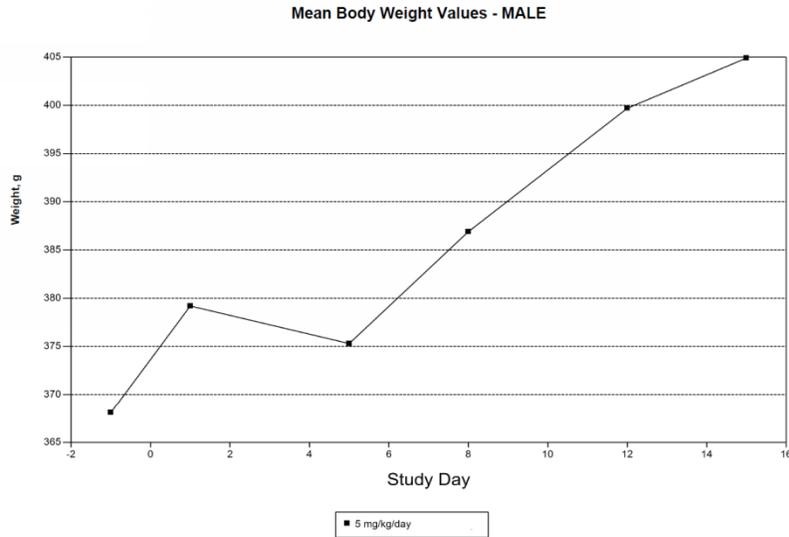
No apparent treatment-related clinical signs.

Body Weight

Body weights for all animals were measured and recorded prior to randomization (within 3 days of arrival) and on Days 1, 5, 8, 12, and 15 during the study.

Body weights showed an appropriate increase in both gravid and non-gravid animals over the course of the study.

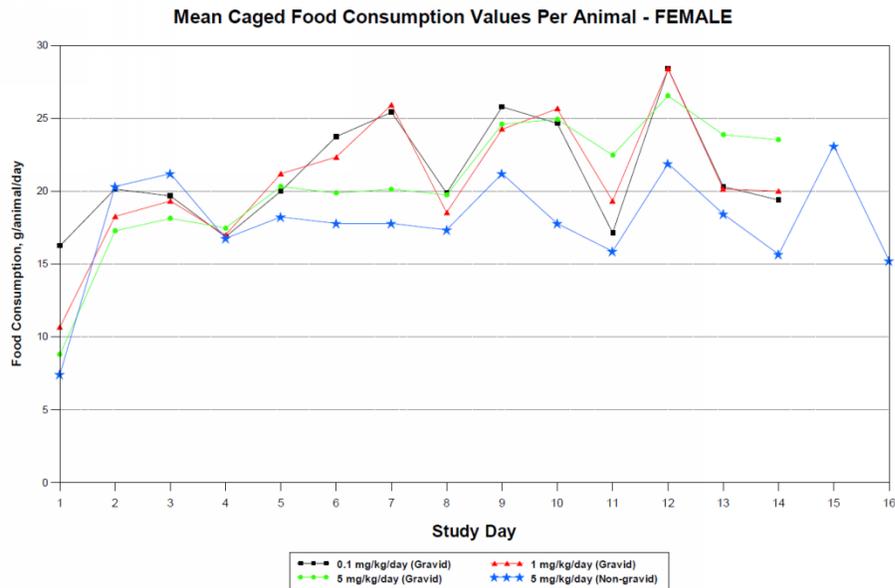


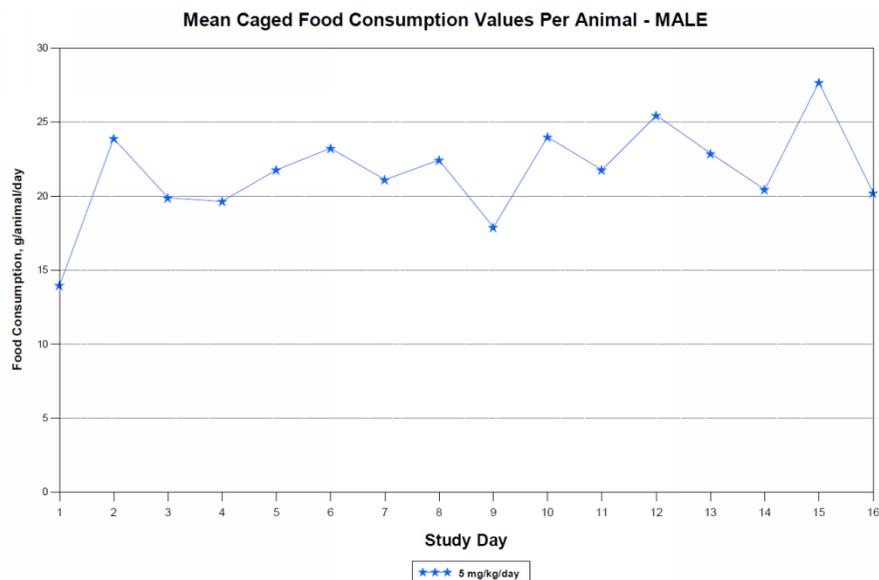


Food Consumption

Food consumption was measured and recorded daily for each animal in Groups 1 through 3 from Days 1 through 14 (GD 6 through 19), and for each animal in Group 4 from Days 1 through 16 during the study.

Mean daily food consumption values for each group showed no adverse effect related to test article administration, and were considered within normal variability in values for animals of this species and age.





Toxicokinetics

Blood samples (approximately 0.4 mL) were collected from five females/group/time point (Groups 1 through 3) or from three animals/sex/group/time point (Group 4) via the sublingual vein for determination of the plasma concentration of the test article.

Samples were collected at 0.5, 1, 2, 4, 12, and 24 hours post-dose on Days 1 and 8 (all groups), at 0.5, 1, 2, 4, 12, 24, 40, 56, and 72 hours post-dose on Days 12 (Groups 1 through 3) and 14 (Group 4). The animals were not fasted prior to blood collection.

In gravid females, systemic exposure (AUC_{0-24h}) and C_{max} values for buprenorphine increased with increasing dose. Systemic exposure to buprenorphine did not appear to change following repeated administration of buprenorphine HCl at 5 mg/kg in males and non-gravid females combined. Steady state in males and non-gravid females may have been achieved by Day 14. Buprenorphine $T_{1/2}$ values generally appeared to be longer with increasing dose and duration of treatment in gravid females.

Buprenorphine PK Summary Table (Gravid Females)							
Day	Dose (mg/kg)	Dose Ratio	AUC_{0-24hr} (ng [*] hr/mL)	AUC_{0-24hr} Ratio	C_{max} (ng/mL)	C_{max} Ratio	$T_{1/2}$ (hr)
1	0.1	1	NA	NA	19.8	1	1.47
	1	10	384	1	94.8	4.8	4.93
	5	50	1140	3	229	11.6	9.50
8	0.1	1	77.5	1	24.1	1	2.55
	1	10	367	4.7	70.3	2.9	5.29
	5	50	1420	18.3	197	8.2	11.2
12	0.1	1	66.4	1	24.9	1	2.36
	1	10	351	5.3	63.5	2.6	6.80
	5	50	1290	19.4	171	6.9	30.6
NA – Not Applicable							

Following daily administration of buprenorphine HCl, systemic exposure to buprenorphine at 5 mg/kg (Group 4 only) appeared to be independent of sex. There were no consistent differences in individual plasma concentration values, AUC, or C_{max} values (generally ≤ 2 -fold) between males and non-gravid females, therefore the values presented in the summary table below are for males and non-gravid females combined.

Buprenorphine PK Summary Table (Males and Non-Gravid Females)				
Day	Dose (mg/kg)	AUC _{0-24hr} (ng*hr/mL)	C_{max} (ng/mL)	T _{1/2} (hr)
1	5	1130	245	NA
8	5	1570	241	8.90
14	5	2330	230	39.4
NA – Not Applicable				

Systemic exposure to buprenorphine at 5 mg/kg appeared to be similar between gravid and non-gravid females, with no consistent differences in individual plasma concentration values, AUC, or C_{max} values.

Dosing Solution Analysis

Documentation of the strength, purity, composition, stability, and other pertinent information for each lot of vehicle component used on study was limited to that information listed on the label of these commercially available products. The Sponsor has provided documentation of the strength, purity, composition, stability, and other pertinent information for the lot of test article used on study. Dosing formulations prepared for the study were evaluated for homogeneity and concentration.

Results of the dosing formulation analysis indicated that the formulations were homogeneous and prepared at the appropriate concentrations.

Necropsy

At study termination, the animals were euthanized by inhalation of CO₂. The pregnancy status of each animal in Groups 1 through 3 was confirmed. Euthanasia was confirmed via exsanguination of the abdominal vena cava, and the carcasses were discarded without further evaluation.

All females in Groups 1 to 3 were confirmed to be pregnant at study termination.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.) and Offspring (Malformations, Variations, etc.) – no data collected

=====

Study title: A 12-Day Pharmacokinetic Study of Buprenorphine in Gravid New Zealand White Rabbits

Study no.: 2335-04
 Study report location: Global Submit Review
 Conducting laboratory and location: (b) (4)
 Date of study initiation: January 8, 2015
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: Buprenorphine, 13-002717, 98.5%
 Dextrose, 33-094-JT, 5%
 Sodium acetate, AM0580646 337, not reported

Key Study Findings

- Pregnant New Zealand White rabbits received single daily SC administration of buprenorphine HCl at a dose of 5 mg/kg/day on Gestation Days (GD) 6-20 and were sampled for buprenorphine blood levels
- Buprenorphine was overall well tolerated, with no significant adverse effects to test article administration noted.
- Mean systemic exposure to buprenorphine, as measured by AUC_{0-24h}:

Day	Dose (mg/kg)	AUC _{0-24hr} (ng*hr/mL)	C _{max} (ng/mL)
1	5	1140	119
8	5	1400	127
12	5	1750	145

Methods

Doses:

Group Assignment				
Group Number	Dose Level (mg/kg/day)	Dose Volume (mL/kg/day)	Dose	
			Concentration (mg/mL)	Number of Females
1	5	2	2.5	6

Frequency of dosing: Once daily on Gestation Days 6-20
 Dose volume: 2 mL/kg
 Route of administration: Subcutaneous
 Formulation/Vehicle: 5% dextrose and sodium acetate
 Species/Strain: New Zealand White Hra:(NZW) rabbits
 Number/Sex/Group: 6
 Satellite groups: none
 Study design: Study to determine plasma levels only, no

reproduction indices
Deviation from study protocol: Nothing significant

Observations and Results

Mortality

All animals were observed for morbidity, mortality, injury, and the availability of food and water twice daily.

All animals survived to study termination and all animals were confirmed to be pregnant at study termination.

Clinical Signs

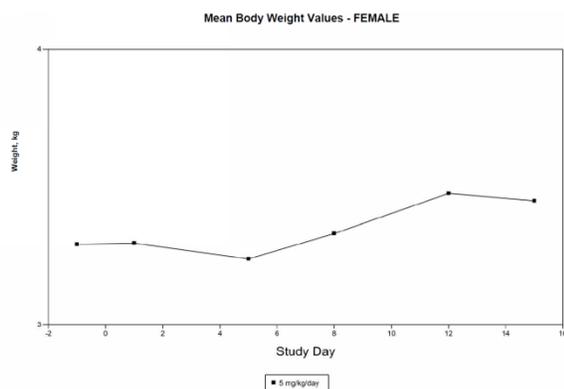
A detailed clinical examination of each animal was performed on Days 1 through 15 (GD 6 through GD 20) during the study.

Clinical findings noted over the course of the study were mainly limited to discoloration and scabbed areas of the skin, observed either at the site of repeat dosing injections or near the blood collection site, and were considered secondary to these procedures.

Body Weight

Body weights for all animals were measured and recorded prior to randomization (within 3 days of arrival) and on Days 1, 5, 8, 12, and 15 during the study.

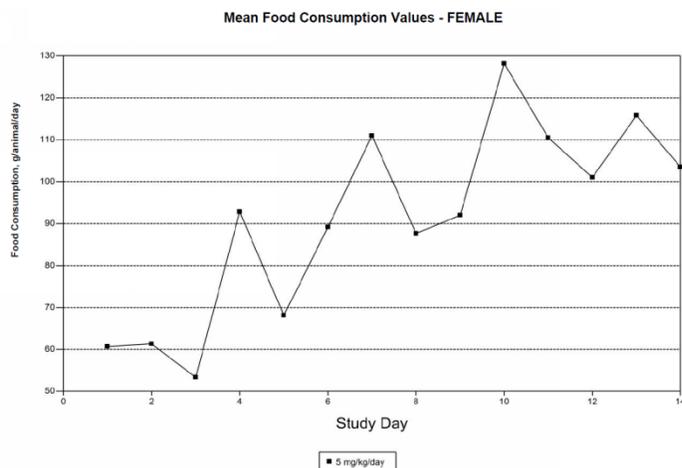
Body weights were considered within a normal range for gravid animals of this age at the initiation of treatment. Body weights were stable over the duration of treatment, showing a slight increase in all animals by Day 15. Several animals (3) exhibited slightly decreased body weights by the Day 5 interval, which corresponded with a decrease in food consumption during this time period.



Food Consumption

Food consumption was measured and recorded daily from Days 1 through 14 (GD 6 through 19) during the study.

Daily food consumption values were decreased in three animals particularly during the first several days of treatment with the test article and were placed on veterinary consultation for this finding. Food consumption values generally increased in these animals as treatment continued and were stabilized by Day 14.



Toxicokinetics

Blood samples (approximately 0.5 mL) were collected from all animals via the jugular vein for determination of the plasma concentrations of the test article. Samples were collected at 0.5, 1, 2, 4, 12, and 24 hours post-dose on Days 1 and 8, and at 0.5, 1, 2, 4, 12, 24, 40, 56, and 72 hours post-dose on Day 12. The animals were not fasted prior to blood collection.

Day	Dose (mg/kg)	AUC _{0-24hr} (ng*hr/mL)	C _{max} (ng/mL)
1	5	1140	119
8	5	1400	127
12	5	1750	145

Dosing Solution Analysis

Documentation of the strength, purity, composition, stability, and other pertinent information for each lot of vehicle component used on study was limited to that information listed on the label of these commercially available products. The Sponsor has provided documentation of the strength, purity, composition, stability, and other pertinent information for the lot of test article used on study. Dosing formulations prepared for the study were evaluated for homogeneity and concentration.

Results of the dosing formulation analysis indicated that the formulations were homogeneous and prepared at the appropriate concentrations.

Necropsy

At study termination, the animals were euthanized by an IV overdose of sodium pentobarbital solution and the pregnancy status of each animal was confirmed. Euthanasia was confirmed via exsanguination of the femoral vessels, and the carcasses were discarded without further evaluation.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.) and Offspring (Malformations, Variations, etc.) – no data collected

6 General Toxicology

No new general toxicology studies were submitted with this NDA resubmission.

7 Genetic Toxicology

No new genetic toxicology studies were submitted with this NDA resubmission.

8 Carcinogenicity

No new carcinogenicity studies were submitted with this NDA resubmission.

9 Reproductive and Developmental Toxicology

No new reproductive and developmental toxicology studies were submitted with this NDA resubmission.

10 Special Toxicology Studies

No new special toxicology studies were submitted with this NDA resubmission.

11 Integrated Summary and Safety Evaluation

Nonclinical Data

Nonclinical AUC_{0-24h} values for buprenorphine in the table below were derived from the tables in the previous nonclinical studies using the last 2 time periods for toxicokinetic sampling, identified to be steady state values. The clinical AUC_{0-24h} value is from the clinical study PRO-810 for 4 Probuphine rods, the maximum recommended human dose (MRHD) for Probuphine. Dose ratios will be used in the label as appropriate (listed previously).

Dose Ratios for Animal to Human Doses Comparing Animal AUC doses in Nonclinical Studies to Human AUC Values at Maximum Recommend Human Dose of 320 mg Buprenorphine HCL contained in 4 Probuphine Rods					
Study	Species	Dose route	Dose (mg/kg)	AUC _{0-24h} ^a (ng * hr/mL)	Dose Ratio ^b nonclinical:clinical (Applicant's value)

28-day feeding	Male and female rat	oral	0.6	43	2 (b) (4) b
			5.5	258	13 (b) (4) b
			56	1940	99 (b) (4) b
	Male and female mouse	oral	100	1045	53 (b) (4) b
Embryo-fetal	Female rat	sc ^d	0.1	72	1 (b) (4) c
	(gravid)		1	359	5 (b) (4) c
			5	1355	18 (b) (4) c
	Female rabbit	sc	5	1575	21 (b) (4) c
	(gravid)				
14-day repeat dose	Male and female rat	sc	5	1995	27 (b) (4) c

a – average of last 2 sampling periods (at steady state)

b – based on steady state human AUC for 4 Probuphine rods from clinical study PRO-810 (AUC_{0-24h} = 19.6 ng*h/mL on Day 28 following implantation)

c – based on (b) (4)

(b) (4)

d – subcutaneous

Pediatric Study Plan

The Applicant requested a full waiver for conducting pediatric clinical studies during the first review cycle and it was granted by the Division. (b) (4)

[Redacted content]

[Redacted content]



12 Appendix/Attachments

N/A

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

/s/

RICHARD D MELLON
02/08/2016



FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Addiction Products
10903 New Hampshire Avenue, Silver Spring, MD 20993

PHARM/TOX MEMO TO FILE

NDA number: 204442
Sponsor: Braeburn Pharmaceuticals
Information to sponsor: Yes (x) No ()
Supporting document number: 23
Submission Type: General Information
Supporting Doc Category/Subcategory: Meeting/Other
Submission Date/Receipt: September 5, 2013/September 5, 2013
Drug Substance/Product: Probuphine® (Buprenorphine HCL/
Ethylene Vinyl Acetate
implant)
Indication: Opioid dependence
Review number: 2 (amended)
Reviewer name: Gary P. Bond, Ph.D.
Division name: Division of Anesthesia, Analgesia
and Addiction Products
Review completion date: October 8, 2013

Recommendation: This review is in response to the applicant's proposed Bridging Toxicokinetic Plan and questions for converting reference NDA label human to nonclinical dose ratios into values that are relevant to blood levels for the proposed drug product Probuphine (buprenorphine HCl). See external comments/recommendations for the full listing of responses.

Probuphine® is a buprenorphine containing sub-dermally implantable formulation. The active pharmacological ingredient, buprenorphine hydrochloride (buprenorphine), is a partial opioid agonist administered in a solid matrix of ethylene vinyl acetate polymer (EVA). Probuphine is intended to provide sustained delivery of buprenorphine for up to 6 months for the maintenance treatment of opioid dependence using an abuse and diversion deterrent formulation.

Background/Prior Regulatory History

- I. The Division issued a complete response letter (CRL of April 30, 2013) to the applicant's NDA submission. The following nonclinical comment was included regarding making product label animal to human exposure ratios, based on the reference NDA label (Subutex/Suboxone), relevant to human exposure to buprenorphine in Probuphine. The Division's comment was as follows:

We do not believe the mg/m² body surface area-derived safety margins modified from the referenced sublingual label as described in the Pregnancy, (b) (4) and Fertility sections are appropriate. In order to support nonclinical labeling of Probuphine doses which produce exposures within or in excess of the exposure levels of the listed drug during any portion of the implants usage you will need to provide persuasive exposure-based scientific justification for safety margins described in nonclinical sections which may require bridging toxicokinetic studies. Otherwise, you will need to conduct reproductive toxicology studies necessary to support sections 8.1 Pregnancy and carcinogenicity studies described in 13.1 Carcinogenicity, Mutagenesis, and Impairment of Fertility.

II. To this CRL comment, the applicant proposed a bridging toxicokinetic plan response on September 5, 2013 as follows:

Reference Listed Drug - The nonclinical safety assessment of Probuphine described in the NDA regarding developmental toxicity and carcinogenicity relies on the findings of safety as described in the Suboxone Label and Subutex Label. The following proposals are provided to support bridging to the reference labels.

- relevant label sections from referenced NDA included in the Appendix by the Division's nonclinical reviewer

Developmental Toxicity - In clinical use, Probuphine is administered as a subdermal implant. Therefore, the subcutaneous (SC) route of administration is the most relevant route of administration to establish a toxicokinetic (exposure) bridge to human exposures. Subcutaneous developmental toxicity studies are reported in the Subutex label for both rat and rabbit along with results of studies using other routes of administration. Buprenorphine was not teratogenic in rats or rabbits after SC, intramuscular (IM), intravenous (IV) or oral dosing. However, significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration (1 mg/kg and up).

Given the intended clinical route of administration and that effects observed in rats following SC dosing occurred at doses equal to or less than effects observed using other routes of administration, Braeburn proposes to conduct bridging toxicokinetic studies in rats and rabbits using the SC route of administration to address the Agency's CRL comment regarding the developmental and reproductive toxicity (DART) studies described in the product label.

The SC toxicokinetic bridging studies will be conducted in gravid rats and rabbits by the subcutaneous route, with a minimum treatment duration approximating the duration normally used in DART studies (ICH S5(R2)):

- Rabbit - Gestation days 6-18
- Rat - Gestation days 6-15

To ensure that sufficient and steady state exposure is achieved in the animals, the duration of dosing of these bridging studies will be 14 days.

The subcutaneous buprenorphine dose levels reported in the Suboxone label and Summary Basis for Approval are 0.1, 1 and 5 mg/kg/day in rats and 5 mg/kg in rabbits. These dose levels will be used in the rat and rabbit bridging studies, respectively. Samples for toxicokinetic analysis will be taken on Days 1 and 14 at multiple time points from 0.5 to 24 hr post-dose (reviewer emphasis). The following parameters will be evaluated: AUC_{0-24hr}, C_{max}, T_{max}, and t_{1/2}. Sufficient numbers of animals will be included at each dose level to ensure sufficient pregnant animals are available for bioanalysis due to the known tendency of rabbits (primarily) and rats to spontaneously abort during pregnancy.

Once the toxicokinetic data are generated, Braeburn intends to calculate animal: human exposure margins based on the calculated AUC data from the nonclinical studies and the maximum anticipated clinical AUC through use of Probuphine. These exposure margins will then be incorporated into the appropriate sections of the Probuphine package insert.

Carcinogenicity - Braeburn proposes

(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

Based on this proposal, Braeburn requests the Agency's comments to the following questions:

1. Does the Agency concur with Braeburn's proposal to provide toxicokinetic data derived from SC administration of buprenorphine for 14 days in gravid rats and rabbits to support animal to human exposure margin calculations in the Pregnancy section of the Probuphine product label?

2. Does the Agency concur with Braeburn's proposal (b) (4) ?
3. Since toxicity was observed in the DART study with rats following SC administration, (the clinically relevant route of administration), the inclusion of data for other routes of administration (IV, IM, PO) does not further inform the prescribing physician to the potential risks of Probuphine for reproductive and developmental toxicity. Braeburn therefore proposes to remove from the label the description of these other routes of administration (IV, IM, PO). Does the FDA agree?

Nonclinical Response to Applicant's Proposed Bridging Toxicokinetic Plan

Introduction – The overall goal for generating the nonclinical toxicokinetic bridging data is to be able to compare human blood levels of buprenorphine from Probuphine exposure to buprenorphine blood levels in animals for the given nonclinical toxicity study (e.g., teratogenicity, carcinogenicity, etc.). This is not a labeling review as that will come after generation of this nonclinical data and deal more specifically on the buprenorphine exposure time course that is unique to the Probuphine implant compared to oral and SC dosing with buprenorphine.

Developmental Toxicity – Use of the SC dose route for rats and rabbits is considered acceptable as the SC routes appear to adequately assess the potential for teratogenic and non-teratogenic effects as listed on the referenced NDA label. Some comments on the proposed testing follow.

As noted by the applicant, the subcutaneous buprenorphine dose levels reported in the Suboxone label and Summary Basis for Approval are 0.1, 1 and 5 mg/kg/day in rats and 5 mg/kg in rabbits. These dose levels will be used in the rat and rabbit bridging studies, respectively. Samples for toxicokinetic analysis will be taken on Days 1 and 14 at multiple time points from 0.5 to 24 hr post-dose. Comments:

1. The proposed dose levels are acceptable.
2. It is assumed that the applicant means that the toxicokinetic samples will be taken on the first day of dosing (day 6 of gestation) and then 14 days later (day 20 of gestation).
3. In order to account for potentially extended nonclinical elimination half-lives, extended time points should be considered for sample collection, most notably after the last dose.

Carcinogenicity – No toxicokinetic bridging study is proposed by the applicant, but this is contrary to the goal of this bridging study as noted previously.

1. The listed doses in the reference NDA label are acceptable (dietary doses of 0.6, 5.5, and 56 mg/kg/day in rats and 100 mg/kg/day in mice).

2. The duration of daily dosing and toxicokinetic sampling should be of appropriate duration so as to adequately define steady state for daily dosing with a long enough sampling time, most notably after the last dose unless justified otherwise.

Impairment of Fertility – No toxicokinetic bridging study is proposed by the applicant, but this is contrary to the goal of this bridging study as noted previously.

- 1) The listed dose in the reference NDA label is acceptable (SC dose of 5 mg/kg/day in rats).
- 2) The duration of daily dosing and toxicokinetic sampling should be of appropriate duration so as to adequately define steady state for daily dosing with a long enough sampling time, most notably after the last dose unless justified otherwise. Use of non-mated males and females is recommended

Internal Comments/Recommendations – none

External Comments/Recommendations

We have received your submission of September 5, 2013 for NDA 204442 (Probuphine) regarding your “Proposed Bridging Toxicokinetic Plan” and have the following comments and responses to your questions.

1. Does the Agency concur with Braeburn’s proposal to provide toxicokinetic data derived from SC administration of buprenorphine for 14 days in gravid rats and rabbits to support animal to human exposure margin calculations in the Pregnancy section of the Probuphine product label?

FDA response - Yes.

*For **Developmental Toxicity**, SC doses of 0.1, 1, & 5 mg/kg/day in rats and 5 mg/kg/day in rabbits as you propose and as listed in the reference NDA label are acceptable. It is assumed you mean that the toxicokinetic samples will be taken on the first day of dosing (day 6 of gestation) and then 14 days later (day 20 of gestation). If so, this is acceptable. In order to account for potentially extended elimination half-lives of buprenorphine, additional time points should be considered for sampling, particularly after the last dose.*

2. Does the Agency concur with Braeburn’s proposal [redacted] (b) (4) [redacted] ?

FDA response - No.

*For **Carcinogenicity**, we do not believe [redacted] (b) (4) [redacted] [redacted] In order to provide a more meaningful description of labeled studies, conduct bridging studies targeting*

dietary doses of 0.6, 5.5, and 56 mg/kg/day in rats and 100 mg/kg/day in mice as listed in the reference NDA label. The duration of daily dosing and toxicokinetic sampling should be appropriate so as to adequately define steady state for daily dosing with a long enough sampling time, most notably after the last dose.

*For **Impairment of Fertility**, you will need to provide bridging TK data for the SC dose of 5 mg/kg/day in rats as described in the reference NDA label. The duration of daily dosing and toxicokinetic sampling should be appropriate so as to adequately define steady state with a long enough sampling time, most notably after the last dose.*

3. Since toxicity was observed in the DART study with rats following SC administration, (the clinically relevant route of administration), the inclusion of data for other routes of administration (IV, IM, PO) does not further inform the prescribing physician to the potential risks of Probuphine for reproductive and developmental toxicity. Braeburn therefore proposes to remove from the label the description of these other routes of administration (IV, IM, PO). Does the FDA agree?

FDA response

If the exposure data obtained in the SC bridging TK study would provide for a safety margin for human exposure to be expressed in the label, the inclusion of nonclinical findings from the other exposure routes is unnecessary. However, if the SC dosing data indicates that exposure does not adequately cover human exposure then study findings utilizing non-SC routes may be of greater relevance and must be included and addressed in the label.

=====

Appendix: relevant parts of sections 8.1 and 13.1 of referenced Subutex label

(NDA (b) (4))

8.1 Pregnancy

Teratogenic Effects:

Buprenorphine was not teratogenic in rats or rabbits after IM or subcutaneous (SC) doses up to 5 mg/kg/day (estimated exposure was approximately 3 and 6 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) and 25 mg/kg/day in rabbits (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats

after SC administration of 1 mg/kg/day and up (estimated exposure was approximately 0.6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), but were not observed at oral doses up to 160 mg/kg/day. Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (estimated exposure was approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the recommended human daily sublingual dose of 16 mg on a mg/m² basis) were not statistically significant.

In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure was approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

Non-teratogenic Effects:

Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine 5 mg/kg/day (approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Fertility, peri- and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), and after SC doses of 0.1 mg/kg/day and up (approximately 0.06 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity:

Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day (estimated exposure was approximately 0.4, 3 and 35 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) for 27 months. As in the buprenorphine/naloxone carcinogenicity study in rat, statistically significant dose-related increases in Leydig cell tumors occurred. In an 86-week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

Impairment of Fertility:

Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily oral doses up to 80 mg/kg/day (estimated exposure was approximately 50 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) or up to 5 mg/kg/day IM or SC (estimated exposure was approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).

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/s/

GARY P BOND
10/08/2013

ADAM M WASSERMAN
10/09/2013



FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Addiction Products
10903 New Hampshire Avenue, Silver Spring, MD 20993

PHARM/TOX MEMO TO FILE

NDA number: 204442
Sponsor: Braeburn Pharmaceuticals
Information to sponsor: Yes (x) No ()
Supporting document number: 23
Submission Type: General Information
Supporting Doc Category/Subcategory: Meeting/Other
Submission Date/Receipt: September 5, 2013/September 5, 2013
Drug Substance/Product: Probuphine® (Buprenorphine HCL/
Ethylene Vinyl Acetate
implant)
Indication: Opioid dependence
Review number: 2
Reviewer name: Gary P. Bond, Ph.D.
Division name: Division of Anesthesia, Analgesia
and Addiction Products
Review completion date: September 25, 2013

Recommendation: This review is in response to the applicant's proposed Bridging Toxicokinetic Plan for converting reference NDA label human to nonclinical dose ratios into values that are relevant to blood levels for the proposed drug product Probuphine (buprenorphine HCl). See external comments for the full listing of recommendations.

Probuphine® is a buprenorphine containing sub-dermally implantable formulation. The active pharmacological ingredient, buprenorphine hydrochloride (buprenorphine), is a partial opioid agonist administered in a solid matrix of ethylene vinyl acetate polymer (EVA). Probuphine is intended to provide sustained delivery of buprenorphine for up to 6 months for the maintenance treatment of opioid dependence using an abuse and diversion deterrent formulation.

Background/Prior Regulatory History

- I. The Division issued a complete response letter (CRL of April 30, 2013) to the applicant's NDA submission. The following nonclinical comment was included regarding making product label animal to human exposure ratios, based on the reference NDA label (Subutex/Suboxone), relevant to human exposure to buprenorphine in Probuphine. The Division's comment was as follows:

We do not believe the mg/m² body surface area-derived safety margins modified from the referenced sublingual label as described in the Pregnancy, (b) (4) and Fertility sections are appropriate. In order to support nonclinical labeling of Probuphine doses which produce exposures within or in excess of the exposure levels of the listed drug during any portion of the implants usage you will need to provide persuasive exposure-based scientific justification for safety margins described in nonclinical sections which may require bridging toxicokinetic studies. Otherwise, you will need to conduct reproductive toxicology studies necessary to support sections 8.1 Pregnancy and carcinogenicity studies described in 13.1 Carcinogenicity, Mutagenesis, and Impairment of Fertility.

II. To this CRL comment, the applicant proposed a bridging toxicokinetic plan response on September 5, 2013 as follows:

Reference Listed Drug - The nonclinical safety assessment of Probuphine described in the NDA regarding developmental toxicity and carcinogenicity relies on the findings of safety as described in the Suboxone Label and Subutex Label. The following proposals are provided to support bridging to the reference labels.

- relevant label sections from referenced NDA included in the Appendix by the Division's nonclinical reviewer

Developmental Toxicity - In clinical use, Probuphine is administered as a subdermal implant. Therefore, the subcutaneous (SC) route of administration is the most relevant route of administration to establish a toxicokinetic (exposure) bridge to human exposures. Subcutaneous developmental toxicity studies are reported in the Subutex label for both rat and rabbit along with results of studies using other routes of administration. Buprenorphine was not teratogenic in rats or rabbits after SC, intramuscular (IM), intravenous (IV) or oral dosing. However, significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration (1 mg/kg and up).

Given the intended clinical route of administration and that effects observed in rats following SC dosing occurred at doses equal to or less than effects observed using other routes of administration, Braeburn proposes to conduct bridging toxicokinetic studies in rats and rabbits using the SC route of administration to address the Agency's CRL comment regarding the developmental and reproductive toxicity (DART) studies described in the product label.

The SC toxicokinetic bridging studies will be conducted in gravid rats and rabbits by the subcutaneous route, with a minimum treatment duration approximating the duration normally used in DART studies (ICH S5(R2)):

- Rabbit - Gestation days 6-18
- Rat - Gestation days 6-15

To ensure that sufficient and steady state exposure is achieved in the animals, the duration of dosing of these bridging studies will be 14 days.

The subcutaneous buprenorphine dose levels reported in the Suboxone label and Summary Basis for Approval are 0.1, 1 and 5 mg/kg/day in rats and 5 mg/kg in rabbits. These dose levels will be used in the rat and rabbit bridging studies, respectively. Samples for toxicokinetic analysis will be taken on Days 1 and 14 at multiple time points from 0.5 to 24 hr post-dose (reviewer emphasis). The following parameters will be evaluated: AUC_{0-24hr}, C_{max}, T_{max}, and t_{1/2}. Sufficient numbers of animals will be included at each dose level to ensure sufficient pregnant animals are available for bioanalysis due to the known tendency of rabbits (primarily) and rats to spontaneously abort during pregnancy.

Once the toxicokinetic data are generated, Braeburn intends to calculate animal: human exposure margins based on the calculated AUC data from the nonclinical studies and the maximum anticipated clinical AUC through use of Probuphine. These exposure margins will then be incorporated into the appropriate sections of the Probuphine package insert.

Carcinogenicity - Braeburn proposes

(b) (4)

[Redacted]

(b) (4)

[Redacted]

Nonclinical Response to Applicant's Proposed Bridging Toxicokinetic Plan

Introduction – The overall goal for generating the nonclinical toxicokinetic bridging data is to be able to compare human blood levels of buprenorphine from Probuphine exposure to buprenorphine blood levels in animals for the given nonclinical toxicity study (e.g., teratogenicity, carcinogenicity, etc.). This is not a labeling review as that will come after generation of this nonclinical data and deal more specifically on the buprenorphine

exposure time course that is unique to the Probuphine implant compared to oral and SC dosing with buprenorphine.

Developmental Toxicity – Use of the SC dose route for rats and rabbits is considered acceptable as the SC routes appear to adequately assess the potential for teratogenic and non-teratogenic effects as listed on the referenced NDA label. Some comments on the proposed testing follow.

As noted by the applicant, the subcutaneous buprenorphine dose levels reported in the Suboxone label and Summary Basis for Approval are 0.1, 1 and 5 mg/kg/day in rats and 5 mg/kg in rabbits. These dose levels will be used in the rat and rabbit bridging studies, respectively. Samples for toxicokinetic analysis will be taken on Days 1 and 14 at multiple time points from 0.5 to 24 hr post-dose. Comments:

1. The proposed dose levels are acceptable.
2. It is assumed that the applicant means that the toxicokinetic samples will be taken on the first day of dosing (day 6 of gestation) and then 14 days later (day 20 of gestation).
3. In order to account for potentially extended nonclinical elimination half-lives, extended time points should be considered for sample collection, most notably after the last dose.

Carcinogenicity – No toxicokinetic bridging study is proposed by the applicant, but this is contrary to the goal of this bridging study as noted previously.

1. The listed doses in the reference NDA label are acceptable (dietary doses of 0.6, 5.5, and 56 mg/kg/day in rats and 100 mg/kg/day in mice).
2. The duration of daily dosing and toxicokinetic sampling should be of appropriate duration so as to adequately define steady state for daily dosing with a long enough sampling time, most notably after the last dose unless justified otherwise.

Impairment of Fertility – No toxicokinetic bridging study is proposed by the applicant, but this is contrary to the goal of this bridging study as noted previously.

- 1) The listed dose in the reference NDA label is acceptable (SC dose of 5 mg/kg/day in rats).
- 2) The duration of daily dosing and toxicokinetic sampling should be of appropriate duration so as to adequately define steady state for daily dosing with a long enough sampling time, most notably after the last dose unless justified otherwise. Use of non-mated males and females is recommended

Internal Comments/Recommendations - none

External Comments/Recommendations

We have received your submission of September 5, 2013 for NDA 204442 (Probuphine) regarding your “Proposed Bridging Toxicokinetic Plan” and have the following comments:

- 1) We consider it necessary for you to conduct toxicokinetic bridging studies for Developmental Toxicity (subcutaneous - SC), Carcinogenicity (dietary), and Impairment of Fertility (SC).
- 2) Developmental Toxicity
 - a. SC doses of 0.1, 1, & 5 mg/kg/day in rats and 5 mg/kg/day in rabbits as listed in the reference NDA label are acceptable.
 - b. It is assumed you mean that the toxicokinetic samples will be taken on the first day of dosing (day 6 of gestation) and then 14 days later (day 20 of gestation). If so, this is acceptable.
 - c. In order to account for potentially extended elimination half-lives of buprenorphine, extended time points should be considered for sampling, particularly after the last dose.
- 3) Carcinogenicity
 - a. Dietary doses of 0.6, 5.5, and 56 mg/kg/day in rats and 100 mg/kg/day in mice as listed in the reference NDA label are acceptable.
 - b. The duration of daily dosing and toxicokinetic sampling should be appropriate so as to adequately define steady state for daily dosing with a long enough sampling time, most notably after the last dose.
- 4) Impairment of Fertility
 - a. A SC dose of 5 mg/kg/day in rats as listed in the reference NDA label is acceptable.
 - b. The duration of daily dosing and toxicokinetic sampling should be appropriate so as to adequately define steady state with a long enough sampling time, most notably after the last dose.
 - c. Non-mated males and females should be used in this bridging study.

=====

Appendix: relevant parts of sections 8.1 and 13.1 of referenced Subutex label
(NDA (b) (4))

8.1 Pregnancy

Teratogenic Effects:

Buprenorphine was not teratogenic in rats or rabbits after IM or subcutaneous (SC) doses up to 5 mg/kg/day (estimated exposure was approximately 3 and 6 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95

times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) and 25 mg/kg/day in rabbits (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (estimated exposure was approximately 0.6 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis), but were not observed at oral doses up to 160 mg/kg/day. Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (estimated exposure was approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) were not statistically significant.

In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure was approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).

Non-teratogenic Effects:

Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine 5 mg/kg/day (approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis). Fertility, peri- and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis), and after SC doses of 0.1 mg/kg/day and up (approximately 0.06 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis). Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity:

Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day (estimated exposure was approximately 0.4, 3 and 35 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) for 27 months. As in the buprenorphine/naloxone carcinogenicity study in rat, statistically significant dose-related increases in Leydig cell tumors occurred. In an 86-week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated

exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).

Impairment of Fertility:

Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily oral doses up to 80 mg/kg/day (estimated exposure was approximately 50 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) or up to 5 mg/kg/day IM or SC (estimated exposure was approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).

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/s/

GARY P BOND
09/25/2013

ADAM M WASSERMAN
09/25/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

**Supervisory Pharmacologist Memorandum
Addendum #2**

NDA NUMBER: **204442**
PRODUCT:
(Proposed) Trade Name: Probuphine® Implant
Established Name: Buprenorphine HCl
SPONSOR: **Titan Pharmaceuticals, Inc.**
REVIEW DIVISION: **Division of Anesthesia, Analgesia and
Addiction Products**
PHARM/TOX SUPERVISOR: **Adam Wasserman, Ph.D.**
DIVISION DIRECTOR: **Bob Rappaport, M.D.**
PROJECT MANAGER: **Lisa Basham, M.S.**
MEMO DATE: **4/29/2013**

This addendum is in reference to a submission received on April 25, 2013 from the Applicant notifying the Division of a GLP report amendment for a Bacterial Reverse Mutation Study of Extracts of the Buprenorphine Drug Delivery System (BDDS; equivalent to Probuphine). The original report (PRO-NTR-0107) contained a mutagenicity assessment of saline or ethanol extracts of the BDDS product. The report contained a significant error which indicated the assessment under the ethanol condition was not valid. This was not identified by the Study Director, Sponsor, nor the primary reviewer or me but it is apparent on closer inspection of the data contained in study report. Briefly, according to the amendment the ethanol extract was dosed undiluted which caused unacceptable toxicity to the bacterial tester strain. Therefore, although there was no increase in revertants indicating mutagenicity the level of revertants was significantly below the negative controls due to the underlying toxicity to the bacteria. Therefore no conclusion as to the lack of mutagenicity potential can be made.

Importantly, the saline condition, which is much more physiologically relevant, was conducted appropriately and demonstrated a negative result. The weight of evidence which includes genotoxicity studies in other in vitro and in vivo studies with the BDDS or placebo implant supports the absence of mutagenic potential. Therefore the lack of an acceptable ethanol extract evaluation is not an

approvability issue and no repeat of this condition is necessary to support approval of the product.

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ADAM M WASSERMAN
04/29/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Supervisory Pharmacologist Memorandum

NDA NUMBER: 204442
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 10/31/2012
PRODUCT:
 (Proposed) Trade Name: Probuphine® Implant
 Established Name: Buprenorphine HCl

INDICATION: Maintenance treatment of opioid dependence
SPONSOR: Titan Pharmaceuticals Inc.
REVIEW DIVISION: Division of Anesthesia, Analgesia and
Addiction Products (HFD-170)

PHARM/TOX REVIEWER: Gary Bond, Ph.D.
PHARM/TOX SUPERVISOR: Adam Wasserman, Ph.D.
DIVISION DIRECTOR: Bob Rappaport, M.D.
PROJECT MANAGER: Lisa Basham, M.S.

EXECUTIVE SUMMARY

I. BACKGROUND

Probuphine is a buprenorphine-containing drug product developed by Titan Pharmaceuticals as a set of implantable rods which is placed subdermally in the upper arm of opioid-dependent individuals for the maintenance treatment of opioid addiction. The drug product, comprised of (b) (4) buprenorphine (80 mg) and (b) (4) ethylene vinyl acetate (EVA), allows for a prolonged release of the active pharmaceutical ingredient buprenorphine over a 6-month period. Buprenorphine, a Schedule III narcotic pharmacologically characterized as a partial mu-opioid receptor agonist, was initially approved in 1981 in injectable form for relief of moderate to severe pain and was subsequently approved in 2002 as a sublingual treatment for opioid dependence as Subutex (NDA 20-732) and Suboxone (NDA 20-733), the latter product containing naloxone as a 4:1 ratio. The prolonged release profile of Probuphine is intended to provide a more constant state of opioid receptor activation as compared to approved sublingual buprenorphine which has a higher peak-trough plasma concentration with daily dosing. The Applicant proposes the continuous release of buprenorphine may therefore reduce withdrawal symptoms encountered with daily sublingual buprenorphine and the subdermal location of the implant will necessarily improve compliance as well as reduce the potential for therapeutic diversion. The Applicant references the Agency's prior finding of Safety and Efficacy of Subutex and Suboxone and submits the present NDA through the 505(b)(2) pathway.

EVA is a polymeric non-biodegradable material integral to the composition to the Probuphine implant rod, and is used in several other FDA approved products such as Implanon (NDA-21-529), a contraceptive implant similar to the Probuphine product which is left in place for 3 years, and NuvaRing (NDA 21-187) a vaginal insert contraceptive which is used for 3 weeks out of every 4 for extended durations.

The present application envisions the insertion of 4 Probuphine rods initially to which a 5th rod may be added if symptomatic improvement is not sufficient. The Probuphine kit will also contain a trochanter dedicated for insertion of the Probuphine rods. This device is under review by the Center for Devices and Radiological Health.

A. Regulatory Summary (Pharmacology/Toxicology)

Several meetings were held with the Applicant during development of the drug product under IND 70,852. The general adequacy of the nonclinical program, including use of EVA as the polymeric material as evaluated in nonclinical studies was considered and the Applicant informed this was acceptable in a meeting held on February 15, 2005. A Pre-NDA meeting was held on October 25, 2011 in which the prior interpretation was reaffirmed. However, the Applicant was informed in pre-meeting advice that nonclinical data described in the approved and referenced NDA labels of Subutex and Suboxone will support

marketing “pending submission of appropriate pharmacokinetic bridging data”. Subsequent discussion at the meeting suggested that this would be “ideal” due to the difficulties in adapting the studies described to the proposed label but that if a mg/m² approach was used – or even if toxicokinetic bridging data was available – the Applicant would need to provide sufficient justification since the referenced product described studies which utilized different routes of administration. Also discussed was the need to provide data supporting the safety of ethylene vinyl acetate compound, particularly the evaluation of the safety of extractables and leachables from this formulation.

B. Nonclinical Evaluation

Among the nonclinical studies submitted to support approval, the Applicant submitted chronic studies of a Probuphine development product (BDDS), implanted for up to 12 months (pilot) and 10 months (GLP-compliant) in dogs as well as evaluations of local tolerance with subcutaneous implantation of BDDS in rabbits up to 26 weeks duration and sensitization and intracutaneous reactivity studies in guinea pigs and rabbits. Studies were in some cases designed to satisfy the International Standardization Organization (ISO) 10993 *Biological Evaluation of Medical Devices* testing guidelines and in most cases used negative (USP polyethylene or EVA-only implanted controls) for comparison. The Applicant additionally submitted a number of genotoxicity studies, an acute systemic toxicity test in mice, and an evaluation of pyrogenicity and intracutaneous local toxicity of BDDS extracts in rabbits order to define the potential toxicities of extractable/leachable compounds from the implant.

Review of nonclinical support was conducted by Gary Bond, Ph.D. Dr. Bond believes the information provided support the approval of the application. I concur with his evaluation. Only local toxicity associated with the BDDS implant was identified and this was slightly more pronounced than observed with the negative/EVA placebo implant. In the major NDA-supportive 10-month toxicity study in the dog, both BDDS and placebo implants demonstrated evidence of “moderate irritation” at the one month interim time-point which on microscopic examination was further described as an inflammatory response characterized principally by increased infiltrating lymphocytes, macrophages, occasional giant cells and fibrosis. The inflammatory response was reduced in severity, scoring as “slight irritation”, when evaluated at 6 weeks and 10 months post-implant placement. There were no other notable toxicologic findings with the BDDS implant, EVA implant, or extracts in the remainder of the nonclinical package. As noted by Dr. Bond, the systemic level of buprenorphine produced by the intended usage of Probuphine rods is well within that of approved sublingual buprenorphine; therefore, the systemic safety of buprenorphine as released by the drug product is not at issue.

There were no product quality issues identified by Dr. Bond which remain unaddressed. Specifications are acceptable by ICH standards for drug substance and product, vinyl acetate monomer is being controlled in a separate

specification for the ethylene vinyl acetate copolymer excipient and, based on data provided by the Applicant, monomer levels released are expected to be below the level of toxicologic concern, particularly if release is spread over time. Other identified extractable compounds from the EVA have specifications set to fall below the levels of toxicologic concern.

II. MAJOR NONCLINICAL ISSUES IDENTIFIED IN PRIMARY REVIEW

1) *DSI audit/Adequacy of the 10-month dog study*

An initial evaluation of the pivotal 10-month dog study (01T-06823-00 “Chronic Toxicity Study of Buprenorphine Delivery System Implanted Subcutaneously for 10 Months in Dog” by the nonclinical reviewer Dr. Suzanne Thornton-Jones raised significant concerns broadly related to a manifestly deficient study report, missing data and examinations, apparent deviations from protocols, and uncertain product characteristics. This led to a request for GLP inspection [REDACTED] ^{(b) (4)} of the conducting laboratory (North American Science Associates; NAMSA) which was undertaken by Hugh McClure III as part of a broader routine surveillance inspection as documented by Michael Skelly, Ph.D. in his memo dated 8/9/2005. A *Form 483* was issued upon conclusion of the inspection. Multiple observations were noted which ultimately led to a recommendation from DSI to the Division to reject the study. These issues included poor/inadequate documentation, apparently conflicting description of test article identity/lots used, inadequate calibration of laboratory equipment, reserve samples not being retained, and significant deviations from protocol which indicated the Study Director was not a single point of control as required under GLP. In addition to the rejection of the study, DSI proposed a Warning Letter which was sent to the Sponsor and the classification by CDER-DSI was “Official Action Indicated”. The Sponsor provided a response to Form 483 findings May 18, 2005 and from NAMSA to the Warning Letter on June 2, 2006. These were not evaluated at the time by DSI but were when requested by the Division as part of the NDA review. Please see the memorandum dated January 31, 2013 by Zhou Chen MD, Ph.D. for details. Briefly, the details submitted by the Sponsor and conducting laboratory, while not addressing all aspects of the 483 observations and Warning Letter items – in particular the lack of single point control of the study director – was sufficient to ensure the basic integrity of the data provided under the Amended Reports submitted. The recommendation of Dr. Chen, supported by OSI management, was for acceptance of the study and use in review of the NDA.

2) *Labeling issues*

The Applicant was previously made aware of Division concerns related to the appropriate inclusion and use of nonclinical data as provided from the referenced sublingual buprenorphine label which were themselves adapted from the injectable Buprenex label. The approved buprenorphine label includes descriptions of multiple studies for teratogenicity using various routes

of administration including IM, SC, IV and oral in rat and rabbit. Carcinogenicity studies conducted in rats and mice utilize daily dietary administration. No nonclinical exposure data was available. Therefore, the doses and findings in the referenced labels are all put into clinical perspective using a body surface area comparison based on daily sublingual dose (mg/m^2). There are no apparent adjustments made for relative bioavailability through these routes. The use of body surface area comparisons is not an ideal means to convey risk in the label even with simple same route animal-human comparisons but becomes increasingly problematic when comparing different routes. For Probuphine, an additional layer of complexity is added by the controlled release properties of buprenorphine from the drug product which is also reflected by the exposure curves. The Applicant proposed to adjust the margins described in the label using mg/m^2 (b) (4)

(b) (4)

(see Clinical Pharmacology review of Dr. David Lee, in particular Figure 2 and Table 3). For the purposes of extrapolating safety margins for carcinogenicity data the C_{avg} may be most appropriate while for reproductive toxicity findings a more conservative use of C_{max} may be most appropriate.

Overall, I do not have confidence that safety margins based on a mg/m^2 body surface area comparison (b) (4)

(b) (4) provides a meaningful risk assessment. I believe to be useful bridging TK data must be obtained to allow the nonclinical studies cited in the labels to be related to clinical exposures with Probuphine. This issue does not constitute a deficiency which would result in a recommendation for a Complete Response as the exposure associated with Probuphine is lower than that of the referenced sublingual buprenorphine products and therefore there is no increase in risk. Therefore, if the application is approved on this cycle I recommend bridging toxicokinetic studies designed to provide exposures in order to interpret the nonclinical studies described in the label be addressed as a Post Marketing Commitment. If the application is given a Complete Response I would recommend this be incorporated as a deficiency especially if the Applicant will be conducting additional studies to establish the efficacy of higher Probuphine doses which would necessarily be associated with higher clinical exposure.

III. RECOMMENDATIONS

A. Recommendation on approvability

I concur with Dr. Bond that the application may be approved from the nonclinical perspective. I do not believe the absence of toxicokinetic bridging data – which would allow the nonclinical studies described in the Subutex/Suboxone labels to be placed in meaningful context – should preclude approval of the Application if it otherwise could occur on this cycle. The basis for this is the lower pharmacokinetic values associated with this implantable buprenorphine relative to the previously approved sublingual products which does not render the absence of this information a safety issue.

B. Recommendation for nonclinical studies

The Applicant should commit to providing toxicokinetic bridging data to buprenorphine nonclinical studies of reproductive toxicity and carcinogenicity as described in the referenced label. The specific language proposed at this time is provided below.

We do not believe the mg/m^2 body surface area-derived safety margins modified from the reference sublingual label as described in the Pregnancy, (b) (4) and Fertility sections of the proposed label are meaningful and informative.

In lieu of conducting reproductive toxicology studies necessary to support sections 8.1 *Pregnancy* and carcinogenicity studies described in 13.1 *Carcinogenesis, Mutagenesis, and Impairment of Fertility* conduct adequate bridging studies in the appropriate species in order to provide pharmacokinetic/toxicokinetic exposure data necessary for interpretation of the existing nonclinical data for your product label.

C. Recommendations on labeling

At this time, nonclinical sections of the proposed label should have safety margins removed due to the lack of an adequate scientific bridge to the existing data as described above. Additional changes to the label will be made based on recommendations from the Pediatric and Maternal Health Staff, which among other aspects, attempts to write the label to be consistent with principles of both current labeling as required by 21 CFR (incorporating Pregnancy category and required statements) as well as a proposed Pregnancy and Lactation Labeling Rule (PLLR; including *Risk Summaries, Clinical Considerations, and Data* sections). The language for this “hybrid” PLLR label will be finalized in a subsequent memo.

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 204442
Supporting document/s: Electronic CTD in DARRTS
Applicant's letter date: October 27, 2012
CDER stamp date: October 31, 2012
Product: Probuphine®
Indication: Opioid Addiction
Applicant: Titan Pharmaceuticals Inc.
Review Division: Division of Anesthesia, Analgesia and
Addiction Products
Reviewer: Gary P. Bond, Ph.D.
Supervisor/Team Leader: Adam M. Wasserman, Ph.D.
Division Director: Bob Rappaport, M.D.
Project Manager: Lisa Basham, M.S.

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 204442 are owned by Titan Pharmaceuticals Inc. or are data for which Titan Pharmaceuticals Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 204442 that Titan Pharmaceuticals Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 204442.

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1 Executive Summary

1.1 Introduction

Probuphine® (also described as Buprenorphine Drug Delivery System – BDDS) is a buprenorphine containing subdermally implantable formulation. The active pharmacological ingredient, buprenorphine hydrochloride (buprenorphine), is a partial opioid agonist administered in a solid matrix of ethylene vinyl acetate polymer (EVA). Probuphine is intended to provide sustained delivery of buprenorphine for up to 6 months for the maintenance treatment of opioid dependence using an abuse and diversion deterrent formulation. Each implant contains 80 mg buprenorphine and (b) (4) mg of EVA. The maximum proposed dose is 5 implants totaling 400 mg buprenorphine.

The human safety of buprenorphine in Probuphine is generally supported as Probuphine exposure data is within Suboxone 505(b)(2) buprenorphine exposure, acceptable product quality specifications and stability, and valid nonclinical studies with an acceptable clinical pharmacology relationship between the nonclinical test product and the proposed drug product. The local toxicity associated with the Probuphine implant was not unexpected as only anticipated implant effects occurred. This support includes the Agency's prior findings of buprenorphine safety and efficacy and submitted pivotal nonclinical studies that most notably include the chronic toxicity of implants with toxicokinetic (TK) measurements. Testing also included a set of medical device-based safety tests conducted on BDDS and/or BDDS placebo (EVA only) extracts according to International Organization for Standardization (ISO) 10993: Biological Evaluation of Medical Devices. Buprenorphine has been marketed for over 30 years as injectable Buprenex (NDA 18-401). 505(b)(2) reference for buprenorphine is made to the approved Subutex (NDA 20-732) and Suboxone (NDA 20-733) sublingual tablet labels for genotoxicity, carcinogenicity, and reproductive toxicity. The submitted nonclinical testing satisfies testing needs as listed in the FDA *Guidance for Industry and Review Staff: Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route* (March 2008).

The human safety of EVA (Inactive Ingredient) usage is generally supported by its use in FDA-approved and marketed products NuvaRing (NDA 21-187) and Implanon (NDA 21-529), but the primary support proposed by the applicant is the submitted nonclinical studies. Nonclinical testing with Probuphine (BDDS) and/or EVA alone (BDDS placebo) includes that as listed for buprenorphine in the preceding paragraph. This submitted nonclinical testing is consistent with the FDA *Guidance for Industry: Nonclinical Safety Studies for the Safety Evaluations of Pharmaceutical Excipients* (May 2005).

1.2 Brief Discussion of Nonclinical Findings

The nonclinical program was designed to support the administration of Probuphine rods (BDDS) by subdermal (subcutaneous) implantation. Inclusion of buprenorphine in EVA achieved the intended effect of producing a sustained systemic release of buprenorphine. The main focus of the nonclinical testing program was primarily on the evaluation of the systemic exposure and potential systemic toxicity of the

buprenorphine, on any potential BDDS placebo (EVA) related systemic effects, on any local toxicity of BDDS and/or BDDS placebo, and on any other effects noted in ISO medical device-based studies. Studies in dogs measured the systemic release and toxicity of buprenorphine. Studies in dogs and rabbits assessed the local toxicity of BDDS and BDDS Placebo. ISO studies measured the acute systemic toxicity, genotoxicity, sensitization, intracutaneous reactivity, pyrogenicity, and cytotoxicity of BDDS and BDDS Placebo extracts. Additional safety issues for human use included characterization of impurities and degradants in the Drug Substance and Drug Product and Extractable and Leachables in the Drug Product and EVA.

The local and systemic safety profile of buprenorphine administered in BDDS was anticipated to be the same as that for buprenorphine HCl and typical implants. Implant studies assessing local and systemic toxicity were conducted in rabbits for 4 weeks, in dogs for 1 month, in rabbits for 26 weeks, in dogs for 8 months, in dogs for 10 months, and in dogs for 12 months. Systemic exposure to buprenorphine generally caused only the anticipated pharmacological effects of buprenorphine as systemic exposure was generally well tolerated with no apparent additional EVA-related systemic toxicity from BDDS or BDDS placebo implants. Local toxicity from the implant was also as expected. One notation that should be made is the quality of the pivotal 10 month nonclinical study. In final review by DSI, the pivotal nonclinical study was determined to be valid.

Systemic Safety of Probuphine Implants for Buprenorphine and EVA

Systemic exposure to buprenorphine generally caused only the anticipated pharmacological effects of buprenorphine as systemic exposure was generally well tolerated with no apparent additional EVA-related systemic toxicity from BDDS or BDDS placebo implants. In the definitive 10 month study in dogs, 30 BDDS or 24 BDDS placebo implants were implanted per dog. These BDDS and BDDS placebo implants were comparable to the clinically tested drug product Probuphine and Probuphine placebo implants. Up to 5 implants are proposed for use in humans for up to 6 months duration. In this study, dog systemic exposure levels of buprenorphine were considerably higher with blood steady state concentrations (C_{SS}) of ~10 ng/mL compared to what occurred in humans during clinical trials at the maximum proposed dose of 5 implants (<1 ng/mL) and to what also occurred with approved Suboxone in the bioequivalence clinical study (~1.4 ng/mL). This data indicates human systemic safety for buprenorphine based on nonclinical data and referenced NDA approved drug data.

In summary, BDDS and BDDS Placebo implants caused no significant systemic toxicity from buprenorphine or EVA at nonclinical doses greater than proposed and greater than approved human doses (buprenorphine only). Levels of buprenorphine at approved human doses of buprenorphine (Suboxone) were also greater than proposed buprenorphine systemic exposure from Probuphine in a bioequivalence study thereby supporting a 505(b)(2) submission.

Local Toxicity of Probuphine and EVA Implants

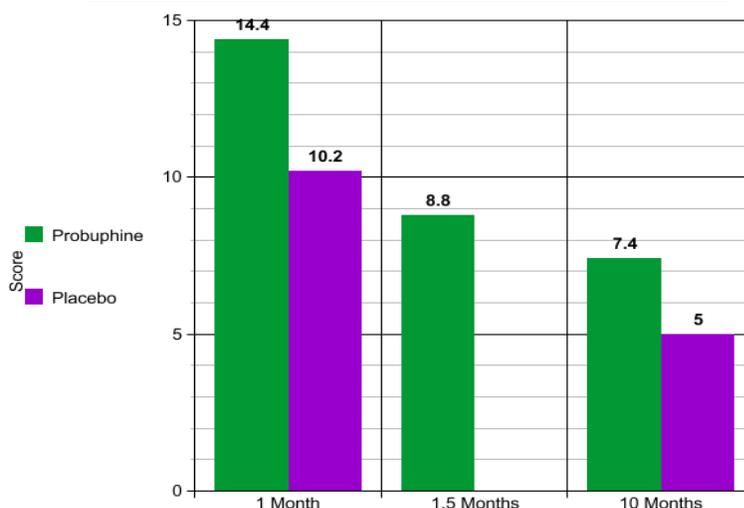
Macroscopically, no notable irritation was observed at the implant sites in any of the studies. Macroscopically, in an 8 month dog study, the implant sites could not be distinguished after a 2 month recovery period when the implants were removed after 8 months.

Smaller BDDS and BDDS placebo implants were moderately irritating at 4 weeks after implantation in male rabbits using microscopic evaluation. These smaller implants ((b)(4)% size of drug product, ~ (b)(4) mg buprenorphine) were of similar proportional composition of buprenorphine and EVA.. The USP negative control (polyethylene) was a slight irritant. At 26 weeks (6 months) also using the smaller implants, BDDS was still moderately irritating and BDDS placebo was a slight irritant suggesting a possible enhanced irritation by buprenorphine as BDDS-related irritation did not decrease from 4 weeks to 26 weeks. The USP negative control (polyethylene) sites were still slightly irritating at 26 weeks.

Enhanced local toxicity from buprenorphine is also suggested at 1 month after implantation in dogs using microscopic evaluation. BDDS (90 mg buprenorphine/implant, full size) was moderately to severely irritating and BDDS placebo was moderately irritating after implantation in male and female dogs suggesting a possible enhanced irritation by buprenorphine-containing implants. At 1.5 months after implantation in this same dog study, BDDS was slightly to moderately irritating after implantation compared to moderately to severely irritating after 1 month suggesting some possible reduction/reversal in implant site irritation. At 10 months in this dog study, BDDS implants were slightly to moderately irritating and BDDS placebo implants were slightly irritating, also suggesting possible reversibility of local irritation effects by 10 months in dogs. Based on these findings, buprenorphine incorporated with EVA appears to have increased local toxicity above that observed from EVA alone. Of note is that implants will be replaced in humans every 6 months, a time point not evaluated for reversibility of irritation in the dog.

In summary, BDDS and BDDS placebo caused significant local toxicity at the implant site in rabbits and dogs with likely enhanced local toxicity resulting from the presence of buprenorphine that was not reduced by 6 months in rabbits. However at an approximate 12-fold greater amount of implants in dogs compared to rabbits, the observed local toxicity/irritation was not proportionally greater than in rabbits and did show some indication of reversibility in dogs but at 10 months (no six months observation time point). The mean local irritation scores in dogs over 10 months are illustrated in the following graph.

Mean Local Irritation Scores from Implants*



* - Nonirritant (0.0-2.9), Slight Irritant (3.0-8.9),
Moderate Irritant (9.0-15.0), Severe Irritant (≥ 15.1)
- Reviewer's graph

ISO-specific Toxicity Studies of Probuphine and EVA Implants

ISO-specific studies for medical devices using BDDS and BDDS Placebo extracts were also conducted to assess acute systemic toxicity, genotoxicity, sensitization, intracutaneous reactivity, pyrogenicity, and cytotoxicity. BDDS extracts did not cause acute systemic toxicity after intraperitoneal injections of extract into the mouse, genotoxicity from extract using a standard *in vivo* and *in vitro* test battery, delayed dermal contact sensitization from extract in the guinea pig, intracutaneous reactivity after subcutaneous injection of extract in the rabbit, a pyrogenic response after intravenous injection of extract in the rabbit ear vein, and cytotoxicity from extract to mouse fibroblast cultures. BDDS Placebo extract did not cause genotoxicity in an *in vitro* chromosomal aberration study using mammalian cells or in an *in vivo* micronucleus assay in intraperitoneally injected mice. The direct applicability of these results to human safety is not known as we do not know the composition and concentration of the extracts. Assuming that buprenorphine, impurities and degradants, and extractables/leachables were contained in the extracts, these tests may suggest that any migrating chemicals do not pose a human health risk.

In summary, BDDS and BDDS placebo extracts were not associated with any additional toxicity in a battery of ISO tests for medical devices.

Additional nonclinical safety assessments

Impurities and degradants in Drug Substance (DS) and Drug Product (DP) and Extractables for EVA are within acceptable specification levels according to ICH Q3A, Q3B, and Q3C guidances, the FDA *Guidance for Industry - Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches* (Dec 2008),

and is consistent with the PQRI Recommendation Document: Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products (September 8, 2006). The PQRI recommendations are also considered for other exposure routes when appropriate.

No effects on the pharmacokinetics (PK) of buprenorphine was observed after external application of heat from five (5) Probuphine implants using 80 mg implants in dogs. Skin surface temperatures increased ~5°C (~40°F) during heat application. The mean concentration-time profiles showed that there was no difference in exposure to buprenorphine in the plasma and PK parameters after 8 hours of heat application to the implant site compared to animals that did not have 8 hours of heat applied to the implant site. There were also no exposure or PK effects following 8 hours of heat application to the implant site five weeks after implantation compared to at four weeks after implantation without heat.

1.3 Recommendations

1.3.1 Approvability

NDA approval is recommended from the nonclinical perspective. The results of a relative bioavailability clinical trial using approved Suboxone and Probuphine indicate that systemic exposure to buprenorphine is comparable and does not exceed approved systemic exposure levels which provide support for systemic safety. In addition, nonclinical data provide evidence for human safety for the expected exposure to buprenorphine and defines potential local toxicity from Probuphine implants.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling - preliminary and subject to further revision

Applicant's Proposed Label from Suboxone Approved Text (nonclinical relevant sections)	Edited label (response to Applicant)	Comment
<p>HIGHLIGHTS OF PRESCRIBING INFORMATION -----INDICATIONS AND USAGE-----</p> <div style="background-color: #cccccc; height: 80px; width: 100%;"></div>	<div style="background-color: #cccccc; height: 80px; width: 100%;"></div>	<p>Changed per FDA Established Pharmacologic Class</p>
<p>----USE IN SPECIFIC POPULATIONS-----</p> <ul style="list-style-type: none"> Proposed statement not included 	<p>• Pregnancy: (b) (4)</p>	<p>New PLLR format</p>

<p>8.1 Pregnancy</p> <p>(b) (4)</p>	<p>(b) (4)</p> <p>(b) (4)</p>	<p>New PLLR format</p> <p>Do not believe (b) (4) IS sufficiently robust for inclusion</p> <p>(b) (4)</p>
	<p>PROBUPHINE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.</p> <p>Risk Summary Based on animal data, Probuphine is predicted to have a moderate probability of increasing the risk of adverse developmental outcomes above background risk. Buprenorphine, the active ingredient in Probuphine, has been shown to be embryocidal in rabbits and cause increases in skeletal abnormalities in rats at the daily Maximum Recommended Human Dose – MRHD).</p>	<p>Add standard statement</p>
<p>(b) (4) Buprenorphine was not teratogenic in rats or rabbits after intramuscular (IM) or subcutaneous (SC) doses up to 5 mg/kg/day (b) (4)</p> <p>After intravenous (IV) doses up to 0.8 mg/kg/day (b) (4) or after oral doses up to 160 mg/kg/day in rats (b) (4)</p> <p>Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (b) (4)</p> <p>Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (b) (4) or oral administration of 1 mg/kg/day or greater (b) (4) were not statistically significant.</p> <p>In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically</p>	<p>(b) (4) Buprenorphine was not teratogenic in rats or rabbits after intramuscular (IM) or subcutaneous (SC) doses up to 5 mg/kg/day (approximately 3 and 6 times, respectively, the daily Maximum Recommended Human Dose – MRHD), after intravenous (IV) doses up to 0.8 mg/kg/day (approximately 0.5 times in the rat and equal to in the rabbit the daily MRHD), or after oral doses up to 160 mg/kg/day in rats (approximately 95 times the daily MRHD). (b) (4) was approximately 30 times the daily MRHD. Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of greater than or equal to 1 mg/kg/day and up (approximately 0.6 times the daily MRHD), but were not observed at oral doses up to 160 mg/kg/day (approximately 100 times the daily MRHD). Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (approximately 6 times the daily MRHD) or oral administration of 1 mg/kg/day or greater (approximately equal to the daily MRHD) were not statistically significant.</p> <p>In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses</p>	<p>New PLLR format</p> <p>Suboxone values for animal to human dose ratios are being maintained. We do not believe it is appropriate to adjust the margins (b) (4)</p> <p>The different exposure time courses of buprenorphine blood levels between Suboxone sublingual and Probuphine observed in clinical study PRO-810 allow no numerically supported change in the dose ratios. Based on PRO-810 data, buprenorphine exposure levels after Suboxone administration were lower than exposure levels after Probuphine administration for some time period during the first month of</p>

<p>significant at IV doses of 0.2 mg/kg/day or greater (b) (4)</p> <p>(b) (4)</p> <p>Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine 5 mg/kg/day (b) (4)</p> <p>(b) (4)</p> <p>Fertility, (b) (4) - and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (b) (4)</p> <p>(b) (4)</p> <p>after IM doses of 0.5 mg/kg/day and up (b) (4)</p> <p>(b) (4)</p> <p>and after SC doses of 0.1 mg/kg/day and up (b) (4)</p> <p>(b) (4)</p> <p>Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (b) (4)</p> <p>(b) (4)</p>	<p>that were statistically significant at IV doses of 0.2 mg/kg/day or greater (approximately equal to the daily MRHD).</p> <p>(b) (4)</p> <p>Dystocia was noted in pregnant rats treated IM with buprenorphine 5 mg/kg/day (approximately 3 times the daily MRHD). Fertility (b) (4) - and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times daily MRHD), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the daily MRHD), and after SC doses of 0.1 mg/kg/day and up (approximately 0.06 times the daily MRHD). Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the daily MRHD).</p>	<p>Probuphine exposure. The applicant is invited to provide alternative rationale to any different, proposed dose ratios (e.g., bridging nonclinical toxicokinetic data as noted in the preNDA meeting).</p>
<p>12.1 Mechanism of Action</p> <p>(b) (4)</p>	<p>(b) (4)</p>	<p>(b) (4)</p> <p>Text will not be changed at this time as added information not considered of value to the physician.</p>
<p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p>Carcinogenicity:</p> <p>(b) (4)</p> <p>Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day (b) (4)</p> <p>(b) (4)</p> <p>statistically significant dose-related increases in Leydig cell tumors occurred. In an 86-week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (b) (4)</p> <p>(b) (4)</p> <p>Mutagenicity:</p>	<p>Carcinogenesis:</p> <p>(b) (4)</p> <p>Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day (approximately 0.4, 3, and 35 times the daily Maximum Recommended Human Dose - MRHD). (b) (4)</p> <p>(b) (4)</p> <p>statistically significant dose-related increases in Leydig cell tumors occurred. In an 86-week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (approximately 30 times the daily MRHD).</p> <p>Mutagenesis:</p>	<p>New PLLR format</p> <p>As with Pregnancy section 8.1, animal to human dose ratios will be kept at Suboxone label values unless justified otherwise.</p> <p>New PLLR format</p>

<p>Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (<i>S. cerevisiae</i>) for recombinant, gene convertant, or forward mutations; negative in <i>Bacillus subtilis</i> "rec" assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay.</p> <p>Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5mg/plate) in a third study. Results were positive in the Green-Tweets (<i>E. coli</i>) survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both in vivo and in vitro incorporation of [3H]thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.</p> <p>Impairment of Fertility: Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure approximately (b) (4)) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure approximately (b) (4)) had no adverse effect on fertility.</p>	<p>No change in text</p> <p>Impairment of Fertility: Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater) produced a reduction in fertility demonstrated by reduced female conception rates (approximately 28 times the daily MRHD). A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day) had no adverse effect on fertility (approximately 6 times the daily MRHD).</p>	<p>As with Pregnancy section 8.1 and carcinogenicity in this section, animal to human dose ratios will be kept at Suboxone label values unless justified otherwise.</p>
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(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number

Drug substance – buprenorphine hydrochloride (53152-21-9)

Generic Name - Probuphine®

Code Name – buprenorphine implant

- buprenorphine hydrochloride (b) (4) with ethylene vinyl acetate copolymer

Chemical Name

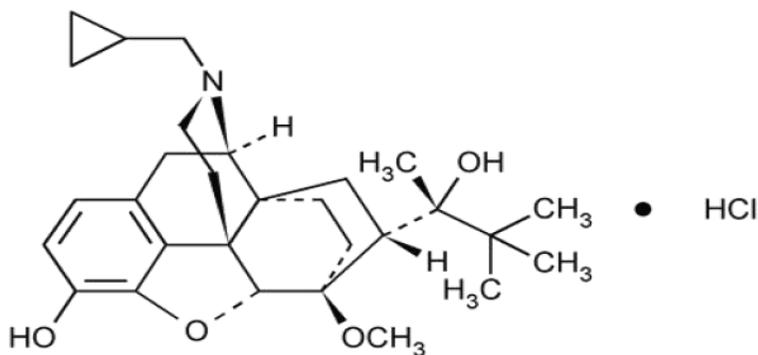
- Buprenorphine
 - o 21-Cyclopropyl-7α-[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-endo-ethano-6,7,8,14-tetrahydrooripavine hydrochloride
- Ethylene Vinyl Acetate copolymer (EVA)
 - o Not available

Molecular Formula/Molecular Weight

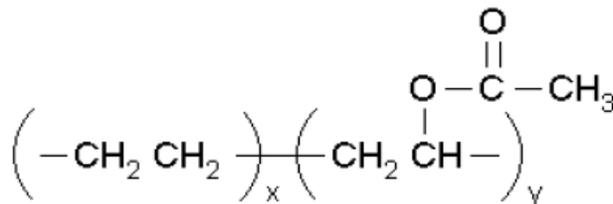
- Buprenorphine
 - o $C_{29}H_{41}NO_4 \cdot HCl / 504.10$
- ethylene vinyl acetate copolymer (EVA)

Structure or Biochemical Description

- Buprenorphine



- Ethylene Vinyl Acetate copolymer (EVA)



Pharmacologic Class

- Buprenorphine
 - o partial opioid agonist
- Ethylene Vinyl Acetate copolymer (EVA)
 - o inactive ingredient/carrier

2.2 Relevant INDs, NDAs, BLAs and DMFs

Buprenorphine: DMF (b) (4)

Application Number	Product Name	Submitter	Dosage Form	Current Status	Status Date	Indication/Subject/Issue
NDA-021306	Butrans (buprenorphine) Transdermal System	PURDUE PHARMA LP	PATCH	Approved	6/30/2010	Management of moderate to severe chronic pain
NDA-022410	Suboxone (Buprenorphine/Naloxone) sublingual film	RECKITT BENCKISER PHARMACEUTICALS INC	FILM	Approved	8/30/2010	Maintenance treatment of opioid dependence
NDA-018401	Buprenex	RECKITT BENCKISER PHARMACEUTICALS INC	INJECTION	Approved	12/29/1981	Relief of moderate to severe pain
NDA-204242	Buprenorphine and Naloxone Sublingual tablets	OREXO AB	TABLET	Pending	9/6/2012	Maintenance treatment of opioid dependence.
NDA-020733	Suboxone (Buprenorphine HCl/Naloxone HCl)	RECKITT BENCKISER PHARMACEUTICALS INC	TABLET	Approved	10/8/2002	Treatment of narcotic addiction
NDA-020732	Subutex (Buprenorphine HCl)	RECKITT BENCKISER PHARMACEUTICALS INC	TABLET	Approved	10/8/2002	Treatment of opiate addiction

- adapted from DARRTS

EVA: NuvaRing (NDA21-187) and Implanon (NDA 21-529)

2.3 Drug Formulation

Drug Substance

Buprenorphine - The drug substance buprenorphine hydrochloride (BPN) is synthesized by Teva Czech Industries, s.r.o. ("Teva Czech") in compliance with the USP monograph.

The total dose of buprenorphine is 80 mg per rod for a maximum of 5 rods or 400 mg. According to ICH Q3A, safety qualification is required at 0.15% at a maximum daily dose of ≤ 2g/day (80 mg in 1 rod or 400 mg buprenorphine in 5 rods). However applicant specifications up to NMT (b)(4)% exceed 0.15% but the drug substance is considered qualified based on approved buprenorphine (DMF (b)(4) and USP monograph) and the release pattern of buprenorphine of no more than (b)(4)% of buprenorphine being released from the rods over 6 months in clinical trial TTP-400-02-1 which measured residual buprenorphine in extracted rods. See Product Quality review for more detail.

Drug Substance Specifications for Buprenorphine Hydrochloride

Parameter	USP	Teva Czech	Titan / DPT
Appearance	Not Specified	White or almost white crystalline powder	White or almost white crystalline powder
Identification:			
A: Infrared Abs	Must match reference spectra	Must match reference spectra	Must match reference spectra
B: Color Test	Immediate Blue Color	Immediate Blue Color	Immediate Blue Color
C: Chloride Test	Meet test requirement	Meet test requirement	Meet test requirement
Specific Optical Rotation	(b)(4)		
Water			
pH			
Impurities			
Individual Impurity			

- Applicant table

All residual solvent specifications are less than those listed in ICH Q3C Residual Solvents Tables.

Total Impurity	NMT (b) (4) %	NMT (b) (4) %	NMT (b) (4) %
Residual Solvents	Not Specified	(b) (4)	Meets requirements for USP <467> (b) (4) limits

- Applicant table

Drug Substance Stability - The results (b) (4) fully complied with the drug substance specifications. All stability indicating parameters were within the proposed limits. Based on these results, the drug substance, BPN, should be stable for at least (b) (4) months when stored (b) (4)

Drug Product

Probuphine® (buprenorphine implant) drug product is a subdermal implant containing 80 mg buprenorphine hydrochloride USP (BPN) in an ethylene vinyl acetate copolymer (EVA) matrix. Each implant measures 26 mm in length and 2.5 mm in diameter. The total weight of each implant is 112.5 mg. Implants are individually packaged in laminated foil pouches. The pouches are terminally sterilized using gamma irradiation.

Composition of Probuphine Finished Drug Product Implant

Component	Quality Standard	Function	mg/implant
Buprenorphine hydrochloride	USP	Active pharmaceutical ingredient	80
Ethylene vinyl Acetate	In house specification	Excipient / Polymeric matrix	(b) (4)

- Applicant table

Finished Product Release Specifications (post-sterilization)

Test	Test Method	Acceptance Criteria
Appearance	DPT 73.4009 DPT 75.1022	White/off white to pale yellow ^a
Implant Diameter	DPT 75.1020	2.50 ± (b) (4) mm
Implant Length	DPT 75.1021	26.0 ± (b) (4) mm
Implant Weight	DPT 75.1024	(b) (4) mg
Weight Uniformity	USP<905>	USP<905>
Content Uniformity	USP<905>	USP<905> (b) (4)
Buprenorphine Hydrochloride Assay	DPT 73.6348	(b) (4) mg Buprenorphine hydrochloride /implant
Dissolution	USP 28 < 711> Apparatus 2 73.6349	Target Release Rate: (b) (4)
Impurities		
Individual unspecified impurities (each)	DPT 73.6348	(b) (4) %
Total impurities		(b) (4) %
Residual Solvent (b) (4)	DPT 73.5843	(b) (4) mg/implant
Sterility ^b	USP<71> Direct Inoculation (b) (4)	Sterile
Endotoxin: LAL ^b	USP<85>	(b) (4) EU/implant

^a Pale yellow as defined as a color equal to (b) (4)

^b Testing performed by third party testing lab (b) (4)

- Applicant table

Stability - Based upon analysis, the 4, 24, 48 and 96 hour dissolution meet the specification for 8 months for lot PRO-510-06-01 and 6 months for lot NP-3 (see Product Quality review). The total impurities and maximum individual impurities meet the specification for 48 months for lots PRO-510-06-01 and PRO-510-07-01 and 36 months for lots PRO-080808004 (AHL-C) and NP-3. The applicant commits to conduct and complete stability studies on the first three commercial lots of the drug product. Such testing will be performed by DPT Laboratories, Ltd. on representative samples in the commercial container closure system stored at 25°C /60%RH after 3, 6, 9, 12, 18, 24, 36, 48, and 60 months and at 40°C /75%RH after 1, 3, and 6 months.

Nonclinical versus clinical batches – Comparability of nonclinical test batches, most importantly in the pivotal chronic dog study compared to the proposed drug product is a buprenorphine content of ~90 mg/rod and ~80 mg/rod, respectively. However, in nonclinical study PRO-NDR-0701, rods having 60, 70, or 80 mg buprenorphine per rod yielded no differing mean blood steady state levels over 6 months, the proposed dosing duration for the drug product. The C_{ss} values for all test groups from 60, 70, or 80 mg buprenorphine/rod and differing manufacturing methods were no different considering mean and standard deviation as mean values ranged from 3.39 to 4.72 ng/mL and all values were within 1 standard deviation of each other. One of the test groups used 80 mg buprenorphine/rod and the proposed drug product manufacturing method. On this basis the pivotal nonclinical chronic dog study is considered for defining human safety from a systemic and local toxicity standpoint noting that higher blood levels in the dog study (C_{ss} of ~10 ng/mL) compared to clinical study/trial values with 4-5 Probuphine rods (C_{ss} of ≤ 1 ng/mL) suggest more local toxicity in dogs as the buprenorphine component in Probuphine has more local irritation than the Probuphine placebo (EVA) alone. This is a positive thing, suggesting less local toxicity in humans which is consistent with moderate to severe irritation in dogs compared to complaints in humans. In addition, the physical characteristics of nonclinical test product were similar to the proposed drug product, allowing use of nonclinical data to be relevant for evaluating potential human toxicity.

Container Closure System

Information concerning the primary and secondary packaging for BPN is provided in the Teva DMF 16419. The primary packaging component for the drug substance, BPN, is a

(b) (4)

The secondary packaging component for the drug substance is a

(b) (4)

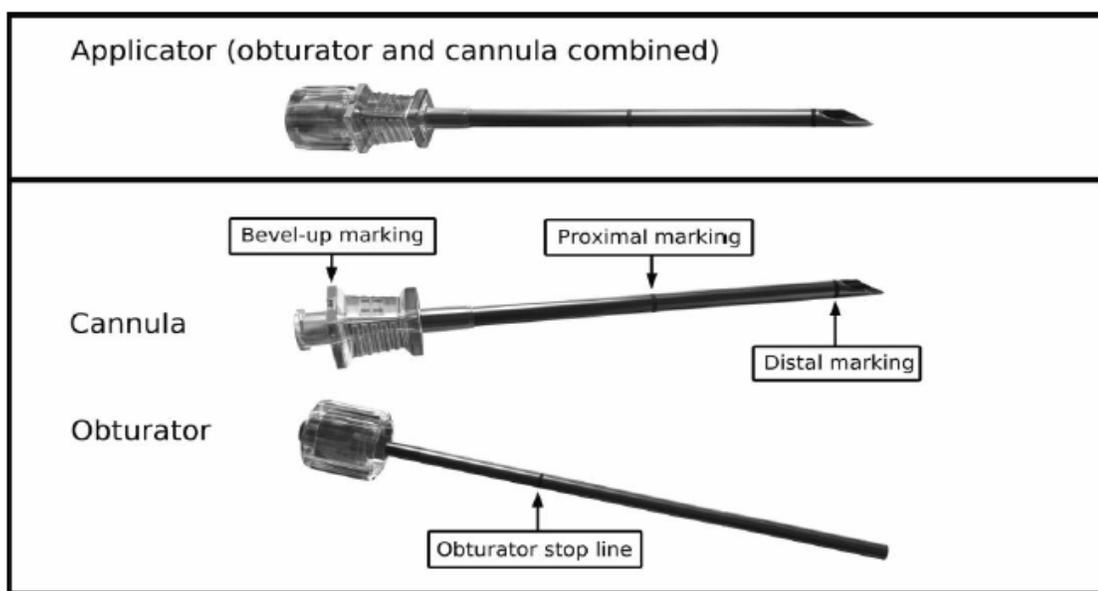
Packaging Materials

Configuration	Material	Specifications
(b) (4)		

- Applicant table

Probuphine Applicator - The Probuphine® Applicator is a sterile, single patient use device that is intended to place Probuphine® in the subdermal space of the body, by trained healthcare providers. Probuphine (buprenorphine hydrochloride/ethylene vinyl acetate) is an implantable formulation of buprenorphine hydrochloride developed for up to 6 months of maintenance treatment of opioid dependence. Probuphine must be removed by the end of the sixth month and may be replaced with new implants at the time of removal, if continued treatment is desired.

The Applicator is comprised of three (3) main components, the Cannula, the Needle Insertable Stylet Rod, and the Cover (Needle Guard). The components of the Applicator are shown in (excluding the Cover). The Cannula and Stylet have interlocking hubs (referred to as Swivel Nuts) manufactured from biocompatible polymeric materials. The Applicator design includes guide and orientation marker visual aids to assist healthcare providers with the proper placement of the Probuphine implants. These markers include orientation markings on both the Cannula and Stylet to facilitate the proper depth of implant placement, and a foil stamp marking on the hub of the Cannula showing the correct "bevel up" position for the cannula which facilitates the correct subdermal insertion of Probuphine.



- Applicant figure

2.4 Comments on Novel Excipients

There are no reported novel excipients. EVA is a non-novel, non-compendial excipient.

Excipient - Ethylene vinyl acetate (EVA) is the only excipient used in the manufacture of Probuphine® implants. Ethylene vinyl acetate copolymer (EVA) is listed in the FDA Inactive Ingredient Guide (IIG) as being used in other approved products for this dosage form. EVA used in Probuphine implants contains (b) (4) %w/w vinyl acetate (VA). EVA is

supplied (b) (4) At ≤ (b) (4) ppm vinyl acetate monomer, the potential maximum exposure from 5 rods is (b) (4) mcg if all VA leaves the rods at one time. This is not the case as the VA leaves the rods over the course of the (b) (4) exposure period making the potential daily exposure less than the concern level for structural alerts of (b) (4) mcg/day assuming that VA leaves the EVA at no different amount that buprenorphine leaves EVA, (b) (4) % of total (see product Quality review).

EVA (b) (4) Specification

Attribute	Test Method	Allowable Range
Appearance	Visual	Translucent Pellets
Identity	FTIR TAP 01-0203-041	Spectrum Matches that of EVA standard
Vinyl Acetate Content	NMR TAP 01-0202-043 or equivalent	(b) (4) %
Melt Index by	ASTM method D1238 or equivalent	(b) (4) min
Biological Reactivity Test (In vitro)	USP <87> Direct contact test	Sample reactivity not greater than grade (b) (4) reactivity
Biological Reactivity Test (In vivo)	USP <88> ^{1,2} Systemic injection test	Conforms to USP ² (b) (4)
Biological Reactivity Test (In vivo)	USP <88> ^{1,2} Intracutaneous test.	Conforms to USP ² (b) (4)
Biological Reactivity Test (In vivo)	USP <88> ^{1,2} Implantation test	Conforms to USP ² (b) (4)
Residual Monomer Vinyl Acetate	GC TAP 01-0404-050	Equal or less than (b) (4) ppm
Residual Monomer Ethylene	GC TAP 01-0404-051	Equal or less than (b) (4) ppm
Residue on Ignition	USP <281>	(b) (4) %

1 (b) (4)
2 (b) (4)

- Applicant table

- EVA in other approved implants
 - Intravaginal NuvaRing (NDA 21-187)
 - 1 ring for 3 of every 4 weeks - chronic (comparable exposure - ~continuous)
 - (b) (4) mg EVA/ring ((b) (4) mg EVA in 5 Probuphine rods)
 - ~12 fold more EVA in NuvaRing supports human safety of Probuphine
 - But, stratified squamous epithelium in vagina versus subdermal/subcutaneous tissue for Probuphine?

- Not carcinogenic after 24-month rat subdermal exposure (~15% of 5 rod Probuphine exposure)
 - no local toxicity effects observed microscopically – usual implant effect
- EVA in approved products and considered non-biodegradable
 - Not currently considered a human safety issue

2.5 Comments on Impurities/Degradants of Concern

Unspecified chromatographic peaks were recorded at various relative retention times (RRT) during the drug product stability studies. Potential unidentified degradation products were reported at various relative retention times but only appeared at random time points; no consistent growth or trend could be determined. No such peaks exceeded (b) (4) % during the stability studies to date. The degradation products/impurities will be monitored during the registration stability and validation studies; if the peaks exceed the identification threshold ((b) (4) %), the impurity will be identified and specifications determined as required by the ICH Q3B(R), Impurities in Drug Products, guidance based upon the levels reported. At the maximum daily dose of buprenorphine 80 mg x 5 rods = 400 mg/day (b) (4) the ICH Q3A and Q3B guideline levels for qualification of 1.0% < 10mg drug substance are satisfied.

Specifications for EVA extractables were set based on the PQRI Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled Products (September 8, 2006). The PQRI recommendations are also used for other exposure routes as a matter of FDA practice. The applicant conducted an extraction study with EVA and packaging components (PRO-NTR-1201) identifying the following extracts:

Results for EVA Placebo Implant Extracts Analyzed by GC/MS or LC/MS

Sample ID	Tentative Identification	Estimated Concentration (mcg/g)
(b) (4)		

- Applicant table

Based on the results of that study and the identified extractables safety limits as per the PQRI document (NMT (b) (4) mcg/day for structural alerts, NMT (b) (4) mcg/day for non-structural alerts, and NMT (b) (4) mcg/day for unknowns) which were agreed upon by the applicant, those agreed upon specification values are as follows using the amount of EVA per rod ((b) (4) mg):

(b) (4)

(b) (4)

EVA qualification will be acceptable by an appropriate supplier (b) (4) or else the applicant must conduct testing on the batches of EVA (see Product Quality review).

2.6 Proposed Clinical Population and Dosing Regimen

Opioid addicts are the proposed clinical population. The proposed dosing regimen is 4-5 Probuphine rods inserted under the armpit for 6 months and then removed with insertion of an additional 4-5 rods under the other armpit. Rotation is back and forth every subsequent 6 months.

2.7 Regulatory Background

Buprenorphine has been marketed for over 30 years as injectable Buprenex (NDA 18-401). 505(b)(2) reference for buprenorphine is made to the approved Subutex (NDA 20-732) and Suboxone (NDA 20-733) sublingual tablet labels with the Maximum Recommended Human dose (MRHD) of 16 mg buprenorphine per day. EVA is used in marketed products NuvaRing (NDA21-187) and Implanon (NDA 21-529).

3 Studies Submitted

3.1 Studies Reviewed

- listed by CTD section numbers for nonclinical study reports

4.2.2 Pharmacokinetics

4.2.2.1 Analytical Methods and Validation Reports

Validation of an HPLC-MS/MS Assay Method for the Determination of Buprenorphine and Norbuprenorphine in Beagle Plasma (PRO-NAL-0202)
- buprenorphine analysis method validation for all studies

4.2.2.2 Absorption

Chronic Toxicity Study of Buprenorphine Drug Delivery System Implanted Subcutaneously in Dogs (Amendment 1) (PRO-NTR-0519)
- buprenorphine pharmacokinetic analysis for pilot and chronic dog studies
- kinetic data included in individual report reviews in section 4.2.3.2

The Determination of Buprenorphine and Norbuprenorphine in Beagle Plasma (Potassium EDTA) Samples in Support of NAMSA Pilot Study Laboratory Number 01T 06823 00 (PRO-NAL-0203)

The Determination of Buprenorphine and Norbuprenorphine by LC-MS/MS in Beagle Plasma Samples in Support of NAMSA Chronic Study Laboratory Number 01T 06823 00 (PRO-NAL-0204)

3-Month Pharmacokinetic Study of an Ethylene Vinyl Acetate (EVA) Copolymer-Based Controlled Release Implant in Dogs (PRO-NDR-0001)

Release Characteristics of Buprenorphine-Containing Implants in Male Beagle Dogs Following Subcutaneous (SC) Implantation (PRO-NDR-0701)

Determination of Buprenorphine Concentrations in Male Beagle Dog Plasma Samples Collected from [REDACTED] ^{(b) (4)} Study X51110 – Bioanalytical Final Report (PRO-NAL-1201)

Release Characteristics of Buprenorphine-Containing Implants in Male Beagle Dogs Following Subcutaneous (SC) Implantation – Final Pharmacokinetic Report (PRO-NDR-1202)

Pharmacokinetics of Buprenorphine Release from Subcutaneous Probuphine® Implants in Dogs after Heat Application (PRO-NDR-1201)

4.2.3 Toxicology

4.2.3.1 Single-Dose Toxicity

ISO Acute Systemic Toxicity Study in the Mouse (Extracts) (PRO-NTR-0106)

4.2.3.2 Repeat-dose Toxicity

Chronic Toxicity Study of Buprenorphine Delivery System Implanted Subcutaneously in Dogs (Pilot Report) (PRO-NTR-0214)

Chronic Toxicity Study of Buprenorphine Delivery System Implanted Subcutaneously for 10 Months in Dogs (PRO-NTR-0215)

4.2.3.3 Genotoxicity

4.2.3.3.1 In-Vitro

Genotoxicity: Bacterial Reverse Mutation Study (Saline and Ethanol Extracts) (PRO-NTR-0107)

Genotoxicity: In Vitro Chromosomal Aberration Study in Mammalian Cells (Extract BDDS) (PRO-NTR-0109)

Genotoxicity: In Vitro Chromosomal Aberration Study in Mammalian Cells (Extract BDDS Placebo) (PRO-NTR-0210)

4.2.3.3.2 In-Vivo

Mouse Bone Marrow Micronucleus Study (BDDS) (PRO-NTR-0211)

Mouse Bone Marrow Micronucleus Study (BDDS Placebo) (PRO-NTR-0212)

4.2.3.6 Local Tolerance

ISO Sensitization Study in the Guinea Pig (Maximization Method) (PRO-NTR-0103)

ISO Acute Intracutaneous Reactivity Study in the Rabbit (Extracts) (PRO-NTR-0104)

ISO Subcutaneous Implantation Study in the Rabbit with Histopathology (Surgical Method, Four Weeks) (PRO-NTR-0108)

ISO Subcutaneous Implantation Study in the Rabbit with Histopathology (Surgical Method, Twenty-six Weeks) (PRO-NTR-0213)

4.2.3.7 Other Toxicity Studies

4.2.3.7.6 Impurities

Risk Assessment of Impurities in Components of Probuphine® Implants and Packaging (PRO-NTR-1201)

4.2.3.7.7 Other

ISO Rabbit Pyrogen Study (Material Mediated) (PRO-NTR-0102)

Cytotoxicity Study Using the ISO Elution Method (1X MEM Extract) (PRO-NTR-0105)

4.3 Literature references

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3.2 Studies Not Reviewed

- listed by CTD section number for nonclinical study reports

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3.3 Previous Reviews Referenced

IND 70,0852

4 Pharmacology

- adapted Applicant's text

The pharmacological properties of buprenorphine have been well characterized in the peer-reviewed literature and in the reference marketed drug product Suboxone Label and Subutex Label, and no changes in the pharmacodynamic properties of buprenorphine are expected with Probuphine. There has been no observed evidence of a chemical interaction between EVA and buprenorphine in the Probuphine product in any of the analytical testing performed, or during long-term stability testing for up to 48 months. In addition, implantation of Probuphine after induction with Suboxone resulted in similar or lower levels of systemic exposure to buprenorphine and the metabolite norbuprenorphine than that of Suboxone alone in a clinical relative bioavailability study in opioid-dependent human subjects (Titan Study PRO-810). Therefore, the basic pharmacodynamic properties of Probuphine are expected to be the same as those described for buprenorphine in the literature and the Suboxone Label and the Subutex Label, and as such, no new pharmacology studies were conducted with buprenorphine or Probuphine implants to support this 505(b)(2) marketing application.

4.1 Primary Pharmacology

The primary pharmacodynamic profile of buprenorphine, an oripavine-based synthetic opioid with mixed agonist-antagonist activity, has been well characterized in a variety of test systems. Norbuprenorphine, a dealkylated metabolite of buprenorphine which can equal or exceed buprenorphine levels in human plasma, is an opioid receptor agonist with high affinity for μ - and κ -opioid receptors, lower affinity for δ -opioid receptors, and no detectable binding at nociceptin receptors. However, norbuprenorphine exhibits

weak pharmacodynamic activity *in vivo* owing to low central nervous system (CNS) permeability and export from the brain by P-glycoprotein transporters.

The co-polymer matrix component of Probuphine, EVA, is contained in several approved and marketed products, including the three-year subdermal implantable drug products Implanon® /Nexplanon®, and has been found to be a safe and inert biocompatible excipient. As indicated above, compatibility of the drug substance with the excipient is evidenced by drug product stability data provided in the submission.

4.2 Secondary Pharmacology

Secondary pharmacodynamic effects on the central nervous, gastrointestinal, cardiovascular, respiratory, and other systems have also been assessed and reported in the literature and approved buprenorphine product labels.

Chronic administration of buprenorphine produces dependence of the opioid type, characterized by withdrawal upon abrupt discontinuation or rapid taper, although the withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset (Suboxone Label; Subutex Label). Because of the partial agonist properties of buprenorphine, opioid withdrawal signs and symptoms may occur in opioid-dependent persons if products containing buprenorphine are administered before the agonist effects of the opioid have subsided (Suboxone Label; Subutex Label). Note that dedicated nonclinical abuse potential studies of Probuphine were not done because buprenorphine is well characterized and controlled as a Schedule III narcotic under the Controlled Substances Act. The applicant, Titan, is relying on data previously presented for marketed products such as Suboxone and Subutex as presented in the published literature that describe the abuse potential and physical dependence of buprenorphine.

4.3 Safety Pharmacology

No safety pharmacology studies were performed with Probuphine. Secondary pharmacodynamic effects, including cardiovascular, respiratory, and CNS effects typically evaluated in the standard safety pharmacology battery of tests, are well known for buprenorphine. Notably, implantation of Probuphine after induction with Suboxone resulted in similar or lower levels of systemic exposure to buprenorphine and the metabolite norbuprenorphine based on maximum plasma concentration (C_{max}) and area under the plasma concentration/time curve (AUC) than that of Suboxone alone in a clinical relative bioavailability study in opioid-dependent subjects (Titan Study PRO-810). Therefore, no new or unexpected secondary pharmacodynamic effects are anticipated with Probuphine.

Pharmacodynamic drug interactions involving buprenorphine are well characterized, and include alteration by benzodiazepines of the usual ceiling effect of buprenorphine-induced respiratory depression and increased CNS depression from concomitant administration of other drugs with CNS-depressant activity (Suboxone Label; Subutex Label). No new drug interactions are expected with Probuphine. Pharmacokinetic drug interactions with buprenorphine are well known and generally involve interaction with CYP3A4 inhibitors, includingazole antifungals, macrolide antibiotics, and human

immunodeficiency virus (HIV) protease inhibitors (Suboxone Label; Subutex Label). Concomitant use of these drugs with buprenorphine may increase plasma buprenorphine concentration and increase the likelihood of buprenorphine-related adverse effects.

5 Pharmacokinetics/ADME/Toxicokinetics

- adapted Applicant's text

Probuphine implants are designed to deliver a sustained dose of buprenorphine for 6 months after subdermal implantation for the treatment of opioid dependence. The implants are composed of two components, the active ingredient buprenorphine and the excipient EVA. The systemic absorption and plasma pharmacokinetics of buprenorphine were evaluated in five *in vivo* studies following subcutaneous implantation of Probuphine implants in dogs. Two of these studies were toxicokinetic assessments conducted as part of pilot and definitive chronic toxicity studies of Probuphine. Of the remaining three studies, one was a study of the effect of external heat application on the pharmacokinetics of buprenorphine released from the Phase 3 clinical Probuphine implant formulation, another study involved pharmacokinetic assessments of a process change in the manufacturing of the Phase 3 clinical Probuphine implant formulatio (b) (4)

and the remaining pharmacokinetic study was for an early Probuphine prototype tested during the formulation development program. Liquid chromatography–tandem mass spectrometry (LC/MS/MS) bioanalytical methods were validated for the quantification of buprenorphine and its *N*-dealkylated metabolite norbuprenorphine in dog plasma and used to generate plasma concentration-time data from which pharmacokinetic parameters were derived.

The pharmacokinetic characteristics of buprenorphine are well documented in the scientific literature and in the reference Suboxone Label and Subutex Label. No changes in the distribution, metabolism, or elimination profiles of systemic buprenorphine are expected to occur from subdermal implantation of Probuphine compared with marketed products. Therefore, no new metabolism, distribution, or elimination studies were performed with Probuphine.

5.1 PK/ADME

- adapted Applicant's text

The pharmacokinetic characteristics of buprenorphine are well documented in the scientific literature and in the reference Suboxone and Subutex Labels. No changes in the distribution, metabolism, or elimination profiles of systemic buprenorphine are expected to occur from subdermal implantation of Probuphine compared with marketed products. Therefore, no new metabolism, distribution, or elimination studies were performed with Probuphine.

Submitted Study Summaries**Validation of an HPLC-MS/MS Assay Method for the Determination of Buprenorphine and Norbuprenorphine in Beagle Plasma (study PRO-NAL-0202) –**

The acceptance criteria as stated in the method validation protocol and (b) (4) SOP PH-BA 1 which closely follows the FDA Guidance for Industry on bioanalytical method validation) were fulfilled for selectivity/specificity, linearity, sensitivity, accuracy, precision, recovery, dilution, reinjection and stability. The method is identified validity for the extraction and analysis of beagle plasma samples within the investigated concentration range of 0.500-100 ng/mL for both buprenorphine and norbuprenorphine. This is a GLP study.

Chronic Toxicity Study of Buprenorphine Drug Delivery System Implanted Subcutaneously in Dogs (Amendment 1) (PRO-NTR-0519) – This report is the buprenorphine pharmacokinetic analysis for the pilot (PRO-NTR-0214) and definitive chronic (PRO-NTR-0215) dog studies based on individual study blood analyses (PRO-NAL-0203 – pilot; PRO-NAL-0204 – definitive). Results included in the individual study reviews in section 6.2.

The Determination of Buprenorphine and Norbuprenorphine in Beagle Plasma (Potassium EDTA) Samples in Support of NAMS Pilot Study Laboratory Number 01T 06823 00 (PRO-NAL-0203) – blood analyses to support report PRO-NAL-203.

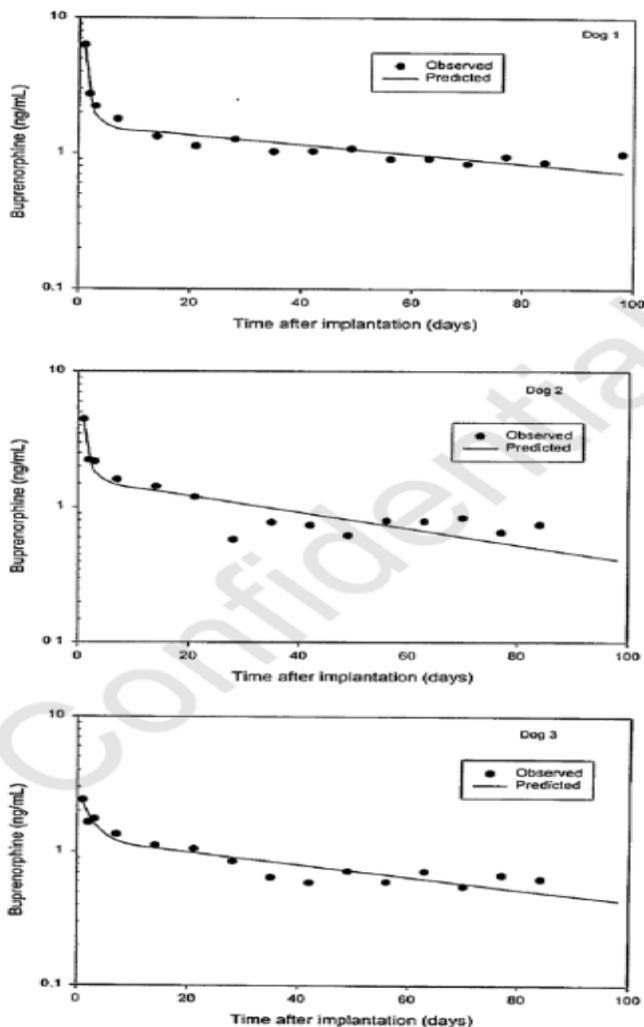
The Determination of Buprenorphine and Norbuprenorphine by LC-MS/MS in Beagle Plasma Samples in Support of NAMS Chronic Study Laboratory Number 01T 06823 00 (PRO-NAL-0204) – blood analyses to support report PRO-NAL-203.

3-Month Pharmacokinetic Study of an Ethylene Vinyl Acetate (EVA) Copolymer-Based Controlled Release Implant in Dogs (PRO-NDR-0001) – The objective of this non-GLP study was to determine the release of buprenorphine from the ethylene vinyl acetate (EVA) copolymer implant (lot 13219-64) in dogs over a 3 month period. Three (3) female dogs received 2 implants of 45 mg buprenorphine each to their backs. The proposed drug product is 4-5 80 mg buprenorphine implants so what is of interest here is the steady state plasma levels form the approximate equivalent of 1 Probuphine rod. Plasma drug levels were measured on Days 1, 2, 3, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, and 84. No mortality or notable clinical signs were observed. All implant sites for all three dogs appeared normal at every observation with one exception; animal no. 1 had a small abrasion near the implant suture site on Days 4, 7 and 14 that appeared to be the result of rubbing the site against the dog run.

Buprenorphine was released in a prolonged manner with a terminal half-life of approximately 2 to 3 months (66.7 ± 17.69 days). Pharmacokinetic values varied greatly between the three dogs as noted by the standard deviations listed in the table but the overall blood levels over time were fairly comparable in the three animals as noted in the blood level graphs for actual and predicted data. Norbuphine was not detected in any samples.

Parameters	Dog 1	Dog2	Dog3	Mean \pm SD
C _{max} (ng/ml)	18.4	10.7	3.0	10.7 \pm 7.70
AUC _{0-∞}	209.5	122.8	118.8	150.4 \pm 51.25
Half-life p (days)	85.1	49.8	65.3	66.7 \pm 17.69

- Reviewer table



- Applicant figure

In summary, the administration of buprenorphine in EV copolymer implant resulted in sustained release of the drug, and maintained measurable plasma drug concentrations throughout the study.

Release Characteristics of Buprenorphine-Containing Implants in Male Beagle Dogs Following Subcutaneous (SC) Implantation (PRO-NDR-0701)

The nonGLP study objective was to evaluate the release characteristics from dose- and formulation-variants of buprenorphine-containing implants over a three-month (groups

1, 3, & 5) or six-month period (groups 2 & 4). Probuphine® implants (80 mg buprenorphine) were manufactured with the same formulation of (b) (4) % w/w buprenorphine HCl, (b) (4) % w/w EVA, with one lot using (b) (4) buprenorphine (PRO-510-05-01) and the other lot using (b) (4) buprenorphine (PPX-1005-1). All other steps and parameters of the manufacturing process were the same for both lots and were the same as those used in the Probuphine® Phase 3 clinical lots. The test articles evaluated in Groups 5 and 6 were Probuphine implants that contained 80 mg buprenorphine and were similar to those used in the Probuphine Phase 3 clinical studies. The final proposed clinical drug product is (b) (4) (PPX-1005-1). Implants varied as follows in amount of buprenorphine and production process listed in order of groups 1 through 6:

Formulation	Buprenorphine HCl Content/ Implant	Method of Preparation
NPPPP1a	60 mg	(b) (4)
NPPPP1b	70 mg	
NPPPP1c	60 mg	
NPPPP1d	70 mg	
PRO-510-05-01	80 mg	
PPX-1005-1	80 mg	

* - PPX-1005-1 reported in amendment to be 90 mg/rod
 - Applicant table

Four (4) male beagle dogs/group were assigned to six treatment groups which received 8 implants each. Groups 1, 3, and 5 evaluated implants in the study animals over a period of 6 months, while groups 2 and 4 evaluated the implants over a period of 3 months. A sixth treatment of 2 group 2 & 4 animals was added seven days after the end of the three-month treatment period and removal of the original implants for an additional 3-month exposure with PPX-1005-1 (manufactured the same as proposed drug product (b) (4)). The test articles evaluated in Groups 1-4 were novel buprenorphine/EVA implant prototypes containing 60 or 70 mg buprenorphine either by formulation or because (b) (4). The Probuphine-like test articles evaluated in Groups 5 and 6 contained 80 mg buprenorphine each and were similar to those used in the Probuphine Phase 3 clinical studies. A table of the study design follows.

Study Design

Group	Animal Numbers	n/sex	Test Article (mg buprenorphine HCl)	# Implants/Animal	Blood Collection Time Points (Day 0 -- Hours)	Blood Collection Time Points (Days)
1	1-4	4/M	NPPPP1a 60 mg/rod	8	Day before implantation & Day 0: 3, 6, 9, 12 hr post-implantation.	1, 2, 3, 4, 5, 6, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 84, 98, 126, 154, 182 [#]
2	5-8	4/M	NPPPP1b 70 mg/rod	8	Day before implantation & Day 0: 3, 6, 9, 12 hr post-implantation.	1, 2, 3, 4, 5, 6, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 84, 98 [#]
3	9-12	4/M	NPPPP1c 60 mg/rod	8	Day before implantation & Day 0: 3, 6, 9, 12 hr post-implantation.	1, 2, 3, 4, 5, 6, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 84, 98, 126, 154, 182 [#]
4	13-16	4/M	NPPPP1d 70 mg/rod	8	Day before implantation & Day 0: 3, 6, 9, 12 hr post-implantation.	1, 2, 3, 4, 5, 6, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 84, 98 [#]
5	17-20	4/M	PRO-510-05-01 80 mg/rod	8	Day before implantation & Day 0: 3, 6, 9, 12 hr post-implantation.	1, 2, 3, 4, 5, 6, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 84, 98, 126, 154, 182 [#]
6* (re-implant)	6, 8, 14, 15	4/M	PPX-1005-1 80 mg/rod	8	Day before implantation & Day 0: 3, 6, 9, 12 hr post-implantation.	1, 2, 3, 4, 5, 6, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 84, 98 [#]

*: Following a 7-day washout period after removal of the implants, complete elimination of buprenorphine from the plasma was verified in animals numbers 6, 8, 14 and 15. These animals were re-implanted with PPX-1005-1 (80 mg/rod) implants.

[#]: Last blood draw was shortly before implant removal.

- Applicant table

Adverse events were limited to buprenorphine-related lethargy and salivation occurring up to approximately 24 hours post-dose in most groups. Emesis and loss of appetite were also reported in a few (5 out of 12) animals in Groups 3 and 4. Local toxicity was observed approximately five days post-dose as 2 of 20 animals developed erythema and irritation at the implant site which resolved with veterinary care. Decreases in body weights were noted in all 5 groups on Day 7 at no more than 10% body weight. By Day 28, body weights were back to Day 0 values. There were no changes in body weight in Group 6 (re-implanted) animals. Overall, the results of this study showed that buprenorphine-containing implants, when surgically implanted, were generally well tolerated in dogs for up to 182 days. Initial, slight, transient clinical signs and decreases in body weights and food consumption in most treatment groups were observed during the first week post-surgery.

Toxicokinetic data was reported in study PRO-NDR-1202. Mean steady-state plasma buprenorphine concentrations (C_{ss}) were generally similar for the 60 mg buprenorphine implants, Group 1 (3.39 ± 0.62 ng/mL) and Group 3 (3.39 ± 0.85 ng/mL); and for the 70 mg buprenorphine implants, Group 2 (4.09 ± 1.19 ng/mL) and Group 4 (4.72 ± 0.70 ng/mL). (b) (4) 80 mg buprenorphine Group 5

implants generated implants with a 60 mg buprenorphine content (Group 3 implants), and resulted in a lowering of the mean C_{max} from 13.2 ± 3.6 to 8.96 ± 2.31 ng/mL, and the mean exposure for the initial peak release period after implantation (AUC_{0-35 days}), from 183 ± 23 to 167 ± 39 ng·day/mL, respectively. The mean C_{ss} for the Group 3 implant (3.39 ± 0.85 ng/mL) was generally similar to that for the Group 5 implant (3.16 ± 0.19 ng/mL), and the mean plasma buprenorphine exposure at steady state (AUC_{35-98 days}) were 210 ± 52 and 226 ± 12 ng·day/mL, respectively. Over the entire three month study interval following implantation, the comparable mean plasma buprenorphine exposure levels (AUC_{0-98 days}) was 378 ± 90 ng·day/mL with Group 3 implants and 409 ± 35 ng·day/mL with Group 5 implants. (b) (4)

The data shows that the pharmacokinetics of buprenorphine release group 5 & 6 lots are generally similar (b) (4)

For these two Probuphine-like (80 mg buprenorphine) test articles Group 5 and Group 6 (more representative of Probuphine as same manufacturing process used), the mean plasma buprenorphine exposure over the first 35 days after implantation (AUC_{0-35 days}), which included the initial peak and gradual decrease to the steady state release period, were similar for both test articles (183 ± 23 and 184 ± 16 ng·day/mL, respectively), although the mean C_{max} value was lower in Group 5 when compared to Group 6 (13.2 ± 3.6 and 22.0 ± 3.0 ng/mL, respectively). In addition, the mean plasma buprenorphine exposure during the evaluated two month steady state release period from Day 35 to Day 98 after implantation (AUC_{35-98 days}) for Group 5 and Group 6 implants were also similar (226 ± 12 and 222 ± 61 ng·day/mL, respectively), as were the mean steady-state plasma buprenorphine concentrations (C_{ss}) (3.16 ± 0.19 and 3.65 ± 0.94 ng/mL, respectively). Over the entire three month (98 day) interval following implantation, the comparable mean plasma buprenorphine exposure levels (AUC_{0-98 days}) were also similar for both Group 5 and Group 6 test articles (409 ± 35 and 405 ± 76 ng·day/mL, respectively).

Of note here is that regardless of the production method and the amount of buprenorphine in each rod, the C_{ss} values for all test groups from 60, 70, or 80 mg buprenorphine/rod and differing manufacturing methods were no different considering mean and standard deviation as mean values ranged from 3.39 to 4.72 ng/mL and all values were within 1 standard deviation of each other. However, this may be a limitation of using only 4 animals/group and normal variation of the index evaluated. Pharmacokinetic data is listed on the following tables.

Summary of the Mean Pharmacokinetic Parameters for Buprenorphine in Male Dog Plasma: Groups 1 through 4

Group	Test ^a Article	Dose Level (mg)		C _{max} (ng/mL)	T _{max} (day)	C _{ss} (ng/mL)	AUC _{0-t} (ng·day/mL)	AUC ₀₋₃₅ (ng·day/mL)	AUC ₃₅₋₉₈ (ng·day/mL)	AUC ₀₋₉₈ (ng·day/mL)
1	NPPPP1a 60 mg buprenorphine /implant	480	Mean	14.6	1.34	3.39	600	218	207	425
			SD	5.3	2.44	0.62	54	28	34	62
			N	4	4	4	4	4	4	4
2	NPPPP1b 70 mg buprenorphine /implant	560	Mean	17.9	0.750	4.09	492	237	255	492
			SD	3.4	0.289	1.19	114	43	72	114
			N	4	4	4	4	4	4	4
3	NPPPP1c 60 mg buprenorphine /implant	480	Mean	8.96	0.875	3.39	571	167	210	378
			SD	2.31	0.835	0.85	160	39	52	90
			N	4	4	4	4	4	4	4
4	NPPPP1d 70 mg buprenorphine /implant	560	Mean	13.0	1.09	4.72	500	203	297	500
			SD	4.3	1.27	0.70	61	20	43	61
			N	4	4	4	4	4	4	4

^a Eight implants were placed subcutaneously per animal for each test article.

C_{ss}: Steady state concentration from Day 35 to Day 98.

Note: End of treatment (t) was 182 days for Groups 1 and 3 and 98 days for Groups 2 and 4.

- Applicant table

Summary of the Mean Pharmacokinetic Parameters for Buprenorphine in Male Dog Plasma: Groups 5 and 6

Group	Test ^a Article	Dose Level (mg)		C _{max} (ng/mL)	T _{max} (day)	C _{ss} (ng/mL)	AUC _{0-t} (ng·day/mL)	AUC ₀₋₃₅ (ng·day/mL)	AUC ₃₅₋₉₈ (ng·day/mL)	AUC ₀₋₉₈ (ng·day/mL)
5	PRO-510-05-01 80 mg buprenorphine/implant	640	Mean	13.2	1.31	3.16	622	183	226	409
			SD	3.6	1.43	0.19	51	23	12	35
			N	4	4	4	4	4	4	4
6	PPX-1005-1 80 mg buprenorphine/implant	640	Mean	22.0	0.156	3.65	405	184	222	405
			SD	3.0	0.063	0.94	76	16	61	76
			N	4	4	4	4	4	4	4

^a Eight implants were placed subcutaneously for each test article.

C_{ss}: Steady state concentration from Day 35 to Day 98.

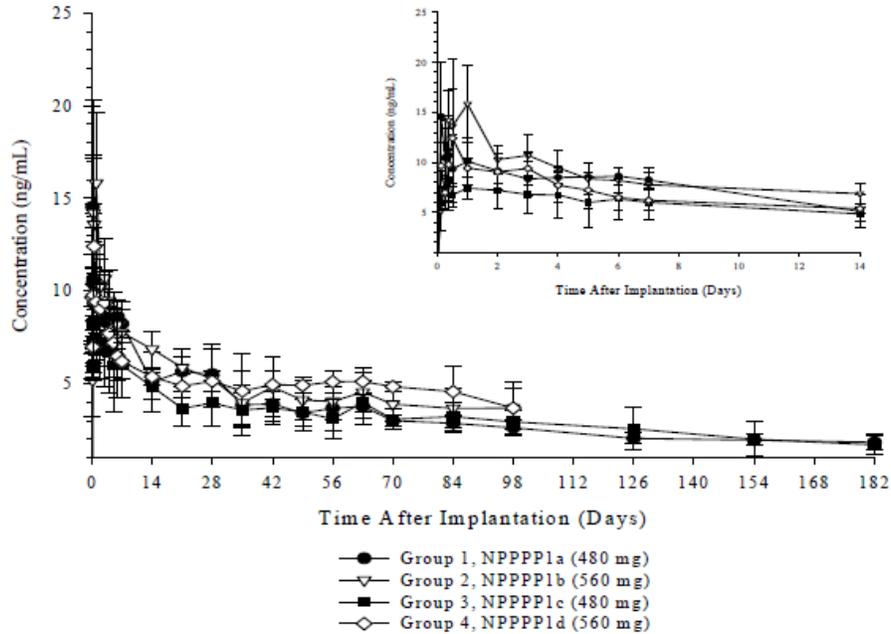
Note: End of treatment (t) was 182 days for Group 5 and 98 days for Group 6.

- Applicant table

The lack of a difference in blood levels among the different amount of buprenorphine exposure groups is also evident in the blood level time courses below. The C_{max} values appear different depending on the buprenorphine dose and manufacturing method but C_{ss} values do not. The higher C_{max} for group 6 may have resulted due to

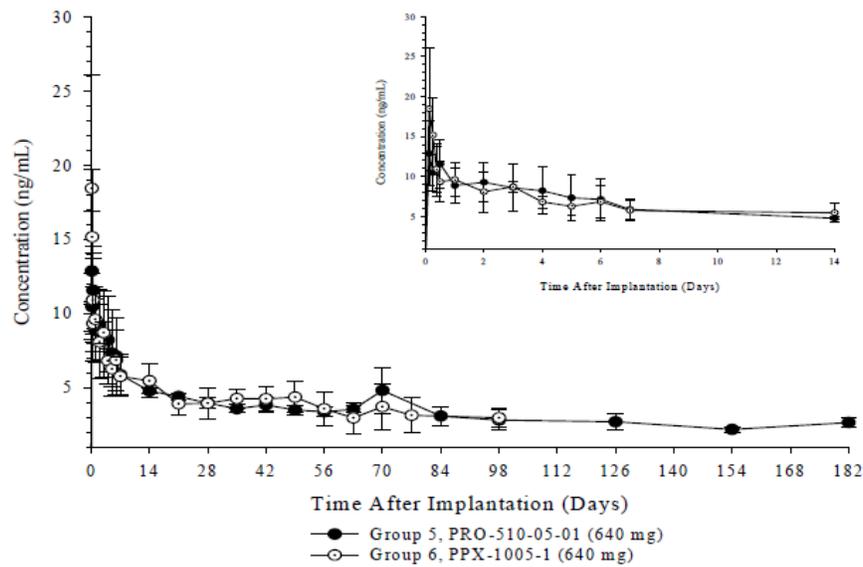
re-implantation as previous implantation sites (~20% larger than the largest C_{max} from the other groups) but C_{ss} was not different.

Mean (±SD) concentrations (ng/mL) of buprenorphine in male dog plasma: Groups 1 through 4, linear-linear scaling



- Applicant figure

Mean (±SD) concentrations (ng/mL) of buprenorphine in male dog plasma: Groups 5 and 6, linear-linear scaling



- Applicant figure

Determination of Buprenorphine Concentrations in Male Beagle Dog Plasma Samples Collected from [REDACTED] (b) (4) Study X5I110 – Bioanalytical Final Report (PRO-NAL-1201) – Blood level analyses used in report PRO-NDR-1202 listed below.

Release Characteristics of Buprenorphine-Containing Implants in Male Beagle Dogs Following Subcutaneous (SC) Implantation – Final Pharmacokinetic Report (PRO-NDR-1202) – Pharmacokinetic data reported in study PRO-NDR-0701 above.

Pharmacokinetics of Buprenorphine Release from Subcutaneous Probuphine® Implants in Dogs after Heat Application (PRO-NDR-1201) - The purpose of this GLP study was to determine the pharmacokinetics of buprenorphine release from subcutaneous Probuphine implants (LOT PRO-080808004) in Beagle dogs following external application of heat. Two (2) groups of 6 males received 5 Probuphine implants each with group 2 also being treated with a heat patch as follows:

Group	PK Phase	Number of Males	Dose Route ^a	Heat Application	Target Dose Level (mg/animal) ^b
1	1	6	SC	No	400
2	1	6	SC	Yes ^c	400
2	2	6	SC	No	NA
2	3	6	SC	Yes ^c	NA

NA Not applicable

PK Pharmacokinetic

SC Subcutaneous

Note: There was 4 weeks between PK Phases 1 and 2, and 1 week between PK Phases 2 and 3.

a Implants were inserted subcutaneously on Day 1 (PK Phase 1); Group 1 implants were removed following completion of PK Phase 1, and Group 2 implants were removed following completion of PK Phase 3.

b Each animal in Groups 1 and 2 (n=12) received one dose of 5 Probuphine® implants (each implant containing 80 mg buprenorphine HCl) on Day 1 (PK Phase 1). Group 1 animals were assessed for plasma PK during Phase 1, while Group 2 animals were assessed for plasma PK in Phases 1, 2, and 3.

c A pre-activated heat patch was applied to the dose site for 8 hours; skin-surface temperature beneath the heat patch was measured at specified times.

- Applicant table

Blood collected as follows:

PK Phase 1 - Blood was collected from all animals predose and at 2, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, 42, and 48 hours post-implantation. Group 2 had heat pad on for 8 hours starting from dosing.

PK Phase 2 - At four weeks following implant insertion (approximately 672 hours post-implantation), blood was collected from all animals at approximately the same time of day as the PK Phase 1 dose administration (time 0) and at 6, 12, 18, and 24 hours following the time 0 collection.

PK Phase 3 - At five weeks following implant insertion (approximately 840 hours post-implantation), blood was collected from all animals at approximately the same time of day as the PK Phase 1 dose administration (time 0) and at 2, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, 42, and 48 hours following the time 0 collection. This group had heat pad on for 8 hours starting from dosing.

Skin Surface Temperature (PK Phases 1 and 3 - Group 2) - Temperature of the skin surface beneath the heat pad applied at the implant site was measured for each animal using a calibrated thermal sensor immediately post-implantation (within 5 minutes) prior to heat pad placement (or at time 0 for PK Phase 3, prior to heat pad placement) and at 2, 4, 6, 8, 10, and 12 hours post-implantation (or post time 0 for PK Phase 3).

All animals appeared healthy prior to dosing and throughout the duration of the study except for initial lethargy, hypothermia, and excessive salivation observed in some animals consistent with the known pharmacological action of buprenorphine associated with the pharmacokinetic-observed initial peak release of buprenorphine from the implants.

Overall, skin surface temperatures in Phases 1 and 3 were similar, and individual animal variability was low for each measured time point. Skin temperatures prior to heat patch placement ranged from 30.4 to 36.3°C, respectively for Phases 1 and 3 (mean of 33.0°C and 34.1°C, respectively). Variability of the skin surfaces temperatures collected prior to heat batch placement may be attributed to lack of full equilibration of the thermal chip to the skin surface, as the chips were exposed to the ambient air prior to placement on the skin. For all animals, skin surface temperatures increased following placement of the heat patch in Phases 1 and 3. From 0 to 2 hours post patch placement, mean skin surface temperatures increased from 33.0 to 41.3°C in Phase 1 and from 34.1 to 40.2°C in Phase 3. During the time the heat patch was in place, individual and group mean skin surface temperatures were consistent and steady for all animals in Phases 1 and 3.

Individual and group mean skin surface temperatures of Group 2 male dogs following subcutaneous insertion of five Probuphine[®] implants

Animal Number	Group	Phase	Individual Skin Surface Temperature (°C)						
			Predose ^a	2	4	6	8	10	12
H05036	2	1	31.2	41.8	41.3	41.5	42.2	35.1	36.0
H05037	2	1	34.5	41.6	40.5	40.6	40.8	35.8	35.6
H05038	2	1	30.4	41.7	41.7	41.7	42.4	35.4	35.3
H05039	2	1	36.3	41.3	40.7	40.5	40.4	35.1	35.7
H05040	2	1	33.5	39.5	38.6	38.6	37.9	36.6	36.7
H05041	2	1	31.8	41.6	40.1	40.5	40.5	35.7	36.3
		Mean	33.0	41.3	40.5	40.6	40.7	35.6	35.9
		SD	2.23	0.873	1.09	1.10	1.62	0.564	0.509
H05036	2	3	34.3	39.8	39.4	39.6	39.3	37.0	36.8
H05037	2	3	33.8	41.0	40.4	40.1	40.3	37.6	37.3
H05038	2	3	33.1	39.3	39.4	39.6	39.5	36.3	36.0
H05039	2	3	33.8	40.6	40.4	40.1	40.2	37.6	37.3
H05040	2	3	34.9	40.4	40.3	40.1	40.4	38.1	37.4
H05041	2	3	34.6	39.9	39.8	40.0	39.9	37.4	37.3
		Mean	34.1	40.2	40.0	39.9	39.9	37.3	37.0
		SD	0.649	0.615	0.481	0.248	0.450	0.619	0.542

SD Standard deviation.

a Prior to heat pad placement, immediately following (within 5 minutes) dose administration in Phase 1, and at time zero in Phase 3.

- Applicant table

The mean concentration-time profiles showed that exposure to buprenorphine in the plasma in PK Phase 1 was similar in animals after 8 hours of heat application to the implant site (Group 2; the mean plasma buprenorphine concentration was 3.69 ng/mL and ranged from 1.45 to 5.63 ng/mL) when compared to animals that did not have 8 hours of heat applied to the implant site (Group 1; the mean plasma buprenorphine concentration was 4.18 ng/mL and ranged from 2.41 to 6.4 ng/mL). Consequently, no heat effect was observed for C_{max} or AUC. The plasma buprenorphine C_{max} and AUC₀₋₄₈ values were 7.96 ng/mL (ranging from 6.11 to 9.81 ng/mL) and 274 ng·hr/mL (ranging from 207 to 355 ng·hr/mL), respectively, when heat was applied to the implant site for 8 hours on Day 1, and were 9.89 ng/mL (ranging from 8.64 to 11.3 ng/mL) and 343 ng·hr/mL (ranging from 286 to 401 ng·hr/mL), respectively, when heat was not applied to the implant (PK Phase 1).

The results in PK Phases 2 and 3 also showed no heat effect. Mean steady-state plasma buprenorphine concentration (C_{ss2}) was 4.37 ng/mL (ranging from 2.61 to 5.42 ng/mL) following 8 hours of heat application to the implant site five weeks after implantation (PK Phase 3). These results are generally similar to the mean steady-state concentration (C_{ss3}) of 3.86 ng/mL (ranging from 2.73 to 4.84 ng/mL) following the removal of external heat (PK Phase 3) and the mean steady state concentration (C_{ss1}) of 3.90 ng/mL (ranging from 3.01 to 4.77 ng/mL) in Week 4 post-implantation when heat was not applied to the implant site (PK Phase 2).

Mean pharmacokinetic parameters for plasma collected from male dogs following subcutaneous insertion of five Probuphine[®] implants

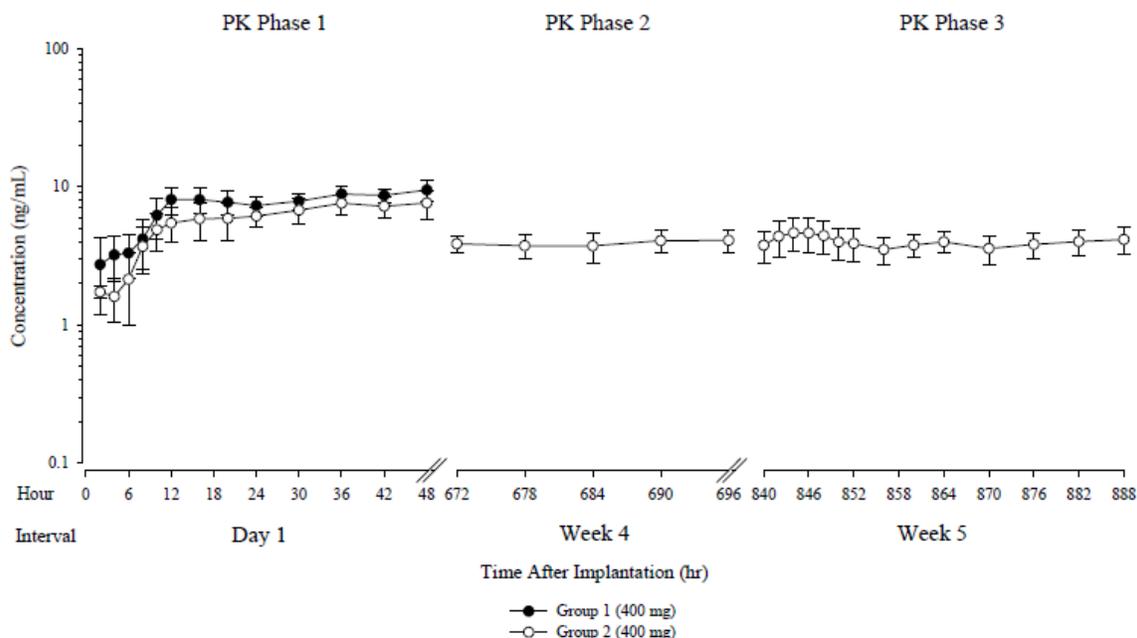
Group	Dose (mg)	PK Phase		C _{max} (ng/mL)	T _{max} (hr)	AUC ₀₋₂₄ (ng·hr/mL)	AUC ₀₋₄₈ (ng·hr/mL)	C ₁₁₁ (ng/mL)	C ₁₁₂ (ng/mL)	C ₁₁₃ (ng/mL)
1	400	Phase 1	Mean	9.89	34.7	NA	343	NA	NA	NA
			SD	0.98	16.7	NA	40	NA	NA	NA
			N	6	6	NA	6	NA	NA	NA
2	400	Phase 1	Mean	7.96	36.0	NA	274	NA	NA	NA
			SD	1.44	15.2	NA	51	NA	NA	NA
			N	6	6	NA	6	NA	NA	NA
		Phase 2	Mean	4.32	14.0	93.1	NA	3.90	NA	NA
			SD	0.68	9.8	17.1	NA	0.69	NA	NA
			N	6	6	6	NA	6	NA	NA
		Phase 3	Mean	4.82	11.0	96.8	NA	NA	4.37	3.86
			SD	1.19	15.2	22.4	NA	NA	1.15	0.79
			N	6	6	6	NA	NA	6	6

NA Not applicable; this parameter was not required for this group/phase.

Notes: No heat was applied to the implant site of Group 1 animals during Phase 1 or to Group 2 animals during Phase 2. External heat was applied to the implant site of Group 2 animals for 8 hours during Phases 1 and 3.

- Applicant table

Mean (\pm SD) concentrations of buprenorphine in male dogs following subcutaneous insertion of five Probuphine[®] implants



PK Phase 1: Heat was not applied to the implant site of Group 1 animals. Heat was applied to the implant site of Group 2 animals for 8 hours.
 PK Phase 2: Heat was not applied to the implant site of Group 2 animals.
 PK Phase 3: Heat was applied to the implant site of Group 2 animals for 8 hours.

- Applicant figure

In summary, no consistent changes in plasma buprenorphine exposure were observed when external heat was applied for 8 hours directly after implantation or when reapplied at the time of steady state release 5 weeks after implantation. Norbuprenorphine plasma concentrations were generally below the limit of quantitation and pharmacokinetic analysis was not conducted.

5.2 Toxicokinetics

Data discussed either in PK/ADME section or along with toxicology study as noted in PK/ADME section.

6 General Toxicology

6.1 Single-Dose Toxicity

ISO Acute Systemic Toxicity Study in the Mouse (Extracts) (PRO-NTR-0106) – The Buprenorphine Drug Delivery System (BDDS) test article (lot 13810-66a, 66b, 66c, 66d, 66e, 66f) was extracted in 0.9% sodium chloride USP solution and cottonseed oil, NF. Based on ISO protocol, 1.7 cm of the 2.6 cm long piece of BDDS was extracted. These extracts were evaluated for systemic toxicity in accordance with the requirements of the International Organization for Standardization 10993: Biological Evaluation of Medical Devices, Part 11: Tests for Systemic Toxicity.

A single dose of the appropriate test article extract was injected into each of five mice per extract by the intraperitoneal route. Similarly, five mice were dosed with each

corresponding reagent control. The animals were observed immediately and at 4, 24, 48, and 72 hours after systemic injection.

Under the conditions of this study, there was no mortality or evidence of systemic toxicity from the extracts. Each test article extract met the test requirements.

6.2 Repeat-Dose Toxicity

Study title: CHRONIC TOXICITY STUDY OF BUPRENORPHINE DELIVERY SYSTEM IMPLANTED SUBCUTANEOUSLY IN DOGS (PILOT REPORT)

Study no.: PRO-NTR-0214 (lab no. OIT 06823 00)
Study report location: eCTD in DARRTS
Conducting laboratory and location: NAMSA, 2261 Tracy Road
Northwood, OH 43619-1397
Date of study initiation: May 24, 2001
GLP compliance: yes
QA statement: yes
Drug, lot #, and % purity: Buprenorphine Drug Delivery system (BDDS), Lots: 13657-06 and possibly others (see definitive study), ~90 mg buprenorphine per implant

Key Study Findings

- The purpose of this study was to determine the number of BDDS implants that could be inserted without causing clinical signs of toxicity, a pilot study for the definitive chronic study
- One male and female dog per group were dosed subcutaneously with 8, 16, or 24 BDDS implants for 12, 8, or 12 months, respectively. Implants were removed from the 10-month group and these animals were sacrificed at 12 months.
- General observations and assessment were conducted but not microscopic examination.
- Under the conditions of the study, no evidence of systemic toxicity from the test article was observed following subcutaneous implantation in the dog. There were no test article-related effects resulting in mortality. There were no abnormalities noted for the physical, ophthalmic, or neurologic examinations.
- Daily clinical observations, body weights, necropsy findings, organ weights and organ/body weight ratios were within acceptable limits and were similar between and within test treatment groups. There were no changes in terminal hematology, clinical chemistry, or urinalysis values in either male or female dogs that were considered to be biologically significant or related to treatment with the test article. No evidence of inflammation or infection was noted macroscopically at the implantation sites.
- Toxicokinetic values were generally proportional to the number of implants. Blood levels immediately declined after removal of the rods at 8 months.

- The Buprenorphine Drug Delivery System was generally well tolerated at all three dose levels following subcutaneous implantation in dogs up to 24 implants per dog for 12 months with exposure levels up to 54.5 ng/mL (Cmax) and 64,117 ng•h/mL (AUC_{0-∞}).

Methods

Doses:	Group I - 8 implants/dog for 12 months - ~720 mg buprenorphine Group II - 16 implants/dog for 8 months then removal and 2 months observation - ~1440 mg buprenorphine Group III - 24 implants/dog for 12 months - ~2160 mg buprenorphine
Frequency of dosing:	Single implantation at beginning (day0)
Route of administration:	Subcutaneously using a trocar device
Dose volume:	NA
Formulation/Vehicle:	BDDS implants
Species/Strain:	Beagle dogs
Number/Sex/Group:	1
Age:	Young adult
Weight:	10-12 kg at implantation
Satellite groups:	none
Unique study design:	The purpose of the study was to evaluate the greatest number of implants that could be implanted without causing clinical signs of toxicity.
Deviation from study protocol:	The original objective of the study was to terminate 4 animals by the end of 4 weeks and to terminate 2 animals at 7 months. The decision to extend the study to 12 months was based on positive safety and pharmacokinetic data observed within the first 4 weeks of the study.

IMPLANTATION SURGERY

The animals were fasted overnight prior to surgery. Dogs were pre-anesthetized and then light anesthesia was induced and maintained with inhalant anesthesia. The hair on the dorsal scapular region on the back was shaved with electric clippers. The implant site was scrubbed with povidone iodine soap, rinsed with alcohol, and painted with povidone antiseptic. The site was draped in a routine fashion.

The previously sterilized test articles were aseptically loaded into the sponsor supplied trocars and were implanted as received from the sponsor in the subcutaneous tissue over the back. A small stab incision was made through the skin to facilitate insertion of the delivery needle. The pre-loaded needle containing the material was inserted

through the skin and into the subcutaneous. The test article was discharged from the trocar with the stylet and the trocar withdrawn, leaving the sample in the subcutaneous tissue. The appropriate number of test article rods was implanted in each dog. The skin incision was sutured closed. The animals were returned to their respective cages and monitored for recovery from the anesthetic. The day of implantation was designated as Day 0.

OBSERVATIONS AND RESULTS

Physicals

Physicals, including neurologic examinations, were conducted at pre-treatment, months 1, 3, & 6, and at termination.

Results - All animals appeared healthy and there were no abnormalities noted at the physical examinations conducted at pretreatment and month 6. Some observations at 1 and 3 months included observations that appeared to be a result of physical trauma. Otherwise, all animals appeared normal at these intervals. All neurological examinations were within normal limits

At the 1 month physical examinations, a Group II female had several abrasions on muzzle some alopecia on the neck. A Group III female had patchy alopecia over the head, shoulders, and trunk and no active excoriations, however, there was evidence of previous abrasions.

At the 3 month examination, that Group III female had an ulcerated skin lesion on the abdomen next to the umbilicus. At the termination examinations, a Group I female and the Group III female had moderate dental calculi.

Mortality and Clinical Signs

Each animal was observed each day once in the morning and once in the afternoon throughout the study for changes in general appearance or behavior. Observations of discharges, urine and bowels characterization and appetite were also noted.

Results – All animals survived the study through month 10. Overall, the health of the animals appeared normal throughout the study with the exception of a female from Group III to be discussed. All animals were noted to be lethargic on the afternoon of surgery, but they had returned to normal by the next day. This was postulated by the conducting lab to be related to the potential sedative effect of the buprenorphine within the test article, with which this reviewer agrees. Other effects were related to physical trauma and not unexpected.

On Day 321, a group III female was noted to be lethargic, cold and unresponsive. This animal was euthanatized for humane reasons. A necropsy was conducted and tissues were collected and processed for microscopic evaluation. Macroscopic evaluation showed that the left apical and cardiac lung lobes were completely consolidated. These

severe lung changes were consistent with aspiration pneumonia. Microscopically the sections of lung contained necrosis, hemorrhage and edema fluid, as well as large bacterial colonies. These findings were supportive of aspiration pneumonia. While the exact cause of death was not determined, the conducting personnel speculated that sedation associated with anesthetic procedures may have caused diminished swallowing reflexes at the time, resulting in food or material entering the respiratory tree. Speculation seems reasonable to this reviewer.

Body Weights

Body weights were recorded prior to implantation, at Day 1, and 7, week 4, then monthly thereafter, the day prior to termination (pre-fasted weight) and the day of termination (fasted weight).

Results - In general, the body weight of each animal remained constant for the duration of the study. Individual weight gain and group mean body weights for both male and female dogs were considered to be clinically acceptable following treatment for dogs of this breed and age. The Group III female that was euthanized had weight loss at month 9 and at termination that was considered to be associated with the clinical condition of diarrhea and pneumonia, respectively.

Feed Consumption

Food consumption was measured at Days 1 and 7 and monthly. The animals were fed a measured amount of feed in the morning of one day. On the morning of the following day, the remaining food was measured.

Results - The food consumption was considered slightly reduced on Day 1. This is consistent with the potential sedative affect of the buprenorphine within the test article. While some variation was noted in food consumption for individual animals at the various intervals there was no clear difference in food consumption between the groups

Ophthalmoscopy

Ophthalmic examinations were conducted at pre-treatment, months 1, 3, 6 and at termination.

Results - The ophthalmic examinations revealed no abnormalities to any of the structures of the eye.

ECG - none

Hematology, Clinical Chemistry, and Urinalysis

Blood and urine specimens were collected prior to implantation, at Day 1, monthly for the first 6 months and at termination. Blood and urine specimens were evaluated for

routine hematology, clinical chemistry, and urinalysis. These analyses were conducted in accordance with the GLP regulations.

Hematology (CBC with differential)	Clinical Chemistry (Diagnostic - Multi Chem)
Bands	Albumin/Globulin Ratio (ALB/GLOB)
Basophils (BASO)	Amylase, serum (AMY)
Albumin (ALB)	Alkaline Phosphates (ALP)
Eosinophils (EOS)	Bilirubin, total (TOT BIL)
Hematocrit (HCT)	Blood Urea Nitrogen (BUN)
Hemoglobin (HGB)	BUN/Creatinine Ratio (BUN/CR)
Lymphocytes (LYMPH)	Mean Corpuscular Hemoglobin
Mean Corpuscular Hemoglobin (MCH)	Concentration (MCHC)
Mean Cell Volume (MCV)	Calcium (Ca)
Monocytes (MONO)	Chloride (Cl)
Neutrophils (NEUTRO)	Cholesterol (CHOL)
Red Blood Cell Count (RBC)	Creatinine serum (CR)
White Blood Cell Count (WBC)	γ -glutamyl transferase (GGT)
Immunoglobulin Analysis - IgA IgG IgM	Globulin, total (TOT GLOB)
Uric Acid (UA)	Glucose, serum (GLU)
	Lactate dehydrogenase (LDH)
	Phosphorus (P)
	Potassium (K)
	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
	Sodium (Na)
	Total protein (TOT PRO)
	Triglycerides (TRI)
	Creatinine (CK)
<u>Urinalysis (Routine with microscopic evaluation on positives)</u>	

Color	Appearance	Specific Gravity
pH	Protein	Glucose
Ketones	Occult Blood	Leukocyte Esterase
Nitrite	Bilirubin	Urobilinogen

Note: If protein, leukocyte, occult blood, nitrite, and turbidity were all negative, a microscopic examination was not conducted.

Results - All values fell within those ranges established as normal for this species. There were no changes in clinical pathology parameters in either sex that were considered to be related to treatment with the test article.

Gross Pathology

Group II dogs were sacrificed on day 309 (8 months exposure and 2 months recovery) and groups I and III were sacrificed on day 359 (12 months exposure) except a group III female which was euthanized for humane reasons (lethargic and unresponsive) on day 321.

A necropsy of the thoracic and abdominal viscera, and pelvic cavity was conducted. The adrenal glands, brain, liver, kidneys, heart, spleen, and gonads were weighed prior to fixation. A full battery of remaining tissues was collected and fixed without assessment. The skin adjacent to the implant site was incised and reflected to expose the implant sites. The subcutaneous tissue and the area around each implant were examined. An incision over the implant was made to expose the sample. The samples were removed and the implant site was observed. Any reaction at the implant site was documented. Four implant sites were collected for microscopic evaluation, while the remaining sites were forwarded to the sponsor for further evaluation which will be reported separately.

Results - For Groups I and III there was no evidence of inflammation or infection noted at the implant sites. For Group II, the test article was previously removed and the implant sites could not be identified.

Organ Weights

The adrenal glands, brain, liver, kidneys, heart, spleen, and gonads were weighed prior to fixation. Paired organs were weighed together.

Results - Absolute organ weights and organ to body weight ratios were similar between and within groups. There were no findings that would be considered to be test article related.

Histopathology

Adequate Battery – no (an adequate battery was saved but not evaluated)

Peer Review – no

The tissues were preserved but, per the protocol, routine microscopic evaluation was not conducted except for four implant sites which were collected for microscopic evaluation, while the remaining sites were forwarded to the sponsor for possible further evaluation.

Histological Findings

For the Group III female that was euthanized as a result of her moribund condition, sections of lung contained necrosis, hemorrhage and edema fluid, as well as large bacterial colonies. These findings were supportive of aspirate pneumonia and not considered related to test implants.

Microscopic evaluation of the saved dose sites was not conducted at the sponsor's discretion.

Special Evaluation - none

Toxicokinetics

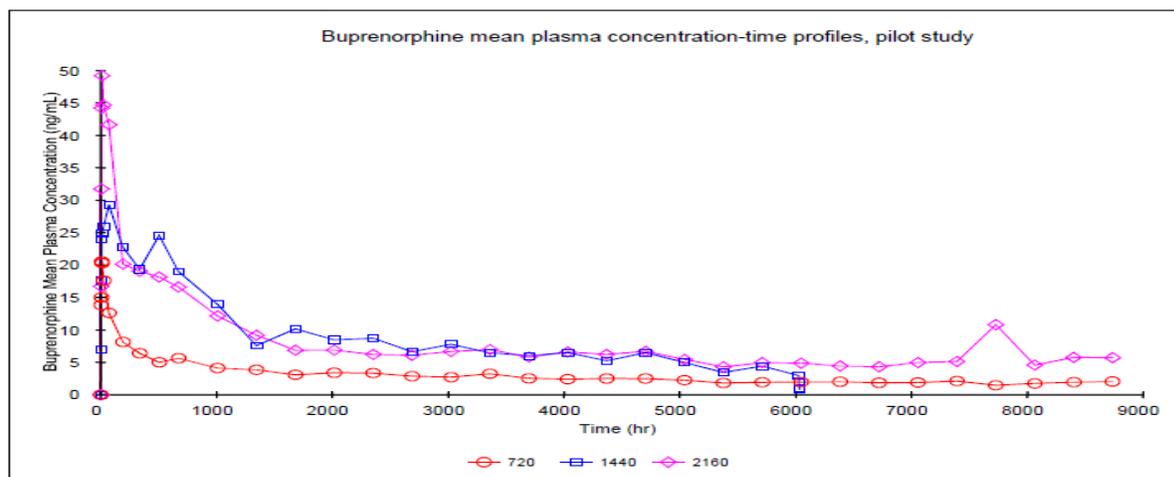
Additional blood specimens were collected at 0, 3, 6, 9, 12, and 24 hours, on Days 3, 8, and 14, weekly for the first month and then bi-weekly thereafter. Blood specimens were also collected from 10 month animals immediately, 3, 6, 9, 12, 24 hours, daily for the first week, and at Week 2, 3, and 4 following explant of the test rods. Blood samples were collected via venipuncture. The specimens were submitted to the sponsor Titan Pharmaceuticals for pharmacokinetic analysis.

Approximately 8 months after implantation, the implants were removed from the dogs in Group II. The dogs were anesthetized and the implants were removed and returned to the sponsor for further evaluation. The animals remained on study for approximately 10 months from the day of implantation (approximately 2 months after implant removal). The rods were explanted in order to obtain data regarding the drug clearance time following prolonged steady state levels of buprenorphine.

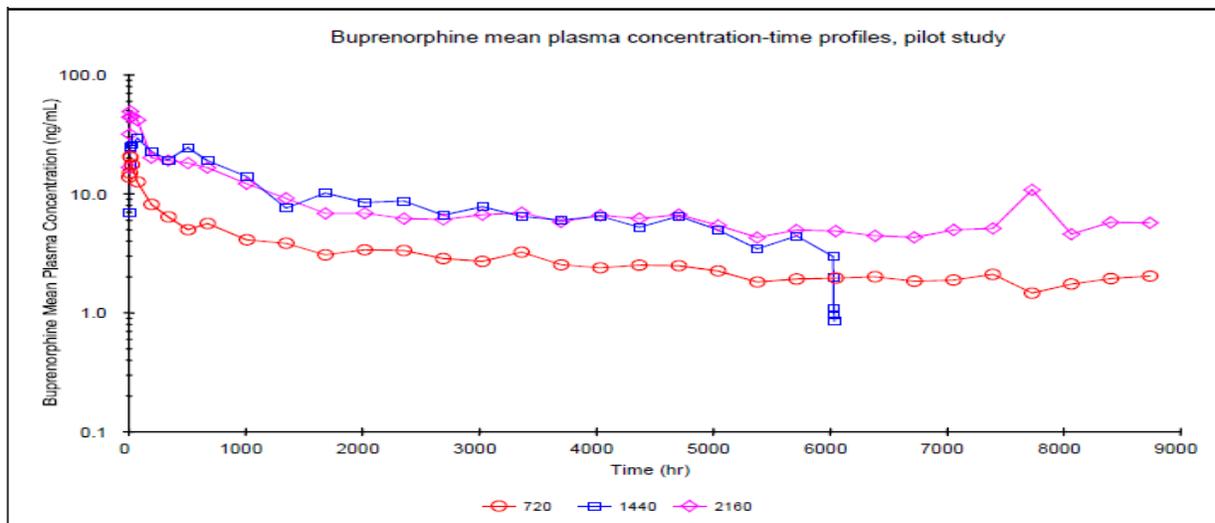
Results – After initial elevated levels of buprenorphine, values were reduced to steady levels by 1-2 months (see linear and semi-log plasma concentration profiles). Note the rapid decrease in blood levels at 8 months when the implants were removed for Group II. Group I is 720, Group II is 1440, & Group III is 2160, referring to approximate mg of buprenorphine in the total number of implants per group. Note the rapid decrease in blood levels of buprenorphine after removal of the implants for group II at 8 months.

Mean Plasma Concentration-Time Profiles (Pilot Study)

(upper panel: Linear Scale; lower panel: Semi-Log Scale)



- Applicant figure



- Applicant figure

Toxicokinetic values were generally dose proportional for the number of implants for Group I (8 implants), Group II (16 implants), and Group III (24 implants) for C_{max}, but sub-proportional for group 3 for AUC as the increase in AUC was ~20% for a 50% increase in the number of implants which could indicate a plateau/saturation effect.

Summary Table of Non-compartmental PK Parameters for Buprenorphine (Pilot Study)

Parameter	Units	Group 1, n=2	Group 2, n=2	Group 3, n=2
C _{max} (mean [SD])	ng/mL	21.55 (0.21)	36.10 (3.4)	54.50 (3.4)
T _{max} (median [range])	hr	10.5 (8.0-12.0)	256.5 (8.0-504)	18.0 (12.0-24.0)
t _{1/2} (mean [SD])	hr	ND	8.63 (0.8)	ND
AUC _{0-∞} (mean [SD])	ng.hr/mL	25761 (2591)	54419 (23415)	64177 (10451)
AUC ₀₋₆ (mean [SD])	ng.hr/mL	ND	64430 (23417)	ND
V _Z /F (mean [SD])	L	ND	371.82 (128.9)	ND
CL/F (mean [SD])	L/hr	ND	30.45 (13.1)	ND

Summary of the non-compartmental PK parameters, mean (SD), derived from plasma concentration time data, following subcutaneous implantation of 8 (Group 1, buprenorphine HCl at 720 mg), 16 (Group 2, buprenorphine HCl at 1440 mg) or 24 (Group 3, buprenorphine HCl at 2160 mg) buprenorphine HCl/EVA implants in 6 dogs in pilot study.

- Applicant table

Dosing Solution Analysis - Test materials were supplied by the sponsor and analyses supported stability.

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Note on following study validity: see appendix at end of this document (section 12) for evaluation by FDA, CDER, Division of Scientific Investigation of the response from the conducting laboratory NAMSA (North American Science Associates, Inc.) regarding 2006 FDA Warning Letter Related to Study 01T-06823-00 "Chronic Toxicity Study of Buprenorphine Delivery System Implanted Subcutaneously for 10 Months in Dogs" submitted with IND 70,852 and NDA 204442 by the sponsor, Titan Pharmaceuticals, Inc., South San Francisco, CA. Based on the NAMSA response also included in this report's Protocol and Report Amendments and the subsequent FDA review, the presented data is generally considered valid, most notably for the 10 month exposure groups.

Study title: Chronic Study of Buprenorphine Delivery System Implanted Subcutaneously for 10 Months in Dogs

Study no.: Lab No. 01T 06823 00
Titan Study No. PRO-NTR-0215
- toxicokinetic study number TIT687003
((b) (4) for Titan), July 19, 2005.

Study report location: eCTD in DARRTS

Conducting laboratory and location: NAMSA
2261 Tracy Road
Northwood, OH 43619-1397

Date of study initiation: July 9, 2001

GLP compliance: yes

QA statement: yes

Drug, lot #, and % purity: - Buprenorphine DDS (BDDS), lots 13657-06, 13933-17, 13933-19, 13922-22, 13657-44 & 13657-51, 90 mg \pm 10% buprenorphine HCl in each BDDS
- Ethylene Vinyl Acetate (EVA), lot 13657-22, 13657-31, & 13657-71purity not found

Key Study Findings:

- Male and female dogs were administered 24 placebo control (Ethylene Vinyl Acetate - EVA) or test (Buprenorphine Drug Delivery System - BDDS) rods to their backs in 3 groups of 8. At 8.5 months, 6 additional rods were administered to a different location on the back of the test group. Four animals/sex/group were sacrificed at 1 month and 10 months. A full battery of toxicological assessments was conducted in this study.
- Aside from transient lethargy and a transient reduction in food consumption, both assumed to be due to the known pharmacological effects of buprenorphine, there

were no test article-related clinical symptoms following subcutaneous implantation in the dog. No treatment-related mortality occurred.

- Other measured indices (e.g., body weights, food consumption, and clinical pathology) were similar for control and test animals and were reported to be within acceptable limits.
- Microscopic evaluation of tissues from the animals revealed no evidence of a systemic treatment-related response as the tissues from the test group were similar with those from the control group.
- Absolute irritation scoring identified the EVA control implants as moderately irritating and the BDDS test implants as moderately to severely irritating at 1 month using the ISO irritation numerical irritation score. At 1.5 months (rods administered at 8.5 months), the BDDS test implants were slight to moderately irritating (no 1.5 month placebo). At 10 months, the EVA control implants were slightly irritating and the BDDS test implants were slight to moderately irritating. In a strict use of the ISO test protocol method, the score for the control (EVA) is subtracted from test (BDDS) score for the overall irritant score for the drug product. On this basis, BDDS is non-irritating to slightly irritating during the study, descriptors we include for reporting completeness purposes but will not use in describing the local toxicity of the test material or placebo.
- The only notable toxicity was local toxicity after dosing with 24 rods placebo for 1 month & 10 months and 24 BDDS rods for 1 month, 1.5 months, & 10 months. Partially reduced irritation occurred over the course of the study for placebo rods (slight to moderately irritating at 1 month to slightly irritating at 10 months) and the BDDS rods (moderately to severely irritating at 1 months to slight to moderately irritating at 1.5 & 10 months). Plasma steady state levels (C_{ss}) of buprenorphine were ~10 ng/mL over the study time period. Over the course of the study, a C_{max} of 80 ng/mL within a few days after administration and the AUC_{0-24} was 254 ng•h/mL for 10 months.

Methods																																				
Doses:	<table border="1"> <thead> <tr> <th>Group</th> <th>Treatment</th> <th>Estimated dose of Buprenorphine (mg/kg)</th> <th>Number of Dogs</th> <th>Termination Interval</th> <th>Number of Implants</th> <th>Number of Additional Implants</th> </tr> </thead> <tbody> <tr> <td>Control</td> <td>EVA</td> <td>0</td> <td>4 Male, 4 Female</td> <td>1 month</td> <td>24</td> <td>0</td> </tr> <tr> <td>Test</td> <td>BDDS</td> <td>226*</td> <td>4 Male, 4 Female</td> <td>1 month</td> <td>24</td> <td>0</td> </tr> <tr> <td>Control</td> <td>EVA</td> <td>0</td> <td>4 Male, 4 Female</td> <td>10 months</td> <td>24</td> <td>0</td> </tr> <tr> <td>Test</td> <td>BDDS</td> <td>226*</td> <td>4 Male, 4 Female</td> <td>10 months</td> <td>24</td> <td>6</td> </tr> </tbody> </table> <p>* Estimated dose based upon an average body weight of 10 kg respectively</p> <ul style="list-style-type: none"> - 10 month BDDS groups received 6 more rods at 8.5 months to “maintain” desired exposure levels 1) 0 (24 EVA implants) and 226 (24 BDDS implants) mg/kg for a 1 month sacrifice 2) 0 (24 EVA implants) and 226 (24 BDDS implants) mg/kg for a 10 months sacrifice - 10 month BDDS group received 6 additional 	Group	Treatment	Estimated dose of Buprenorphine (mg/kg)	Number of Dogs	Termination Interval	Number of Implants	Number of Additional Implants	Control	EVA	0	4 Male, 4 Female	1 month	24	0	Test	BDDS	226*	4 Male, 4 Female	1 month	24	0	Control	EVA	0	4 Male, 4 Female	10 months	24	0	Test	BDDS	226*	4 Male, 4 Female	10 months	24	6
Group	Treatment	Estimated dose of Buprenorphine (mg/kg)	Number of Dogs	Termination Interval	Number of Implants	Number of Additional Implants																														
Control	EVA	0	4 Male, 4 Female	1 month	24	0																														
Test	BDDS	226*	4 Male, 4 Female	1 month	24	0																														
Control	EVA	0	4 Male, 4 Female	10 months	24	0																														
Test	BDDS	226*	4 Male, 4 Female	10 months	24	6																														

	rods at 8.5 months which were implanted to maintain desired systemic exposure level - number of implants intended to be multiple levels of proposed 4-5 rods for 6 months in humans
Frequency of dosing:	Single dose (second single dose for 8.5 month BDDS implant sites)
Route of administration:	Subcutaneously to the back by trocar method
Dose volume:	NA (8 rods/site in spiral pattern at 3 sites in the back)
Formulation/Vehicle:	EVA rods - the polymer is described as inert and not biodegradable within the body, with little or no reaction following implantation.
Species/Strain:	Beagle dogs
Number/Sex/Group:	4/sex/group for 1 month and 10 month sacrifices
Age:	Young adult
Weight:	9-12 kg
Satellite groups:	none
Unique study design:	The 10 month BDDS group received 6 additional rods at 8.5 months which were implanted to maintain a desired systemic exposure level of ~10 ng/mL of buprenorphine
Deviation from study protocol:	- FDA CDER Division of Scientific Investigations (DSI) audited the conducting laboratory for this study and determined that the study was invalid in 2005 but then study was considered valid/suitable for review in 2013 after DSI review of sponsor's response to 2005 DSI audit in 2006 (see appendix in section 12 for full DSI report)

Observations and Results

Mortality

Each animal was observed each day, once in the morning and once in the afternoon throughout the study.

One control male was found dead on day 84 with prior normal appearance and behavior. No cause of death could be determined.

Physical Examinations

Physical examinations were conducted at 11 days prior to implantation for the 10 month group, 13 days prior to implantation for the 1 month group, and at 1, 3, 6, & 10 months during the study. The physical exam included observation of the animal, as well as palpation and auscultation.

All animals appeared healthy and there were no treatment-related effects noted at the physical examinations.

Clinical Signs

Each animal was observed each day, once in the morning and once in the afternoon throughout the study for changes in general appearance or behavior. Observations of discharges, urine and bowels characterization and appetite were also noted.

Control animals appeared normal. All buprenorphine group animals were noted to be lethargic on the afternoon of the original surgery, but they had returned to normal by the next day. This observation, as well as diarrhea, was apparently a pharmacological effect of the buprenorphine within the test article. Reversible, local irritation was observed in some control and treated animals.

SUMMARY OF CLINICAL OBSERVATIONS OF INDIVIDUAL DOGS

1 Month Group

Animal Number	Gender	Group	Clinical Observations (Days 0-30)
CRIADF	Male	Control	Animal noted with an irritated area on the right front shoulder on Day 3 (present until healed on Day 27), otherwise appeared normal.
CRIAES	Male	Control	Appeared Normal
CRIAGF	Male	Control	Appeared Normal
CRIATR	Male	Control	Appeared Normal
CRIAAG	Female	Control	Appeared Normal
CRIACX	Female	Control	Appeared Normal
CRIAFX	Female	Control	Appeared Normal
CRIAKL	Female	Control	Appeared Normal
CRIABM	Male	Test	Animal was lethargic at Day 0 afternoon observations, had diarrhea on Day 2, otherwise appeared normal.
CRIAFJ	Male	Test	Animal was lethargic at Day 0 afternoon observations, otherwise appeared normal.
CRIAHI	Male	Test	Animal was lethargic at the Day 0 afternoon observations, otherwise appeared normal.
CRIAKU	Male	Test	Animal was lethargic at Day 0 afternoon observation, had an area of irritation on the right shoulder and mid-dorsal region at Day 7. A discharge developed at Day 26 and the animal was placed on oral antibiotics (Cefaclor 250mg three times a day for 5 days). The irritation continued through termination, otherwise appeared normal.
CRIALD	Female	Test	Animal was lethargic at Day 0 afternoon observations, otherwise appeared normal.
CRIALV	Female	Test	Animal was lethargic at Day 0 afternoon observations, otherwise appeared normal.
CRIASC	Female	Test	Animal was lethargic at Day 0 afternoon observations, otherwise appeared normal.
CRIASE	Female	Test	Animal was lethargic at Day 0 afternoon observations, otherwise appeared normal.

- Applicant table

SUMMARY OF CLINICAL OBSERVATIONS OF INDIVIDUAL DOGS10 Month Group

Animal Number	Gender	Group	Clinical Observations (Days 0-297)
CRIAEX	Male	Control	Appeared normal
CRIAGJ	Male	Control	Appeared normal
CRIAJK	Male	Control	Appeared normal on days 0-83; animal found dead on day 84.
CRIANR	Male	Control	Appeared normal
CRIAAT	Female	Control	Appeared normal
CRIAGB	Female	Control	Appeared normal
CRIALL	Female	Control	Appeared normal
CRIANZ	Female	Control	Appeared normal
CRIACB	Male	Test	Animal was lethargic at Day 0 afternoon observations, otherwise appeared normal
CRIACR	Male	Test	Animal was noted to be lethargic and have diarrhea at the afternoon observations on day 0. An erosion on the skin associated with the implant site; treated with antibiotic ointment on days 15-22; otherwise appeared normal
CRIAKH	Male	Test	Animal was lethargic at Day 0 afternoon observations, otherwise appeared normal
CRIAAU	Male	Test	Animal was lethargic at Day 0 afternoon observations, otherwise appeared normal
CRIADH	Female	Test	Animal was lethargic at Day 0 afternoon observations. Animal was noted to have numerous scabs on ventral neck area from previous fur clippings which healed by day 10; otherwise appeared normal
CRIAHA	Female	Test	Animal was lethargic at Day 0 afternoon observations, otherwise appeared normal
CRIAHX	Female	Test	Animal was lethargic at Day 0 afternoon observations, otherwise appeared normal
CRIALH	Female	Test	Animal was lethargic on Day 0 afternoon observations. Animal was found limping and not putting weight on left rear leg at day 5 afternoon observations. Animal appeared to have erythema and slight swelling on the ventral thorax on day 212; treated with a non-steroidal antibiotic (Vetro-biotic) on days 213-227; otherwise appeared normal

- Applicant table

Body Weights

Body weights were recorded the day of rod implantation, on Day 1, bi-weekly during the first 4 weeks, then monthly thereafter, the day prior to termination (pre-fasted weight), and the day of termination (fasted weight).

There were no apparent treatment-related effects of body weights.

SUMMARY OF BODY WEIGHT DATA (kg)

Interval	Gender	N=	Control			Test		
			Mean	±	SD	Mean	±	SD
Day 0	Male	8	10	±	1	10	±	1
Day 1	Male	8	10	±	1	10	±	1
Week 2	Male	8	11	±	1	10	±	1
Week 4 (prefast)	Male	8	11	±	1	10	±	1
Week 4 (fasted)	Male	4	10	±	1	10	±	1
Month 2	Male	4	11	±	1	10	±	1
Month 3	Male	4†	11	±	1	10	±	1
Month 4	Male	4†	11	±	1	11	±	1
Month 5	Male	4†	12	±	1	10	±	0
Month 6	Male	4†	12	±	0	10	±	0
Month 7	Male	4†	12	±	0	10	±	0
Month 8	Male	4†	12	±	0	10	±	0
Month 9*	Male	4†	12	±	1	10	±	0
Month 10 (prefast)	Male	4†	12	±	1	11	±	1
Month 10 (fasted)	Male	4†	12	±	0	10	±	0
Day 0	Female	8	10	±	1	10	±	1
Day 1	Female	8	10	±	1	9	±	1
Week 2*	Female	8	10	±	1	9	±	1
Week 4 (prefast)*	Female	8	10	±	1	9	±	1
Week 4 (fasted)	Female	4	8	±	1	10	±	1
Month 2	Female	4	9	±	1	9	±	1
Month 3	Female	4	10	±	1	9	±	1
Month 4	Female	4	10	±	1	9	±	1
Month 5	Female	4	10	±	1	9	±	1
Month 6	Female	4	10	±	1	9	±	1
Month 7	Female	8	10	±	1	9	±	1
Month 8	Female	8	10	±	0	10	±	1
Month 9*	Female	8	10	±	0	9	±	1
Month 10 (prefast)	Female	8	10	±	1	10	±	1
Month 10 (fasted)	Female	4	9	±	0	9	±	1

SD = Standard Deviation

* = Data showed a statistically significant difference between control and test groups (p<0.05)

† = n = 3 for the control male group

- Applicant table

Feed Consumption

Food consumption was measured on Days 1 & 7 and monthly thereafter. The procedures involved providing animals a measured amount offered in the morning of one day. Then on the morning of the following day, the remaining food was measured.

There were no apparent treatment-related effects on food consumption except for an early reduction in body weight resulting from initial buprenorphine dosing.

SUMMARY OF FOOD CONSUMPTION (g)

Interval	Gender	N=	Control		Test	
			Mean ± SD		Mean ± SD	
Day 1	Male	8	395.5	± 105.8	26.0	± 39.2
Day 7	Male	8	420.6	± 83.3	297.4	± 104.2
Month 2	Male	4	357.1	± 57.0	439.0	± 15.9
Interval	Gender	N=	Control		Test	
			Mean ± SD		Mean ± SD	
Day 1	Female	8	202.1	± 62.5	2.3	± 3.0
Day 7	Female	8	327.5	± 104.4	203.8	± 150.2
Month 2	Female	4	256.3	± 62.5	271.5	± 54.3

- modified Applicant table

Ophthalmoscopy

Ophthalmic examinations, were conducted at 11 days prior to implantation for the 10 month group, 13 days prior to implantation for the 1 month group, and at 1, 3, & 6 months during the study. The ophthalmic exam included slit-lamp and indirect Ophthalmoscopy examinations.

The ophthalmic examinations were reported to reveal no abnormalities to any of the structures of the eyes as listed in the Ocular Report.

Neurology

Neurologic examinations, were conducted at 11 days prior to implantation for the 10 month group, 13 days prior to implantation for the 1 month group, and at 1, 3, & 6 months during the study. The neurologic exam included observation of behavior, gait, and reflexes.

All neurological examinations were reported to be within normal limits as listed in the Neurology Report.

ECG – none conducted

Clinical Pathology - Blood and urine specimens were collected 8-11 days prior to implantation, on Day 1, monthly, and at termination and forwarded to a reference clinical pathology laboratory.

Hematology

The following hematology parameters (CBC with differential) were evaluated:

Bands	
Basophils (BASO)	Mean Corpuscular Hemoglobin
Eosinophils (EOS)	Concentration (MCHC)
Hematocrit (HCT)	Mean Cell Volume (MCV)
Hemoglobin (HGB)	Immunoglobulin Analysis
Lymphocytes (LYMPH)	IgA
(MCH)	IgG
	IgM

Hematologic parameters revealed no treatment-related differences between the test and control groups, and all mean values were within a normal range. While several parameters were noted with differences, these differences were typically in just one sex and not consistent over several intervals. Most of changes noted occurred at the Day 1 interval. As compared to pretreatment values, at Day 1, for all groups, there tended to be a minor increase in the total leukocyte counts due to a relative neutrophilia and slight lymphopenia. This pattern was more pronounced in the test animals vs. the controls. This pattern of leukocytosis with a relative decrease in lymphocytes and increase in neutrophils was considered by the sponsor to be indicative of a temporary stress leukogram (an increase of neutrophils without a left shift and a decrease of lymphocytes and eosinophils as a result of systemic stress. The reason for this change being more pronounced (and statistically significant) in the test animals as opposed to the controls was attributed to the prolonged sedation following the implant procedure and associated anesthesia. This sedation was directly related to the known sedative and analgesic properties of the drug, buprenorphine within the test article. Collectively, analysis of the data revealed no changes or abnormalities suggestive of a treatment related effect (other than mentioned above) nor was there any significant change from pretreatment levels seen at any of the various intervals. Presented in the following table are those parameters showing statistically significant differences between the test and respective control group and the sporadic nature of the changes.

Parameter	Sex	Day 1	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10
RBC	Female	↑			↑	↑						↑
HGB	Female	↑			↑	↑						
HCT	Female	↑			↑	↑						
MCHC	Male	↑										
WBC	Male	↑										
Neutrophil	Male	↑										
	Female	↑										
Lymphocyte	Male	↓										
	Female	↓										
Monocyte	Male									↓	↓	↑
Eosinophil	Male								↑			↑
	Female	↓									↓	

↑ = value for parameter statistically higher than the concurrent control group
 ↓ = value for parameter statistically lower than the concurrent control group

- Applicant table

Clinical Chemistry

The following clinical chemistry parameters (Diagnostic - Multi Chem) were evaluated:

- | | |
|-----------------------------------|----------------------------------|
| Albumin/Globulin Ratio (ALB/GLOB) | Albumin (ALB) |
| Alkaline Phosphates (ALP) | Amylase, serum (AMY) |
| Bilirubin, total (TOT BIL) | Blood Urea Nitrogen (BUN) |
| BUN/Creatinine Ratio (BUN/CR) | Calcium (Ca) |
| Chloride (Cl) | Cholesterol (CHOL) |
| Creatinine kinase (CK) | γ-glutamyl transferase (GGT) |
| Lactate dehydrogenase (LDH) | Phosphorus (P) |
| Potassium (K) | Aspartate aminotransferase (AST) |
| Alanine aminotransferase (ALT) | Sodium (Na) |
| Total protein (TOT PRO) | Triglycerides (TRI) |

A review of all clinical chemistry parameters revealed no toxicologically relevant differences between the test and control groups. All mean values were within a normal expected range. While several parameters were noted with differences, these differences were typically in just one sex for one group. If both groups had differences, the direction of the difference was different between sexes and/or groups. Collectively, no treatment-related effects were observed. More importantly, no real changes from pretreatment levels were observed as effects from the implanted rod by itself and the drug product are both important safety issues. As a result, the differences noted were attributed to random biological variation and the small group sizes. Presented in the following table are those parameters showing statistically significant differences between the test and respective control group and the sporadic nature of the changes.

Parameter	Sex	Day 1	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10
BUN	Female					↑						
CR	Male				↑							
BUN/CR	Female					↑						
Ca	Male					↓		↓				
	Female	↑										
P	Male						↓					
	Female	↑								↓		
Na	Male	↑										
K	Male	↓										
	Female	↓								↓		
Cl	Male	↓	↑									
	Female	↓			↓		↓	↓			↓	
ALP	Male		↓				↓					
	Female	↑				↓						
LDH	Male						↓					
AST	Male	↓										
	Female			↑								↑
ALT	Male		↓									
	Female	↑		↑								
TOT PRO	Male		↓			↓				↓		
	Female	↑				↑		↑				
ALB	Male	↑										
TOT GLOB	Male		↓							↓		
	Female					↑		↑				
Alb/Glob	Male					↑						
CHOL	Male		↓	↓		↓	↓			↓		↓
	Female			↓								
TRI	Female	↓	↓									
GLU	Male			↑					↑			
	Female	↑										
IgM	Male									↓	↓	

↑ = value for parameter statistically higher than the concurrent control group
 ↓ = value for parameter statistically lower than the concurrent control group

- Applicant table

Urinalysis

The following urinalysis parameters were evaluated with microscopic evaluations in positives. If protein, leukocyte, occult blood, nitrite and turbidity were all negative, a microscopic examination was not performed.

Color Ketones
 Specific Gravity Leukocyte esterase
 Protein Bilirubin

Appearance Occult Blood
 pH Nitrite
 Glucose Urobilinogen

While some fluctuation was seen in the various parameters, all values were within a normal expected range and there were no patterns of change suggestive of toxic or pathologic effects.

Necropsy – conducted at 1 and 10 months after initial implantation.

Implant Sites - The skin adjacent to the implant site was incised and reflected to expose the implant sites. The subcutaneous tissue and the area around each implant were examined. An incision over the implant was made to expose the sample. The sample was removed and the implant site was observed. Any reaction at the implant site was documented. Four implant sites (4 test and 4 control) were collected for microscopic evaluation, while the remaining sites were forwarded to the sponsor for further evaluation which may be reported separately. The implant sites were scored for irritation severity using ISO and ASTM guidelines.

A gross examination of the abdominal, thoracic viscera, and pelvic cavity was conducted at 1 and 10 months after initial implantation.

The following tissues were collected:

Brain (5 sections): Transverse section through right cerebrum through hippocampus and optic chiasm
Transverse section through left cerebrum through lateral geniculate body and cus cerebi
Transverse through superior and inferior colliculus and lateral lemniscus
Transverse through mid-cerebellum through inferior cerebellar peduncle and midbrain
Pituitary

Spinal cord: cervical, thoracic and lumbar cord

Sciatic nerve: Left

Muscle (other tissues with muscle include heart, intestine, etc):

Peripheral skeletal muscle (semimembranosus)

Diaphragm

Tongue - Cranial and caudal

Eyes: Standard sagittal section (optic nerve/ disk, sclera, iris, retina, cornea, conjunctiva)

Salivary gland: Parotid

Esophagus: Cranial and caudal with trachea attached for cranial section

Stomach: Fundus, body and pylorus

Duodenum: Standard section with pancreas attached

Jejunum: middle

Ileum: with cecum

Cecum: see ileum

Colon: midway

Rectum: distal

Liver: 1 section from left lateral, right medial (with gall bladder attached), and right lateral
Gall bladder: see liver
Spleen: 2 random selections
Kidney: both
Urinary bladder: Apex and mid-body
Endocrine: Pancreas - see duodenum
Thyroid/parathyroid - both glands
Adrenal glands - both glands
Lymphoid tissues: Mandibular, mesenteric, and ileocolocecal
Thymus (if present)
Tonsil -
Heart: Left and right ventricular free wall (with papillary muscles)
Intraventricular septum
Thoracic aorta
Larynx/pharynx: 1 cross-section
Trachea: see esophagus
Lung: left cranial lobe and right caudal
Hematopoietic cells/bone: Sternum
Femur
Testis: Cross section with epididymis
Prostate:
Ovaries: both
Uterus: each horn
Mammary gland: Inguinal section (included with skin section)
Skin: See above
Implant sites- all
All macroscopic lesions in addition to above tissues

Macroscopic Observations of Implant Sites:

At the 1 month interval necropsy after reflection of the skin over the implant sites, two test dogs were noted to have evidence of inflammation and infection, described as either cellulitis or abscess. Approximately 30-40% of the implants were broken upon removal from the tissue. At the 10 month interval no evidence of inflammation or infection was observed. Upon removal, it was noted that 70% of the original test implants and 8.3% of the additional test implants implanted at 8.5 months were broken in 2-3 pieces. No control implants were broken. Note that in human clinical studies broken implants were also observed only in BDDS groups and were partly attributed to the removal technique which was improved over time and resulted in reduced broken rods.

Supporting macroscopic observations tables at 1 month and 10 months and for broken rods follow. Additional macroscopic information contained in the Gross Pathology section that follows the tables.

SUMMARY OF IMPLANT OBSERVATIONS AND NECROPSY FINDINGS OF INDIVIDUAL DOGS1 Month Group

Animal Number	Gender	Group	Observation of Implant Sites	Necropsy (Systemic Tissue) (Day 30)
CRIADF	Male	Control	Macroscopically normal	Minimal valvular endocardiosis of mitral valve; otherwise macroscopically normal
CRIAES	Male	Control	Macroscopically normal	Macroscopically normal
CRIAGF	Male	Control	Macroscopically normal	Macroscopically normal
CRIATR	Male	Control	Macroscopically normal	Macroscopically normal
CRIAAG	Female	Control	Macroscopically normal	Macroscopically normal
CRIACX	Female	Control	Macroscopically normal	Macroscopically normal
CRIAFX	Female	Control	Macroscopically normal	Macroscopically normal
CRIAKL	Female	Control	Macroscopically normal	Macroscopically normal
CRIABM	Male	Test	Macroscopically normal	Macroscopically normal
CRIAFJ	Male	Test	On caudal group of implants, a 2 ½" by 1" x 1" subcutaneous cellulitis area formed (not connected with the implants); cellulitis area on the middle group of implants 3" x 4" x 2" in size (connected with the implants); cranial site was macroscopically normal	Macroscopically normal
CRIAHI	Male	Test	Macroscopically normal	Macroscopically normal
CRIAKU	Male	Test	4 cm x 2 cm x 3 cm abscess at the middle group of implants, abscessed area in cranial group was 3 cm x 1 cm x 1 cm large and had an implant within it; caudal site was macroscopically normal	Macroscopically normal
CRIALD	Female	Test	Macroscopically normal	Macroscopically normal
CRIALV	Female	Test	Macroscopically normal	Macroscopically normal
CRIASC	Female	Test	Macroscopically normal	Macroscopically normal
CRIASE	Female	Test	Macroscopically normal	Macroscopically normal

- Applicant table

SUMMARY OF IMPLANT OBSERVATIONS AND NECROPSY FINDINGS OF INDIVIDUAL DOGS

10 Month Group

Animal Number	Gender	Group	Observation of Implant Sites	Necropsy (Systemic Tissue) (Day 297)
CRIAEX	Male	Control	Macroscopically normal	Macroscopically normal
CRIAGJ	Male	Control	Macroscopically normal	Macroscopically normal
CRIAJK	Male	Control	Macroscopically normal	Macroscopically normal
CRINANR	Male	Control	Macroscopically normal	Macroscopically normal
CRIAAT	Female	Control	Macroscopically normal	Macroscopically normal
CRIAGB	Female	Control	Macroscopically normal	Macroscopically normal
CRIALL	Female	Control	Macroscopically normal	Macroscopically normal
CRINANZ	Female	Control	Macroscopically normal	Macroscopically normal
CRICAB	Male	Test	Macroscopically normal	Thymus taken was only residual tissue; animal appeared to have limited body fat; otherwise macroscopically normal
CRICAR	Male	Test	Macroscopically normal	Macroscopically normal
CRIAKH	Male	Test	Macroscopically normal	Macroscopically normal
CRIAAU	Male	Test	Macroscopically normal	Macroscopically normal
CRIDAH	Female	Test	Macroscopically normal	Animal appeared thin; limited body fat; otherwise macroscopically normal
CRIAHA	Female	Test	Macroscopically normal	Macroscopically normal
CRIAHX	Female	Test	Macroscopically normal	Macroscopically normal
CRIALH	Female	Test	Macroscopically normal	Very little thymus noted; otherwise macroscopically normal

- Applicant table

SUMMARY OF BROKEN IMPLANT RODS

Animal	Group	Original # Broken/Total	Re-implant # Broken/Total
CRIAEX	Control	0/24	NA
CRIAGJ	Control	0/24	NA
CRINANR	Control	0/24	NA
CRIAAT	Control	0/24	NA
CRIAGB	Control	0/24	NA
CRIALL	Control	0/24	NA
CRICAB	Test	6/24	0/6
CRICAR	Test	20/24	2/6
CRIAKH	Test	23/24	0/6
CRIALH	Test	18/24	0/6
CRIAAU	Test	9/24	2/6
CRIAHA	Test	21/24	0/6
CRIDAH	Test	21/24	0/6
CRIAHX	Test	17/24	0/6

NA = Not Applicable

- re-implant means a new implant at a naive site at 8.5 months in the BDDS group

- modified Applicant table

Gross Pathology

A gross examination of the abdominal, thoracic viscera, and pelvic cavity was conducted at 1 and 10 months after initial implantation.

The necropsy of all dogs revealed no treatment-related pathologic changes or abnormalities. For the control animal found dead on day 84, congestion of the sclera, hemorrhagic and congested submandibular and axillary lymph nodes, dark mesenteric lymph nodes, distended stomach and small intestine, and a relatively small spleen were observed. A congested and slightly rounded liver, congested pancreas, slightly congested kidneys, and congestion of all lobes of the lungs were observed. While there was no obvious cause of death, based on the information available, the sponsor did not consider this death to be related to treatment. The reviewer considers the death incidental/not treatment-related.

Two male test dogs had macroscopically evident abscesses involving some of their implant sites (see histopathology section for table). The abscesses were characterized by accumulations of numerous vacuolated macrophages and lesser numbers of degenerative and viable neutrophils encapsulated by a band of fibrous tissue infiltrated by plasma cells and lymphocytes. Even though both animals to develop abscesses were male test animals, the abscesses were not a result of a treatment-effect or gender-based treatment-effect, but were considered by the sponsor to represent random complications involving the implantation of 24 test articles into an animal. One female test animal had microgranulomas within the test article-tissue interface of one of the four implant sites microscopically examined (see histopathology section table). The microgranulomas were very limited in size and extent and were not considered biologically significant by the sponsor. The reviewer has no reason to disagree.

Organ Weights

The adrenal glands, brain, liver, kidneys, heart, spleen, and gonads were weighed prior to fixation. Paired organs were weighed together.

Absolute organ weights and organ to body weight ratios were generally similar between and within test and control groups.

Histopathology

Adequate Battery - yes
Peer Review - no (blinded review)

Histological Findings (systemic) - Findings were generally within normal histological limits and essentially comparable between test and control animals. There was no evidence of systemic toxicity at 1 or 10 months post-implantation with additional test

article implanted at 8.5 months in test animals. The spontaneous background alterations and variations of normal observed microscopically in this study were considered to be within the expected range and failed to demonstrate a treatment-effect or a gender-based treatment-effect.

As noted in the gross pathology (macroscopic) results, two male test dogs had macroscopically evident abscesses involving some of their implant sites. The abscesses were characterized by accumulations of numerous vacuolated macrophages and lesser numbers of degenerative and viable neutrophils encapsulated by a band of fibrous tissue infiltrated by plasma cells and lymphocytes. Even though both animals to develop abscesses were male test animals, the abscesses were not considered by the sponsor to be a result of a treatment-effect or gender-based treatment-effect, but represent random complications involving the implantation of 24 test articles into an animal. One female test animal had microgranulomas within the test article-tissue interface of one of the four implant sites microscopically examined. The microgranulomas were very limited in size and extent and were not considered biologically significant by the sponsor.

MACROSCOPIC FINDINGS CORRELATED TO MICROSCOPIC FINDINGS

1 Month Termination

Animal Identification	Macroscopic Finding	Microscopic Finding
CRIADF (male, control)	Minimal multifocal nodular valvular endocardiosis (mitral valve)	Not present in evaluated sections due to the minimal and multifocal nature of the alteration
CRIAFJ (male, test)	Abscess at a single implant area	Abscess (see description in Results and Discussion section)
CRIAKU (male, test)	Abscess at a single implant area	Abscess (see description in Results and Discussion section)

10 Month Termination

Animal Identification	Macroscopic Finding	Microscopic Finding
CRIACB	Thin with limited body fat	Not applicable
	Thymus, residual tissue present	Normal involution

- BDDS dosed animal
- adapted Applicant table

Several histological findings were observed in the placebo and test groups that could be caused physical by trauma, foreign body reaction/inflammation, or some other cause. Regardless, there were no control-specific systemic effects so the observations are likely related to the EVA exposure with possible contribution from the buprenorphine (see tables). Mild diffuse lymphoid hyperplasia with minimal suppurative inflammation/tonsillitis was observed in at least 50% of the animals at 1 month and 100% of the animals at 10 months indicating that there is may be some progressive

inflammation that could be due to exposure to placebo or test materials. However, without a true negative control group, these findings could be background.

SUMMARY OF MICROSCOPIC ALTERATIONS BY TREATMENT GROUP AND GENDER
1 MONTH GROUP

(% = percent of animals with alterations)

Tissue/Organ Identification	Alteration	CONTROL MALE	CONTROL FEMALE	TEST MALE	TEST FEMALE
LUMBAR SPINE	Minimal bilateral dilated myelin sheaths	25%	75%	75%	50%
TONSIL	Mild diffuse lymphoid hyperplasia with suppurative inflammation	50%	75%	50%	100%

SUMMARY OF MICROSCOPIC ALTERATIONS BY TREATMENT GROUP AND GENDER
10 MONTH GROUP

(% = percent of animals with alterations)

Tissue/Organ Identification	Alteration	CONTROL MALE	CONTROL FEMALE	TEST MALE	TEST FEMALE
LIVER	Mild diffuse hepatocellular glycogen storage	100%	100%	100%	75%
TONSIL	Mild diffuse lymphoid hyperplasia with suppurative inflammation with minimal suppurative tonsillitis	100%	100%	100%	100%

- adapted Applicant tables

Histological Findings (local)

Irritation present at the implantation site due to the drug product (BDDS) was graded as to its severity using ISO 10993-6 and ASTM F 981 – 99 guidelines. One of the evaluation tables is listed in appendix 1 of this study review as an example. A note on the basis for the used scoring method is that implants are space-occupying masses that are associated with trauma from the implant procedure. The report notes that for Inert articles (not tested in this study) such as USP Negative Control plastic, implanted by a minimal traumatic procedure (trocar method), individual or group average ISO protocol-based irritation scores range between 5 and 12 up to 6 weeks post-implantation and between 1 and 10 after 6 weeks using the grading scheme used in this study. The negative control responses (EVA rods) were considered baseline responses using as no truly negative controls were used.

Scoring was as follows:

- non-irritant (0.0 up to 2.9)
- moderate irritant (9.0 up to 15.0)
- slight irritant (3.0 up to 8.9)
- severe irritant (>15)

The following calculations based on the subsequent tables list the group mean scores at 1 and 10 months. Taken individually, the EVA control implants were moderately irritating and the BDDS test implants were moderately to severely irritating at 1 month. At 10 months, the EVA control implants were slightly irritating and the BDDS test implants were slight to moderately irritating. Using the ISO irritation scoring method, where the score for the control (EVA) was subtracted from test (BDDS) score for the overall irritant score for the drug product, EVA and BDDS non-irritating to slightly irritating during the study as described below.

- males at 1 month: 12.4 (BDDS) – 10.6 (EVA) = 1.8 (non-irritant)
- females at 1 month: 16.4 - 9.65 = 6.75 (slight irritant)
- males at 10 months: 7.9 - 4.4 = 3.5 (slight irritant)
9.8 – 4.4 = 5.4 (slight irritant)
– re-implanted rod at 8.5 months
- females at 10 months: 6.9 - 5.5 = 1.4 (non-irritant)
7.7 – 5.5 = 2.2 (non-irritant)
– re-implanted rod at 8.5 months

AVERAGE INDIVIDUAL IRRITANT RANKING SCORES
1 MONTH GROUP

APPEARS THIS WAY ON ORIGINAL

Treatment Group	SCORE
CONTROL MALE	
CRIADF	12.5
CRIAES	7.0
CRIAGF	11.3
CRIATR	11.5
CONTROL FEMALE	
CRIAAG	12.0
CRIACX	12.0
CRIAFX	8.3
CRIA KL	6.3
TEST MALE	
CRIABM	12.0
CRIAFJ	15.0
CRIAHI	12.5
CRIA KU	10.0
TEST FEMALE	
CRIALD	20.5
CRIALV	11.0
CRIASC	17.0
CRIASE	17.0

$\bar{x} = 10.6$

$\bar{x} = 9.65$

$\bar{x} = 12.4$

$\bar{x} = 16.4$

- Applicant table

AVERAGE INDIVIDUAL IRRITANT RANKING SCORES
10 MONTH GROUP

APPEARS THIS WAY ON
ORIGINAL

Treatment Group	SCORE	
CONTROL MALE		
CRIAEX	5.7	
CRIAGJ	3.5	
CRIANR	4.0	
CONTROL FEMALE		
CRIATT	6.5	
CRIAGB	4.5	
CRIALL	5.0	
CRIANZ	6.0	
TEST MALE	Original	Recent
CRIACB	8.0	11.0
CRIACR	8.5	9.0
CRIAKH	6.0	5.0
CRIALH	9.0	14.0
TEST FEMALE	Original	Recent
CRIAUU	4.0	7.0
CRIAHA	7.0	9.0
CRIADH	9.7	7.7
CRIAHX	7.0	7.0

$$\bar{x} = 4.4$$

$$\bar{x} = 5.5$$

- Original 10 month scores are for the original implants and Recent 10 month scores are for the implants inserted at 8.5 months (1.5 month duration)
- adapted Applicant table

Based on the ISO test method scoring (ISO 10993-6:2007), the test article is a slight irritant as compared to the control article for the original implants at the 1 month termination as well as for the rods implanted at 8.5 months with a 10 month scoring. The test article is a nonirritant as compared to the control article at the 10 month termination. The local response to the test article was biologically appropriate and was reported by the sponsor to be within the expected range for an article with its physical characteristics (a loaded drug delivery device) versus the control article (non-loaded drug delivery device) and for the differences in the post-implantation duration. The response to the test article decreased 10 months post-implantation to being nonirritant, indicating a decreased/possibly reversing reaction. The tissue response to the recently implanted test article (1.5 months post-implantation), was reduced as compared to the original implanted test article 1-month post-implantation. The significance of this 1-2 point reduction is questionable and the etiology of the decreased response was not determined. There was no evidence of an enhanced immunological or inflammatory response to the recently implanted test article (see example scoring sheet in the appendix at the end of this study review for indices observed). The subtle

histomorphological differences between the test and control implant sites at both study intervals were reported by the sponsor to be most likely due to the leachable drug (reviewer agrees).

More realistically, considering the control (EVA only - BDDS Placebo) and test rods (BDDS) individually, controls were moderately irritating and test rods were moderately to severely irritating at 1 month. At 10 months, controls were slightly irritating and test rods were slightly to moderately, suggesting some reduction/reversal in implant site irritation.

Special Evaluation – none

Toxicokinetics

Blood specimens were collected at 0, 3, 6, 9, 12, & 24 hours, on Days 3, 8, & 14 after implantation and bi-weekly thereafter. Samples were also collected at 2, 4, 6, 9, 12 & 24 hours, and 3, 8, 15 & 21 days and 4 and 6 weeks after the re-implantation procedure. The specimens were submitted to the client for blood analysis (report PRO-NAL-0-204) pharmacokinetic analysis (report PRO-NTR-0519).

Buprenorphine dosing was with 24 rods for 1 month and 24 rods for 8.5 months with an additional 6 rods implanted until the 10 month study termination. 24 Rods is a dose of 90 mg buprenorphine for each rod or 2160 mg total (216 mg/kg for 10 kg dogs). 30 Rods is a dose of 2700 mg buprenorphine (270 mg/kg for a 10 kg dog).

The combined male and female toxicokinetic (TK) values are listed in the table. Values were not gender specific. Group A2 data is after the initial rod administration and group B2 data is after the additional 6 rods were administered at 8.5 months after the initial rod administration. While the B2 values are larger, they will not be used in safety assessment as the A2 exposure levels for the full term to be used in humans (i.e., 6 months) is more representative of the exposure time period. On this basis, at the only dose tested, which leads to anticipated local toxicity, the TK values to be compared to human exposure levels at proposed human doses (4-5 rods) are 64.4 ng/mL (C_{max}) and 18,812 ng•h/mL (AUC_{0-tz}).

Summary Table of Non-compartmental PK Parameters for Buprenorphine (Definitive Study)

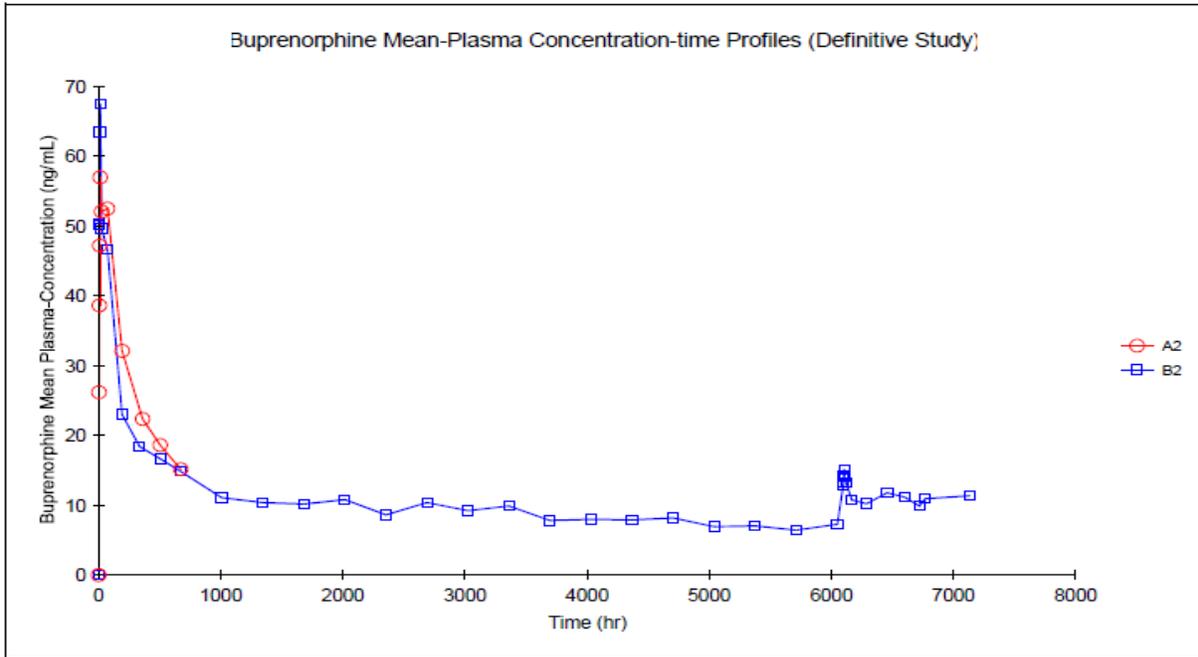
Parameters	Units	Group A2 (n=8)	Group B2 (n=8)
C _{max}	ng/mL	64.41 (9.5)	80.33 (42.4)
*T _{max}	hr	24.00 (12.0-72.0)	12.00 (3.0-72.0)
AUC _{0tz}	ng.hr/mL	18812 (3688)	76214 (9830)

Summary of the non-compartmental PK parameters, mean (SD), derived from plasma concentration time data, following subcutaneous implantation of buprenorphine HCl/EVA implants (2160 mg) in 16 dogs in definitive study.

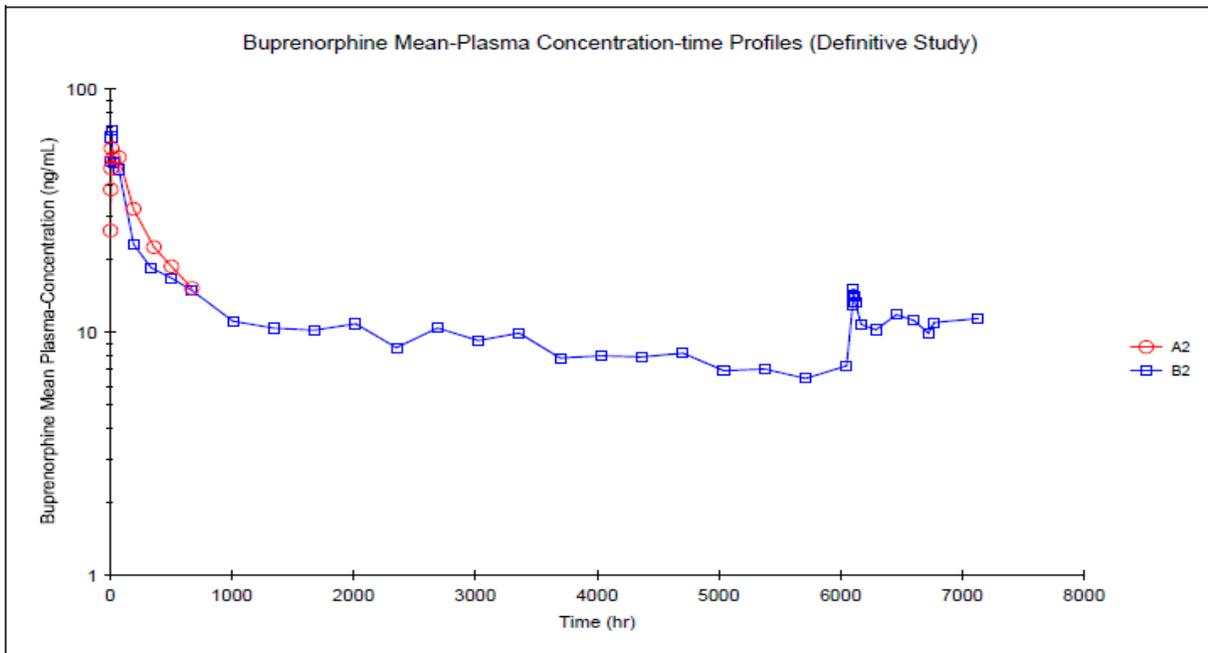
* = median (range)

- adapted Applicant table

Mean Plasma Concentration-Time Profiles (Definitive Study)
(upper panel: Linear Scale; lower panel: Semi-Log Scale)



- Applicant figure



- Applicant figure

Stability and Homogeneity – test material was stable as noted in report amendments

Study Appendix – microscopic subcutaneous implant scoring system for irritation

Implant Scoring System

Cell Type/ Response	Score				
	0	1	2	3	4
Polymorphonuclear cells	0	Rare, 1-5/phf	5-10/phf	Heavy infiltrate	Packed
Lymphocytes	0	Rare, 1-5/phf	5-10/phf	Heavy infiltrate	Packed
Plasma cells	0	Rare, 1-5/phf	5-10/phf	Heavy infiltrate	Packed
Macrophages	0	Rare, 1-5/phf	5-10/phf	Heavy infiltrate	Packed
Giant cells	0	Rare, 1-2/phf	3-5/phf	Heavy infiltrate	Sheets
Necrosis	0	Minimal	Mild	Moderate	Severe

Response	Score				
	0	1	2	3	4
Fibroplasia	0	Minimal capillary proliferation, focal, 1-3 buds	Groups of 4-7 capillaries with supporting fibroblastic structures	Broad band of capillaries with supporting structures	Extensive band of capillaries with supporting fibroblastic structures
Fibrosis	0	Narrow band	Moderately thick band	Thick band	Extensive band
Fatty infiltrate	0	Minimal amount of fat associated with fibrosis	Several layers of fat and fibrosis	Elongated and broad accumulation of fat cells about the implant site	Extensive fat completely surrounding the implant
Foreign Debris	= Number of implant sites that contain material other than the test or control articles (such as hair)				
Traumatic necrosis	0	Focal, rare necrotic myofibers	Groups of necrotic myofibers	Continuous and broad areas of myofiber necrosis	Complete obliteration of the implant site

phf = per high powered (400X) field

- Applicant table

Example irritation scorecards (control and test females with representative scores of mean group scores at 1 and 10 months):

MICROSCOPIC EVALUATION OF IMPLANT SITES

GROUP: CONTROL FEMALE (EVA)
Interval Implanted: 1-MONTH

Implant Site	CRIAAG				CRIACX			
	Site 1	Site 2	Site 3	Site 4	Site 1	Site 2	Site 3	Site 4
Inflammation								
Polymorphonuclear	1	1	1	1	1	2	1	1
Lymphocytes	2	2	2	2	3	2	2	2
Plasma Cells	0	0	0	0	0	0	0	0
Macrophages	3	2	2	2	2	2	1	1
Giant Cells	0	0	0	0	0	0	0	0
Necrosis	0	0	0	0	0	0	0	0
SUB TOTAL (X2)	12	10	10	10	12	12	8	8
Fibroplasia	0	0	0	0	0	0	0	0
Fibrosis	3	1	1	1	2	2	2	2
Fatty Infiltrate	0	0	0	0	0	0	0	0
SUB TOTAL	3	1	1	1	2	2	2	2
TOTAL	15	11	11	11	14	14	10	10
ANIMAL TOTAL	48				48			
Animal Average	12.0				12.0			
Traumatic Necrosis	0	0	0	0	0	0	0	0
Foreign Debris	0	0	0	0	0	0	0	0
No. Slides/ Areas Examined	2	2	2	2	2	2	2	2

MICROSCOPIC EVALUATION OF IMPLANT SITES

GROUP: TEST FEMALE (BDDS)
Interval Implanted: 1-MONTH

Implant Site	CRIASC				CRIASE			
	Site 1 ^a	Site 2 ^a	Site 3 ^a	Site 4 ^a	Site 1 ^b	Site 2 ^b	Site 3 ^b	Site 4 ^b
Inflammation								
Polymorphonuclear	1	1	1	1	1	1	1	1
Lymphocytes	3	2	3	2	3	2	3	2
Plasma Cells	1	1	1	1	1	1	1	0
Macrophages	2	3	2	3	3	2	3	4
Giant Cells	0	0	0	0	0	0	0	1
Necrosis	0	0	0	0	0	0	0	0
SUB TOTAL (X2)	14	14	14	14	16	12	16	16
Fibroplasia	0	0	0	0	0	0	0	0
Fibrosis	3	3	3	3	2	2	2	2
Fatty Infiltrate	0	0	0	0	0	0	0	0
SUB TOTAL	3	3	3	3	2	2	2	2
TOTAL	17	17	17	17	18	14	18	18
ANIMAL TOTAL	68				68			
Animal Average	17.0				17.0			
Traumatic Necrosis	0	0	0	0	0	0	0	0
Foreign Debris	0	0	0	0	0	0	0	0
No. Slides/ Areas Examined	2	2	2	2	2	2	2	1

MICROSCOPIC EVALUATION OF IMPLANT SITES

GROUP: CONTROL FEMALE (EVA)
Interval Implanted: 10-MONTH

Implant Site	CRIALL				CRIANZ			
	Site 1	Site 2	Site 3	Site 4	Site 1	Site 2	Site 3	Site 4
Inflammation								
Polymorphonuclear	0	0	0	NA	0	0	0	0
Lymphocytes	1	1	1	NA	1	1	1	1
Plasma Cells	0	0	0	NA	1	0	0	1
Macrophages	1	1	1	NA	1	1	1	1
Giant Cells	0	0	0	NA	0	0	0	0
Necrosis	0	0	0	NA	0	0	0	0
SUB TOTAL (X2)	4	4	4	NA	6	4	4	6
Fibroplasia	0	0	0	NA	0	0	0	0
Fibrosis	1	1	1	NA	1	1	1	1
Fatty Infiltrate	0	0	0	NA	0	0	0	0
SUB TOTAL	1	1	1	NA	1	1	1	1
TOTAL	5	5	5	NA	7	5	5	7
ANIMAL TOTAL	15				24			
Animal Average								
Traumatic Necrosis	0	0	0	NA	0	0	0	0
Foreign Debris	0	0	0	NA	0	0	0	0
No. Slides/ Areas Examined	1	1	1	NA	1	1	1	1

MICROSCOPIC EVALUATION OF IMPLANT SITES

GROUP: TEST FEMALE (BDDS)
Interval Implanted: 10-MONTH

Implant Site	CRIADH							
	ORIGINAL				RE-IMPLANT			
	Site 1	Site 2	Site 3	Site 4	Site 1	Site 2	Site 3	Site 4
Inflammation								
Polymorphonuclear	0	0	0	NA	0	0	0	0
Lymphocytes	2	2	1	NA	1	1	1	1
Plasma Cells	1	1	1	NA	1	1	1	1
Macrophages	2	2	0	NA	0	0	0	0
Giant Cells	0	0	1	NA	2	1	1	1
Necrosis	0	0	0	NA	0	0	0	0
SUB TOTAL (X2)	10	10	6	NA	8	6	6	6
Fibroplasia	0	0	0	NA	0	0	0	0
Fibrosis	1	1	1	NA	1	1	1	1
Fatty Infiltrate	0	0	0	NA	0	0	0	0
SUB TOTAL	1	1	1	NA	1	1	1	1
TOTAL	11	11	7	NA	9	7	7	7
ANIMAL TOTAL	29				23			
Animal Average	9.7				7.7			
Traumatic Necrosis	0	0	0	NA	0	0	0	0
Foreign Debris	0	0	0	NA	0	0	0	0
No. Slides/ Areas Examined	1	1	1	NA	1	1	1	1

- Applicant tables

7 Genetic Toxicology

Note: For the pharmacological active ingredient, buprenorphine, a 505(b)(2) reference is made to the approved Subutex (NDA 20-732) and Suboxone (NDA 20-733) tablets and Suboxone sublingual film (NDA 22-410) labels for genetic toxicology data for

buprenorphine. All listed genetic toxicology studies reviewed in this following section are tests of drug product or placebo extracts using medical device-based ISO protocols.

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Genotoxicity: Bacterial Reverse Mutation Study (Saline and Ethanol Extracts) (PRO-NTR-0107) - A *Salmonella typhimurium* and *Escherichia coli* reverse mutation standard plate incorporation study was conducted to evaluate whether a saline or 95% Ethanol (EtOH) 72-hour extracts of BDDS (combined lots No. 13810- 66a, 66b, 66c, 66d, 66e, 66f) would cause mutagenic changes in the average number of revertants for histidine-dependent *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and in tryptophan-dependent *Escherichia coli* strain WP2uvrA in the presence and absence of S9 metabolic activation. Based on ISO protocol, 1.7 cm of the 2.6 cm long piece of BDDS was extracted. This study was conducted to satisfy, in part, the genotoxicity requirement of the International Organization for Standardization: Biological Evaluation of Medical Devices, Part 3: Tests for Genotoxicity, Carcinogenicity and Reproductive Toxicity.

The test article extracts were found to be noninhibitory to growth of the tester strains. Under the conditions of this valid assay, the saline and ethanol test article extracts were considered to be nonmutagenic. In no case was there a 2-fold or greater increase in the mean number of revertants of tester strains TA98, TA100, TA1535, TA1537, and WP2uvrA in the presence of either test article extract. Each positive control mean exhibited at least a 3-fold increase over the respective mean of the *S. typhimurium* tester strain employed and at least a 2-fold increase over the respective mean of the *E. coli* tester strain. The positive control Dexon for tester strains TA98, TA100, & TA1537 is paradimethylaminobenzene diazosulfonic acid sodium salt). One note is that the lab work sheet noted DMSO extraction but was reported as ethanol extraction which is not considered to alter the overall lack of genotoxicity. The study was referred to as GLP but dosing solutions were not analyzed as is pert protocol for this ISO test. Study tables included on following pages.

STANDARD PLATE INCORPORATION ASSAY - REVERSION RATES FOR TESTER STRAINS

	<i>Salmonella typhimurium</i>								<i>Escherichia coli</i>	
	TA98		TA100		TA1535		TA1537		WP2uvrA	
	CFTP	Mean	CFTP	Mean	CFTP	Mean	CFTP	Mean	CFTP	Mean
Saline w/o S9 negative control	27		128		21		11		40	
	26	27	128	144	22	17	8	10	48	43
	27		176		8		10		42	
Saline w/ S9 negative control	40		160		18		11		43	
	31	35	176	171	11	12	16	14	49	47
	35		176		8		6		50	
Saline test article extract w/o S9	26		128		11		6		47	
	30	32	128	133	10	13	6	5	45	44
	40		144		17		3		40	
Saline test article extract w/ S9	24		176		13		4		62	
	14	23	146	169	9	8	4	4	45	45
	30		184		3		3		27	
Dexon w/o S9 positive control	1,808		1,408				896			
	2,096	1,787	1,136	1,067			768	821		
	1,456		656				800			
Dexon w/ S9 positive control	368		880				288			
	684	617	168	541			440	389		
	800		576				440			
2-aminofluorene w/o S9 positive control*			384							
			424	379						
			328							
2-aminofluorene w/ S9 positive control†			1,200							
			864	1,105						
			1,250							
Sodium azide w/o S9 positive control					3,264					
					3,264	3,264				
					3,264					
Sodium azide w/ S9 positive control					600					
					328	1,227				
					2,752					
2-aminoanthracene w/o S9 positive control*									60	
									51	55
									53	
2-aminoanthracene w/ S9 positive control†									189	
									192	207
									240	
Methylmethane- Sulfonate w/o S9 positive control									816	
									1,872	1,339
									1,328	
Methylmethane- Sulfonate w/ S9 positive control									1,120	
									1,072	907
									528	

CFTP = Counts from triplicate plates Mean = Mean of triplicate plates = Not Applicable

*Negative control for S9 †Positive control for S9

- Applicant table

STANDARD PLATE INCORPORATION ASSAY - REVERSION RATES FOR TESTER STRAINS

	<i>Salmonella typhimurium</i>								<i>Escherichia coli</i>	
	TA98		TA100		TA1535		TA1537		WP2uvrA	
	CFTP	Mean	CFTP	Mean	CFTP	Mean	CFTP	Mean	CFTP	Mean
ETOH	31		235		13		7		51	
w/o S9	30	34	160	203	14	15	10	10	47	49
negative control	40		214		18		13		48	
ETOH	45		248		14		14		62	
w/ S9	40	42	252	250	24	17	10	13	65	64
negative control	40		250		13		15		65	
ETOH	0		0		6		0		23	
test article	0	0	2	3	10	7	0	0	20	15
extract w/o S9	0		7		5		0		1	
ETOH	0		0		6		0		23	
test article	0	0	0	0	7	8	0	0	28	28
extract w/ S9	0		0		10		0		32	
Dexon	4,464		3,936				1,104			
w/o S9	3,520	3,861	3,960	3,944			1,104	1,099		
positive control	3,600		3,936				1,088			
Dexon	2,912		3,744				656			
w/ S9	2,176	2,528	3,744	3,744			768	715		
positive control	2,496		3,744				720			
2-aminofluorene			1,272							
w/o S9			1,200	1,339						
positive control*			1,544							
2-aminofluorene			1,848							
w/ S9			2,008	1,925						
positive control†			1,920							
Sodium azide					6,080					
w/o S9					6,080	6,080				
positive control					6,080					
Sodium azide					7,120					
w/ S9					7,120	7,120				
positive control					7,120					
2-aminoanthracene									58	
w/o S9									55	57
positive control*									58	
2-aminoanthracene									196	
w/ S9									230	209
positive control†									200	
Methylmethane-Sulfonate w/o S9									1,024	
positive control									784	912
Methylmethane-Sulfonate w/ S9									928	
positive control									1,328	952
									824	
									704	

CFTP = Counts from triplicate plates Mean = Mean of triplicate plates = Not Applicable

*Negative control for S9 †Positive control for S9

- Applicant table

7.2 *In Vitro* Assays in Mammalian Cells

Genotoxicity: In Vitro Chromosomal Aberration Study in Mammalian Cells (Extract BDDS) (PRO-NTR-0109)

The objective of this study was to evaluate the potential genotoxicity of an extract of the test article Buprenorphine Drug Delivery System (BDDS – combined lots 13810-66a, 66b, 66c, 66d, 66e, 66f) using an *in vitro* Chromosomal Aberrations (CA) mammalian cell culture test procedure. Based on ISO protocol, 5 cm of BDDS was extracted. The CA test employed Chinese Hamster Ovary (CHO) cells to detect chromosome structural changes. The detection of the aberrations was accomplished by observing chromosomes in metaphase, which have been stained with Giemsa.

A single extract of the test article was prepared using McCoy's SA Medium (37°C for 24 hours). A monolayer of CHO cells was exposed to the test article extract in triplicate cultures in the presence and absence of S9 rat liver microsomes for metabolic activation. Parallel testing was also conducted with a negative and positive control. Culture medium was used as the negative control. Mitomycin C (MMC) served as the positive control in the absence of S9 and cyclophosphamide (CP) served as the positive control in the presence of S9.

Under the conditions of this valid assay, exposure of CHO cells to the extract of BDDS did not result in statistically significant increases in the proportion of cells with structural aberration, nor did they exceed the incidence of aberrations reflected in conducting laboratory's historical control data. Greater than or equal to 50% cell lysis was not observed in the test flasks. The negative and positive controls performed as anticipated. The study was referred to as GLP but dosing solutions were not analyzed as is per protocol for this ISO test. Study table included on the following page.

AVERAGE PERCENT CELLS WITH ABERRATIONS AND CHI-SQUARE (χ^2) VALUES

	Total Aberrations	Simple	Complex	Other
With Metabolic Activation				
Negative Control (McCoy's 5A Medium)	2.00%	2.00%	0.00%	0.00%
Positive Control (Cyclophosphamide)	60.70%	52.70%	18.70%	0.00%
χ^2	204.7*	168.6*	60.1*	†
Test Article (BDDS)	1.30%	1.30%	0.00%	0.00%
χ^2	0.4	0.4	†	†
Without Metabolic Activation				
Negative Control (McCoy's 5A Medium)	2.00%	2.00%	0.00%	0.00%
Positive Control (Mitomycin C)	48.70%	38.00%	14.70%	0.00%
χ^2	150.5*	107.6*	46.3*	†
Test Article (BDDS)	0.30%	0.30%	0.00%	0.00%
χ^2	3.6	3.6	†	†

† = χ^2 calculations were not possible since the percent cells with aberrations was zero.

* = Significantly different from the negative control.

$\chi^2 = 3.841$ (critical value)

Note: Aberrations were recorded and grouped into three categories for statistical analysis:

1) simple, 2) complex, and 3) other. Simple aberrations are chromatid gap, isochromatic gap, chromatid breaks, chromosome breaks, and double minute fragments. Complex aberrations are complex rearrangements, triradials, quadraradials, dicentrics, rings, chromosome intrachanges, and interstitial deletions. A cell with >10 aberrations, one which is pulverized, or one with uncoiled chromosome is placed in the other category.

- Applicant table

Genotoxicity: In Vitro Chromosomal Aberration Study in Mammalian Cells (Extract BDDS Placebo) (PRO-NTR-0210)

The objective of this study was to evaluate the potential genotoxicity of an extract of the test article Buprenorphine Drug Delivery System placebo (BDDS Placebo – combined lots 13657-22 & 13810-01) using the *in vitro* Chromosomal Aberrations (CA) mammalian cell culture test procedure. The CA test employed Chinese Hamster Ovary (CHO) cells to detect chromosome structural changes. The detection of the aberrations was accomplished by observing chromosomes in metaphase, which have been stained with Giemsa.

A single extract of the test article was prepared using McCoy's SA Medium (37°C for 24 hours). Based on ISO protocol, ~5 cm of BDDS was extracted. A monolayer of CHO

cells was exposed to the test article extract in triplicate cultures in the presence and absence of S9 rat liver microsomes for metabolic activation. Parallel testing was also conducted with a negative and positive control. Culture medium was used as the negative control. Mitomycin C (MMC) served as the positive control in the absence of S9 and cyclophosphamide (CP) served as the positive control in the presence of S9.

Under the conditions of this assay, exposure of CHO cells to the extract of BDDS placebo did not result in statistically significant increases in the proportion of cells with structural aberration, nor did they exceed the incidence of aberrations reflected in NAMSA historical control data. The negative and positive controls performed as anticipated. The study was referred to as GLP but dosing solutions were not analyzed as is per protocol for this ISO test.

AVERAGE PERCENT CELLS WITH ABERRATIONS AND CHI-SQUARE (χ^2) VALUES

	Total Aberrations	Simple	Complex	Other
With Metabolic Activation				
Negative Control (McCoy's 5A Medium)	2.00%	2.00%	0.00%	0.00%
Positive Control χ^2 (Cyclophosphamide)	60.70% 204.7*	52.70% 168.6*	18.70% 60.1*	0.00% †
Test Article χ^2 (BDDS PLACEBO)	1.30% 0.4	1.30% 0.4	0.00% †	0.00% †
Without Metabolic Activation				
Negative Control (McCoy's 5A Medium)	2.00%	2.00%	0.00%	0.00%
Positive Control χ^2 (Mitomycin C)	48.70% 150.5*	38.00% 107.6*	14.70% 46.3*	0.00% †
Test Article χ^2 (BDDS PLACEBO)	1.00% 1.0	1.00% 1.0	0.00% †	0.00% †

† = χ^2 calculations were not possible since the percent cells with aberrations was zero.

* = Significantly different from the negative control.

$\chi^2 = 3.841$ (critical value)

Note: Aberrations were recorded and grouped into three categories for statistical analysis: 1) simple, 2) complex, and 3) other. Simple aberrations are chromatid gap, isochromatic gap, chromatid breaks, chromosome breaks, and double minute fragments. Complex aberrations are complex rearrangements, triradials, quadraradials, dicentrics, rings, chromosome intrachanges, and interstitial deletions. A cell with >10 aberrations, one which is pulverized, or one with uncoiled chromosome is placed in the other category.

- Applicant table

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)**Mouse Bone Marrow Micronucleus Study (BDDS) (PRO-NTR-0211)**

A Mouse Bone Marrow Micronucleus (MNU) study was conducted to determine whether a test article extract would cause genotoxic changes in chromosomes or the mitotic apparatus of murine polychromatic erythrocytes (PCEs). The test article Buprenorphine Drug Delivery System (BDDS – combined lots 13810-66a, 66b, 66c, 66d, 66e, 66f) was extracted in 0.9% sodium chloride USP solution (and evaluated for genotoxicity using the MNU model. Based on ISO protocol, 1.7 cm of the 2.6 cm long piece of BDDS was extracted. This study was conducted to satisfy, in part, the genotoxicity requirement of the International Organization for Standardization: Biological Evaluation of Medical Devices, Part 3: Tests for Genotoxicity, Carcinogenicity and Reproductive Toxicity.

For 2 consecutive days (days 1 and 2), ten mice (five per sex) were injected intraperitoneally with the test article extract at a dose of 12.50 ml/kg. Similarly, ten mice were dosed with saline as the negative control condition. On day 2, ten additional mice were dosed with the positive control, 50 mg/kg cyclophosphamide (12.50 ml/kg). All animals were observed immediately following injection and daily for general health. On day 3, the animals were euthanatized. The bone marrow was collected from the femurs and smears were prepared. The polychromatic erythrocytes were evaluated microscopically for the presence of micronuclei. The percentage of polychromatic erythrocytes among total erythrocytes was determined. The percentage of PCEs among total erythrocytes counted (% PCE) was determined as an index of bone marrow toxicity. The percentage of PCEs among total erythrocytes was not analyzed statistically.

Under the conditions of this study, the test article extract was not considered to be genotoxic to the mouse. There was no statistically significant increase in the number of micronucleated PCEs for the extract-treated animals. The negative and positive controls performed as expected. There was no evidence of systemic or bone marrow toxicity indicating that dose levels were less than challenging. The study was referred to as GLP but dosing solutions were not analyzed as is per protocol for this ISO test.

GROUP MICROSCOPIC EVALUATION DATA

Treatment	Sex	Number of Mice	Percent PCE (mean ± SD)	Micronucleated PCEs per 1000 PCEs (mean ± SD)	Micronucleated PCEs per Total PCEs Scored
Test Article	Male	5	30.8 ± 7.8	1.5 ± 0.6	15/10,000
	Female	5	32.6 ± 7.4	1.6 ± 1.0	16/10,000
Negative Control	Male	5	31.8 ± 6.3	2.0 ± 0.8	20/10,000
	Female	5	41.6 ± 5.2	2.3 ± 0.8	23/10,000
Positive Control	Male	5	31.6 ± 5.0	21.5 ± 3.1*	215/10,000
	Female	5	37.4 ± 6.2	17.3 ± 3.9*	173/10,000

NCE = Normochromatic erythrocytes

PCE = Polychromatic erythrocytes

Percent PCE = 100 X PCE/(PCE + NCE)

*p <0.5 (statistically significant) as compared to the negative control

- Applicant table

Mouse Bone Marrow Micronucleus Study (BDDS Placebo) (PRO-NTR-0212)

A Mouse Bone Marrow Micronucleus (MNU) study was conducted to determine whether a placebo test article extract would cause genotoxic changes in chromosomes or the mitotic apparatus of murine polychromatic erythrocytes (PCEs). The test article Buprenorphine Drug Delivery System placebo (BDDS placebo – combined lots 13657-22 & 13810-01) was extracted in 0.9% sodium chloride USP solution (72 hours at 50°C) and evaluated for genotoxicity using the MNU model. Based on ISO protocol, 1.6 cm of the 2.6 cm long piece of BDDS placebo was extracted. This study was conducted to satisfy, in part, the genotoxicity requirement of the International Organization for Standardization: Biological Evaluation of Medical Devices, Part 3: Tests for Genotoxicity, Carcinogenicity and Reproductive Toxicity.

For 2 consecutive days (days 1 and 2), ten mice (five per sex) were injected intraperitoneally with the test article extract at a dose of 12.50 ml/kg. Similarly, ten mice were dosed with saline as the negative control condition. On day 2, ten additional mice were dosed with the positive control, 50 mg/kg cyclophosphamide (12.50 ml/kg). All animals were observed immediately following injection and daily for general health. On day 3, the animals were euthanatized. The bone marrow was collected from the femurs and smears were prepared. The polychromatic erythrocytes were evaluated microscopically for the presence of micronuclei. The percentage of polychromatic erythrocytes among total erythrocytes was determined. The percentage of polychromatic erythrocytes among total erythrocytes was determined. The percentage of PCEs among total erythrocytes counted (% PCE) was determined as an index of bone marrow toxicity. The percentage of PCEs among total erythrocytes was not analyzed statistically.

Under the conditions of this study, the test article extract was not considered to be genotoxic to the mouse. There was no statistically significant increase in the number of micronucleated PCEs for the extract-treated animals. The negative and positive controls performed as expected. There was no evidence of systemic or bone marrow toxicity indicating that dose levels were less than challenging. The study was referred to as GLP but dosing solutions were not analyzed as is per protocol for this ISO test.

GROUP MICROSCOPIC EVALUATION DATA

Treatment	Sex	Number of Mice	Percent PCE (mean ± SD)	Micronucleated PCEs per 1000 PCEs (mean ± SD)	Micronucleated PCEs per Total PCEs Scored
Test Article	Male	4†	29.0 ± 5.0%	1.8 ± 1.2	14/8,000
	Female	5	35.0 ± 6.0%	0.9 ± 0.4*	9/10,000
Negative Control	Male	5	31.8 ± 6.3%	2.0 ± 0.8	20/10,000
	Female	5	41.6 ± 5.2%	2.3 ± 0.8	23/10,000
Positive Control	Male	5	31.6 ± 5.0%	21.5 ± 3.1*	215/10,000
	Female	5	37.4 ± 6.2%	17.3 ± 3.9*	173/10,000

NCE = Normochromatic erythrocytes

PCE = Polychromatic erythrocytes

Percent PCE = $100 \times \text{PCE} / (\text{PCE} + \text{NCE})$

*p < 0.5 (statistically significant) as compared to the negative control

†The PCE counts for animal number 74 were below 2000 (see DEVIATION).

- Applicant table

7.4 Other Genetic Toxicity Studies

- none

8 Carcinogenicity

505(b)(2) reference is made to the approved Subutex (NDA 20-732) and Suboxone (NDA 20-733) tablets and Suboxone sublingual film (NDA 22-410) labels for carcinogenicity data for buprenorphine. We also note the approved use of EVA in NuvaRing (NDA21-187) and in Implanon (NDA 21-529) for chronic exposure.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

505(b)(2) reference is made to the approved Subutex (NDA 20-732) and Suboxone (NDA 20-733) tablets and Suboxone sublingual film (NDA 22-410) labels for reproductive data for buprenorphine. We also note the approved use of EVA in NuvaRing (NDA21-187) and in Implanon (NDA 21-529) for chronic exposure.

9.2 Embryonic Fetal Development

505(b)(2) reference is made to the approved Subutex (NDA 20-732) and Suboxone (NDA 20-733) tablets and Suboxone sublingual film (NDA 22-410) labels for reproductive data for buprenorphine. We also note the approved use of EVA in NuvaRing (NDA21-187) and in Implanon (NDA 21-529) for chronic exposure.

9.3 Prenatal and Postnatal Development

505(b)(2) reference is made to the approved Subutex (NDA 20-732) and Suboxone (NDA 20-733) tablets and Suboxone sublingual film (NDA 22-410) labels for reproductive data for buprenorphine. We also note the approved use of EVA in NuvaRing (NDA21-187) and in Implanon (NDA 21-529) for chronic exposure.

10 Special Toxicology Studies

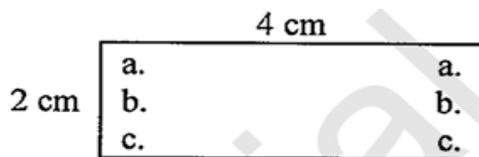
10.1 Local Tolerance

ISO Sensitization Study in the Guinea Pig (Maximization Method) (PRO-NTR-0103)

A guinea pig maximization test of the Buprenorphine Drug Delivery System extract (BDDS – combined lot No. 13810- 66a, 66b, 66c, 66d, 66e, 66f) was conducted to evaluate the potential for delayed dermal contact sensitization. This study was conducted based on the requirements of the International Organization for Standardization 10993: Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Sensitization.

The test article was extracted in 0.9% sodium chloride USP (SC) and cottonseed oil, NF (CSO) at 50°C for 72 hours. Based on ISO protocol, ~1 cm of the 2.6 cm long piece of BDDS was extracted. In induction phase I, a day after exposure site clipping, each

extract was intradermally injected into ten test guinea pigs (per extract) and covered with an occlusive patch in an attempt to induce sensitization. The vehicle was similarly injected and occlusively patched to five control guinea pigs (per vehicle). Three rows of intradermal injections (two per row) were given to each animal within an approximate 2 cm x 4 cm boundary of the fur clipped area as illustrated below:



- Applicant figure

Control Animals:

- a. 0.1 ml of 50:50 (v/v) mixture of Freund's Complete Adjuvant (FCA) and the chosen vehicle
- b. 0.1 ml of vehicle
- c. 0.1 ml of a 1:1 mixture of the 50:50 (v/v) vehicle/FCA mixture and the vehicle

Test Animals:

- a. 0.1 ml of 50:50 (v/v) mixture of FCA and the chosen vehicle
- b. 0.1 ml of test extract
- c. 0.1 ml of a 1:1 mixture of the 50:50 (v/v) vehicle/FCA mixture and the test extract

Induction phase II - Six days after the injections, the same area used during Induction phase I was clipped free of fur and treated with 0.5 to 1 gram of a 10% sodium lauryl sulfate (SLS) suspension in petrolatum. The suspension was massaged into the skin over the injection site to provoke a mild acute inflammation. The area was left uncovered. The day following SLS treatment, any remaining SLS residue was gently removed with a gauze pad. A 2 cm x 4 cm section of filter paper, saturated with 0.3 ml of freshly prepared test article extract (SC or CSO), was then topically applied to the previously injected sites of the test animals. The control animals were similarly patched with the appropriate reagent control. Each patch was secured with a nonreactive tape and the trunk of each animal was wrapped with an elastic bandage. At 48 hours, the binders and patches were removed.

Challenge phase - Following a period of 14 days, the test and control animals received a challenge patch of the appropriate test article extract and the reagent control to sites clipped the previous day.

TREATMENT GROUP (n)	CHALLENGE SITE	
	LEFT FLANK	RIGHT FLANK
Test (10 SC, 10 CSO)	Reagent Control	Test Extract
Control (5 SC, 5 CSO)	Reagent Control	Test Extract

- Applicant table

Each patch was secured to the skin with semioclusive hypoallergenic adhesive tape. The trunk of each animal was wrapped with an elastic bandage to maintain well-occluded sites for the 24 hour exposure. The sites were wiped gently with gauze after

patch removal. At 24 hours after patch removal, the challenged sites and surrounding area were shaved. Observations for dermal reactions were conducted at 2-4 hours following the shave and at 48 and 72 hours after challenge patch removal. Prior to scoring at each interval, sites were wiped with 35% isopropyl alcohol. Erythema and edema were scored for on scales of 0-4 and duration.

All scores for test and control sites were 0 (no erythema or edema) for test and control sites. Under the conditions of this study, the SC and CSO test article extracts showed no evidence of causing delayed dermal contact sensitization in the guinea pig. The study was referred to as GLP but dosing solutions were not analyzed.

ISO Acute Intracutaneous Reactivity Study in the Rabbit (Extracts) (PRO-NTR-0104)

The test article, Buprenorphine Drug Delivery System (BDDS – combined lots No. 13810- 66a, 66b, 66c, 66d, 66e, 66f), was extracted in 0.9% sodium chloride USP solution and cottonseed oil, NF at 50°C for 72 hours. Based on ISO protocol, 1.7 cm of the 2.6 cm long piece of BDDS was extracted. These extracts were evaluated for intracutaneous reactivity based on the requirements of the International Organization for Standardization 10993: Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Sensitization. The purpose of the study was to determine whether leachables extracted from the material would cause local dermal irritant effects following injection into rabbit skin.

A 0.2 ml dose of the appropriate test article extract was injected by the intracutaneous route into five separate sites on the right side of the back of each of three rabbits. Similarly, the corresponding reagent control was injected on the left side of the back of each rabbit. The injection sites were observed immediately after injection. Observations for erythema and edema were conducted at 24, 48, and 72 hours after injection and averaged for each animal.

ERYTHEMA (ER)		EDEMA (ED)	
0	No erythema	0	No edema
1	Very slight erythema (barely perceptible)	1	Very slight edema (barely perceptible)
2	Well-defined erythema	2	Well-defined edema (edges of area well-defined by definite raising)
3	Moderate erythema	3	Moderate edema (raised approximately 1 mm)
4	Severe erythema (beet redness) to eschar formation preventing grading of erythema	4	Severe edema (raised more than 1 mm, and extending beyond exposure area)

- Applicant table

Under the conditions of this study, there was no evidence of significant irritation from the extracts injected intracutaneously into rabbits. The Primary Irritation Index (PII) for the extracts was negligible. The study was referred to as GLP but dosing solutions were not analyzed.

Extract	Animal Number	Test Score Average	Control Score Average	Primary Irritation Score	Primary Irritation Score Total	Primary Irritation Index Characterization
SC	63995	0.0	0.0	0.0	0.0	Negligible
	63997	0.0	0.0	0.0		
	63996	0.0	0.0	0.0		
CSO	63995	0.8	1.0	0.0	0.0	Negligible
	63997	0.5	0.5	0.0		
	63996	0.0	0.0	0.0		

- Applicant table

ISO Subcutaneous Implantation Study in the Rabbit with Histopathology (Surgical Method, Four Weeks) (PRO-NTR-0108)

The test article, Buprenorphine Drug Delivery System (BDDS), was surgically implanted in subcutaneous tissue of three (3) male rabbits. The subcutaneous tissue was evaluated for evidence of irritation or toxicity based on the requirements of the International Organization for Standardization 10993: Biological Evaluation of Medical Devices, Part 6: Tests for Local Effects after Implantation.

Rabbits were implanted at four (4) sites each with 10 mm pieces of BDDS (combined lots No. 13810- 66a, 66b, 66c, 66d, 66e, 66f - ~^(b)₍₄₎ mg buprenorphine/implant) or BDDS placebo (combined lots 13657-22 & 13810-01) on right or left sides of the back, respectively. Original test lot implant length is 25.7 mm. Buprenorphine:EVA ratio (i.e., concentration) was unchanged from intact test material. Two (2) USP negative control implants (polyethylene) were inserted on each side of the back. Animals were euthanized four (4) weeks later. Subcutaneous tissues were excised and the implant sites were examined macroscopically. A microscopic evaluation of fixed representative tissue sites from each rabbit was conducted to further define any tissue capsule formation and irritation response using the following scoring system:

- 0 - No capsule, no adverse reaction (other than minimal hemorrhage)
- 1 - Up to 0.5 mm capsule or reaction area
- 2 - 0.6 to 1.0 mm capsule or reaction area
- 3 - 1.1 to 2.0 mm capsule or reaction area
- 4 > 2.0 mm capsule or reaction area

No clinical effects (e.g., on body weight) or macroscopic observations of dose sites occurred.

BODY WEIGHTS AND MACROSCOPIC SCORES

Rabbit Number/ Gender	Weight (kg)		Test	USP Negative Control	Sponsor Provided Control
	Day 0	Day 28			
*63764 Male	3.1	3.4	1 1 0 0	0 0 0 0	1 0 0 0

*63444 Male	3.2	3.3	1 0 0 0	0 0 0 0	1 0 0 0
*63439 Male	3.3	3.7	1 1 0 0	0 0 0 0	0 1 1 0
Average			0.4	0.0	0.3

*Previous use history traceable in laboratory records.

- Applicant table

Microscopic scores were rated as follows individually and after subtraction of the USP negative control scores using the following scoring system:

___ Nonirritant (0.0-2.9), ___ Slight Irritant (3.0-8.9),
 ___ Moderate Irritant (9.0-15.0), ___ Severe Irritant (>15.1)

ISO SUBCUTANEOUS IMPLANTATION STUDY IN THE RABBIT
MICROSCOPIC EVALUATION OF IMPLANT

SITES Test Article: BDDS

Interval Implanted: 4 Weeks

	TEST			USP NEGATIVE CONTROL PLASTIC		
	63764	63444	63439	63764	63444	63439
Rabbit Number:	63764	63444	63439	63764	63444	63439
Inflammation						
Polymorphonuclear	2	2	3	1	2	1
Lymphocytes	1	1	1	1	1	1
Plasma Cells	0	0	0	0	0	0
Macrophages	2	2	2	1	1	1
Giant Cells	0	0	0	0	0	0
Necrosis	0	0	0	0	0	0
SUB TOTAL (X2)	10	10	12	6	8	6
Fibroplasia	1	1	1	0	0	0
Fibrosis	1	1	1	2	2	2
Fatty Infiltrate	0	0	0	0	0	0
SUBTOTAL	2	2	2	2	2	8
TOTAL	12	12	14	8	10	8
GROUP TOTAL	38			26		
AVERAGE*	TEST 12.7 (-) CONTROL 8.7 = 4.0					
*Used to determine Irritant Ranking Score shown below as the Conclusion. A negative difference was recorded as zero.						
Traumatic Necrosis	0	0	0	0	0	0
Foreign Debris	0	0	0	0	0	0
No. Sites Examined	4	4	4	4	4	3

- Applicant table

Sponsor provided control: BDDS - Placebo
Interval Implanted: 4 Weeks

Rabbit Number:	SPONSOR CONTROL			USP NEGATIVE CONTROL PLASTIC		
	63764	63444	63439	63764	63444	63439
Inflammation						
Polymorphonuclear	3	1	3	1	2	1
Lymphocytes	2	1	2	1	1	1
Plasma Cells	0	0	0	0	0	0
Macrophages	2	2	2	1	1	1
Giant Cells	0	0	0	0	0	0
Necrosis	0	0	0	0	0	0
SUB TOTAL (X2)	14	8	14	6	8	6
Fibroplasia	1	1	1	0	0	0
Fibrosis	1	1	1	2	2	2
Fatty Infiltrate	0	0	0	0	0	0
SUBTOTAL	2	2	2	2	2	2
TOTAL	16	10	16	8	10	8
GROUP TOTAL	42			26		
AVERAGE*	TEST 14.0	(-) CONTROL 8.7	= 5.3			
*Used to determine Irritant Ranking Score shown below as the Conclusion. A negative difference was recorded as zero.						
Traumatic Necrosis	0	0	0	0	0	0
Foreign Debris	0	0	0	0	0	0
No. Sites Examined	4	4	4	4	4	3

- Applicant table

Under the conditions of this study, there were no significant macroscopic reactions. Microscopically, BDDS and BDDS placebo were classified as slight irritants as compared to the USP negative control material with irritation score differences of 4.0 and 5.3, respectively. Scoring absolute irritation only, both the BDDS (score of 12.7) and BDDS placebo (score of 14.0) were moderate irritants at 4 weeks after insertion while the USP negative control was a slight irritant (score of 8.7).

ISO Subcutaneous Implantation Study in the Rabbit with Histopathology (Surgical Method, Twenty-six Weeks) (PRO-NTR-0213)

The test article, Buprenorphine Drug Delivery System (BDDS) was surgically implanted in subcutaneous tissue of three (3) male rabbits. The subcutaneous tissue was evaluated for evidence of irritation or toxicity based on the requirements of the International Organization for Standardization 10993: Biological Evaluation of Medical Devices, Part 6: Tests for Local Effects after Implantation. The purpose of the study was to evaluate the potential for a local irritant or toxic response to material implanted in direct contact with subcutaneous tissue.

Rabbits were implanted at four (4) sites each with 10 mm pieces of BDDS (combined lots No. 13810- 66a, 66b, 66c, 66d, 66e, 66f - ~^(b)₍₄₎ mg buprenorphine/implant) on the right and left sides of the back. USP negative control (polyethylene) and BDDS placebo (combined lots 13657-22 & 13810-01) were implanted at two (2) sites on the right or left sides, respectively. Original test lot implant length is 25.7 mm. Buprenorphine:EVA ratio (i.e., concentration) was unchanged from intact test material. Animals were euthanatized twenty six weeks later. Subcutaneous tissues were excised and the implant sites were examined macroscopically. A microscopic evaluation of representative tissue sites from each rabbit was conducted to further define any tissue response.

A microscopic evaluation of fixed representative tissue sites from each rabbit was conducted to further define any tissue capsule formation and irritation response using the following scoring system:

- 0 - No capsule, no adverse reaction (other than minimal hemorrhage)
- 1 - Up to 0.5 mm capsule or reaction area
- 2 - 0.6 to 1.0 mm capsule or reaction area
- 3 - 1.1 to 2.0 mm capsule or reaction area
- 4 > 2.0 mm capsule or reaction area

No clinical effects (e.g., on body weight) or macroscopic observations of dose sites occurred.

BODY WEIGHTS AND MACROSCOPIC SCORES

Rabbit Number/ Gender	Weight (kg)							Test	USP Negative Control	Sponsor Provided Control
	Day 0	Day 28	Day 56	Day 84	Day 112	Day 140	Day 181			
*63440 Male	3.4	3.6	3.5	3.7	3.8	3.9	4.0	0	0	0
								0	0	0
								1	0	0
								1	0	0
*63412 Male	3.4	3.5	3.7	3.8	3.9	4.0	4.1	0	0	0
								0	0	0
								0	0	0
								0	0	0
*63433 Male	3.4	3.5	3.7	3.8	3.7	3.9	4.0	0	0	0
								0	0	0
								0	0	0
								0	0	0
Average:								0.2	0.0	0.0

*Previous use history traceable in laboratory records.

- Applicant table

Microscopic scores were rated as follows individually and after subtraction of the USP negative control scores using the following scoring system:

- ___ Nonirritant (0.0-2.9), ___ Slight Irritant (3.0-8.9),
- ___ Moderate Irritant (9.0-15.0), ___ Severe Irritant (>15.1)

**ISO SUBCUTANEOUS IMPLANTATION STUDY IN THE RABBIT (SURGICAL METHOD)
MICROSCOPIC EVALUATION OF IMPLANT SITES**

Test Article: BDDS

Interval Implanted: Twenty-six Weeks

	TEST			NEGATIVE CONTROL		
Rabbit Number:	63440	63412	63433	63440	63412	63433
Inflammation						
Polymorphonuclear	3	1	1	1	1	1
Lymphocytes	3	1	1	1	1	1
Plasma Cells	0	0	0	0	0	0
Macrophages	3	2	2	1	1	1
Giant Cells	0	0	0	0	0	0
Necrosis	0	0	0	0	0	0
SUB TOTAL (X2)	18	8	8	6	6	6
Fibroplasia	0	0	0	0	0	0
Fibrosis	3	2	2	2	2	2
Fatty Infiltrate	0	0	0	0	0	0
SUB TOTAL	3	2	2	2	2	2
TOTAL	21	10	10	8	8	8
GROUP TOTAL	41			24		
AVERAGE*	TEST 13.7 (-)			CONTROL 8.0 = 5.7		
*Used to determine Irritant Ranking Score shown below as the Conclusion. A negative difference was recorded as zero.						
Traumatic Necrosis	0	0	0	0	0	0
Foreign Debris	4	4	4	0	0	0
No. Sites Examined	4	4	4	3	4	4

- Applicant table

**ISO SUBCUTANEOUS IMPLANTATION STUDY IN THE RABBIT
MICROSCOPIC COMPARISON OF IMPLANT SITES**

Sponsor Provided Control: BDDS Placebo

Interval Implanted: 26 Weeks

	Sponsor Provided Control			NEGATIVE CONTROL		
Rabbit Number:	63440	63412	63433	63440	63412	63433
Inflammation						
Polymorphonuclear	1	1	1	1	1	1
Lymphocytes	2	1	1	1	1	1
Plasma Cells	0	0	0	0	0	0
Macrophages	1	1	1	1	1	1
Giant Cells	0	0	0	0	0	0
Necrosis	0	0	0	0	0	0
SUB TOTAL (X2)	8	6	6	6	6	6
Fibroplasia	0	0	0	0	0	0
Fibrosis	2	2	2	2	2	2
Fatty Infiltrate	0	0	0	0	0	0
SUB TOTAL	2	2	2	2	2	2
TOTAL	10	8	8	8	8	8
GROUP TOTAL	26			24		
AVERAGE*	TEST 8.7 (-)			CONTROL 8.0 = 0.7		
*Used to determine Irritant Ranking Score shown below as the Conclusion. A negative difference was recorded as zero.						
Traumatic Necrosis	0	0	0	0	0	0
Foreign Debris	4	4	4	0	0	0
No. Sites Examined	4	4	4	3	4	4

- Applicant table

Under the conditions of this study, there were no significant macroscopic reactions. Microscopically, BDDS was classified as a slight irritant as compared to the USP negative control material (difference of 5.7) and the BDDS placebo (difference of 0.7). Scoring absolute irritation only, BDDS was moderately irritating (score of 13.7), BDDS placebo was slightly irritating (score of 8.7), and USP negative control (score of 8.0) was slightly irritating at 26 weeks after insertion.

10.2 Other Toxicity Studies

Risk Assessment of Impurities in Components of Probuphine® Implants and Packaging (PRO-NTR-1201)

This report will not be described here, but may be referenced in section 2.5 (Impurities/Degradants of concern).

ISO Rabbit Pyrogen Study (Material Mediated) (PRO-NTR-0102)

The test article, Buprenorphine Drug Delivery System placebo (BDDS Placebo – combined lots 13657-22 & 13810-01), was extracted in sterile, nonpyrogenic saline (0.9% sodium chloride USP solution) at 50°C for 72 hours. Based on ISO protocol, ~6 cm of BDDS was extracted. The warmed extract was evaluated in the rabbit for material mediated pyrogenicity. The test was conducted based on the current USP, but was modified for an extract of the test article. The procedure is recommended in the International Organization for Standardization: Biological Evaluation of Medical Devices, Part II: Tests for Systemic Toxicity.

The purpose of this study was to determine whether an extract of the test article induced a pyrogenic response following intravenous injection in three rabbits. *In vivo* biological reactivity was evaluated following a single injection of the extract. A single dose of 10 mL/kg was intravenously injected via the marginal ear vein into each of three rabbits. Rectal temperatures were measured and recorded prior to injection and at 30 minute intervals between 1 and 3 hours after injection.

No single animal showed a temperature increase of 0.5°C or more above its baseline temperature, meaning that the extract was no pyrogenic by USP test standards.

Rabbit Number	Weight (kg)	Dose Volume (ml)	Baseline	TEMPERATURE - DEGREES CELSIUS					Maximum Rise
				Hours after Injection					
				1.0	1.5	2.0	2.5	3.0	
63918	2.5	25	39.8	40.0	39.9	39.9	39.9	39.9	0.2
63890	2.7	27	39.3	39.4	39.4	39.4	39.4	39.4	0.1
63891	2.8	28	39.8	39.8	39.8	39.8	39.8	39.6	0.0
TOTAL RISE:									0.3

- Applicant table

Under the conditions of this study, the total rise of rabbit temperatures during the 3 hour observation period was within acceptable USP limits. The BDDS placebo extract was judged as nonpyrogenic.

Cytotoxicity Study Using the ISO Elution Method (1X MEM Extract) (PRO-NTR-0105)

An *in vitro* biocompatibility study was conducted on the test article extract of the Buprenorphine Drug Delivery System (BDDS – combined lots No. 13810- 66a, 66b, 66c, 66d, 66e, 66f), to determine the potential for cytotoxicity based on the International Organization for Standardization 10993: Biological Evaluation of Medical Devices, Part 5: Tests for Cytotoxicity: *in vitro* Methods guidelines. The test was performed to determine whether leachables extracted from the material would cause cytotoxicity.

Single extracts of the test, negative control, and positive control articles were prepared using single strength Minimum Essential Medium supplemented with 5% serum and 2% antibiotics (1X MEM) at 37°C for 24 hours. Based on ISO protocol, 1.7 cm of the 2.6 cm long piece of BDDS was extracted. This test extract was placed onto three separate confluent monolayers of L-929 mouse fibroblast cells propagated in 5% CO₂ for 48 hours. Three separate monolayers were prepared for the reagent control, negative control and for each dilution of the positive control. All monolayers were incubated at 37°C in the presence of 5% CO₂ for 48 hours. The monolayers in the BDDS , reagent control (1x MEM), negative control (USP polyethylene extract), and positive control (polyvinyl chloride) wells were examined microscopically at 48 hours to determine any change in cell morphology.

The confluency of the monolayer was recorded as (+) if present and (-) if absent. In addition, the color of the test medium was observed and compared to the negative control medium. A color shift toward yellow was associated with an acidic pH range and a color shift toward magenta to purple was associated with an alkaline pH range. Each culture well was evaluated for percent lysis and cellular characteristics using the following criteria:

Grade	Reactivity	Observations	
0	None	Discrete intracytoplasmic granules	No lysis
1	Slight	Not more than 20% of the cells are round, loosely attached, and without intracytoplasmic granules	Not more than 20% lysis
2	Mild	Not more than 50% of the cells are round and devoid of intracytoplasmic granules	Not more than 50% lysis
3	Moderate	Not more than 70% of the cell monolayer contains rounded cells	Not more than 70% lysis
4	Severe	Nearly complete destruction of the cell monolayer	Greater than 70% lysis

- Applicant table

For the test to be valid, the reagent control and the negative control must have had a reactivity of none (grade 0) and the positive control must have been a grade 3 or 4. The

test sample met the requirements of the test if the biological response was less than or equal to grade 2 (mild). The test would have been repeated if the controls did not perform as anticipated and/or if all three test wells did not yield the same conclusion.

For the pH observation, the test medium was similar to the negative control medium at 48 hours.

Under the conditions of this study, the IX MEM test extract showed no evidence of causing cell lysis or toxicity. The IX MEM BDDS extract met the requirements of the test since the grade was less than a grade 2 (mild reactivity). The reagent control, negative control, and the positive control performed as anticipated.

REACTIVITY GRADES FOR ELUTION TESTING

Well	Confluent Monolayer	Percent Rounding	Percent Cells Without Intracytoplasmic Granules	Percent Lysis	Grade	Reactivity
Test (1A)	(+)	0	0	0	0	None
Test (1B)	(+)	0	0	0	0	None
Test (1C)	(+)	0	0	0	0	None
Negative Control (1A)	(+)	0	0	0	0	None
Negative Control (1B)	(+)	0	0	0	0	None
Negative Control (1C)	(+)	0	0	0	0	None
Reagent Control (1A)	(+)	0	0	0	0	None
Reagent Control (1B)	(+)	0	0	0	0	None
Reagent Control (1C)	(+)	0	0	0	0	None
Positive Control (1A) 1:4 Dilution	(-)	90	90	80	4	Severe
Positive Control (1B) 1:4 Dilution	(-)	90	90	80	4	Severe
Positive Control (1C) 1:4 Dilution	(-)	90	90	80	4	Severe

(+) = Present (-) = Absent

- Applicant table

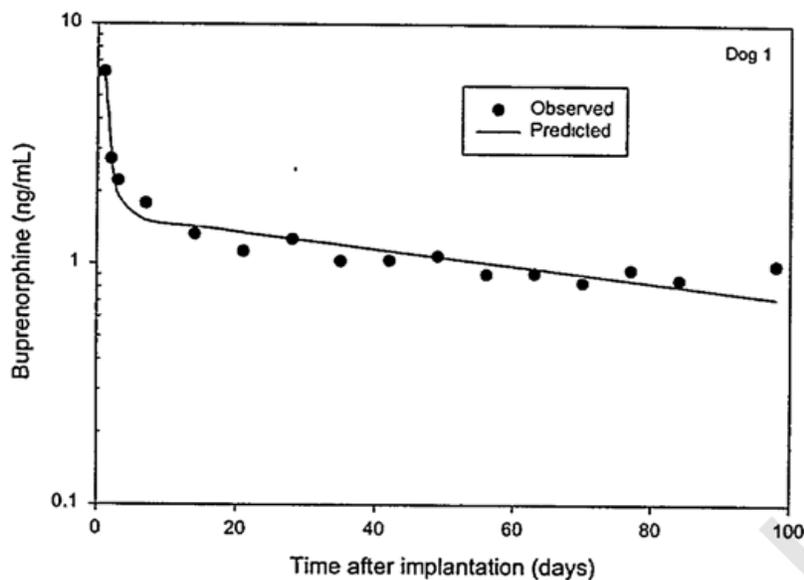
11 Integrated Summary and Safety Evaluation

Introduction - Probuphine®, also described as Buprenorphine Drug Delivery System (BDDS) in the nonclinical testing, is a buprenorphine containing subdermally implantable formulation. The active pharmacological ingredient, buprenorphine hydrochloride (buprenorphine), is a partial opioid agonist administered in a solid matrix of ethylene vinyl acetate polymer (EVA). Probuphine is intended to provide sustained delivery of buprenorphine for up to 6 months for the maintenance treatment of opioid dependence using an alleged abuse and diversion deterrent formulation. Each implant contains 80 mg buprenorphine and (b) (4) mg of EVA (total weight of 112.5 mg). The maximum proposed dose is 5 implants (total dose of 400 mg buprenorphine).

The human safety of buprenorphine in Probuphine is generally supported by Probuphine data satisfying 505(b)(2) submission requirements for buprenorphine exposure, acceptable product quality specifications and stability, and valid nonclinical studies with an acceptable clinical pharmacology relationship between the nonclinical test product and the proposed drug product. This support includes the Agency's prior findings of buprenorphine safety and efficacy and submitted pivotal nonclinical studies that most notably include the chronic toxicity of implants with toxicokinetic (TK) measurements. Testing also included a set of medical device-based safety tests conducted on BDDS and/or BDDS placebo (EVA only) extracts according to International Organization for Standardization (ISO) 10993: Biological Evaluation of Medical Devices. Buprenorphine has been marketed for over 30 years as injectable Buprenex (NDA 18-401). 505(b)(2) reference for buprenorphine is made to the approved Subutex (NDA 20-732) and Suboxone (NDA 20-733) sublingual tablet labels for genotoxicity, carcinogenicity, and reproductive toxicity. The submitted nonclinical testing satisfies testing needs as listed in the FDA *Guidance for Industry and Review Staff: Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route* (March 2008).

The human safety of EVA (Inactive Ingredient) is generally supported by its use in FDA-approved and marketed products NuvaRing (NDA 21-187) and Implanon (NDA 21-529), by EVA monomer level specifications and by submitted nonclinical studies. Nonclinical testing with Probuphine and/or EVA alone (BDDS placebo) includes that as listed for buprenorphine in the preceding paragraph. This submitted nonclinical testing is consistent with the FDA *Guidance for Industry: Nonclinical Safety Studies for the Safety Evaluations of Pharmaceutical Excipients* (May 2005).

Nonclinical Testing - The nonclinical program was designed to support the administration of Probuphine rods (BDDS) by subdermal (subcutaneous) implantation. Inclusion of buprenorphine in EVA achieved the intended effect of producing a sustained systemic release of buprenorphine. For illustration purposes only, not for quantitative purposes, following is a typical release figure in a dog for over 3 months (study PRO-NDR-0001). This time course of release of buprenorphine from BDDS or Probuphine is consistent across all nonclinical and clinical studies as will be demonstrated in the safety assessment section below.



Comparability of nonclinical test materials to clinical test product - In general, buprenorphine release rates from implants containing differing amounts of buprenorphine tested in nonclinical studies is comparable to those used in clinical studies over 3 and 6 months as indicated most directly in nonclinical study PRO-NDR-0701. Formulations PRO-510-05-01 & PPX-1005-1 are similarly manufactured as those used in Phase 2 & 3 clinical studies. Three (3) of six Phase 3 clinical studies used the PRO-510 formulation series, most notably the Bioavailability study with Probuphine and Suboxone (study PRO-810). The mean steady state plasma concentrations (C_{ss}) for the test materials of differing amounts of buprenorphine in the dog were within 1 standard deviation of each other's mean. This information suggests that for the implants used in the nonclinical tests with differing amounts of buprenorphine, no real difference in exposure to buprenorphine is anticipated and the nonclinical test products are considered valid for testing for potential clinical test product buprenorphine exposure and Probuphine toxicity.

Blood Steady State Concentrations (C_{ss}) of Buprenorphine (BPN) in Dogs Implanted with Eight Implants for 3 to 6 Months using Differing Types of Implants with Differing Amounts of Buprenorphine ^a		
Formulation	mg BPN/rod	C_{ss} (ng/mL)
NPPPP1a	60	3.39 ± 0.62
NPPPP1b	70	4.09 ± 1.2
NPPPP1c	60	3.39 ± 0.85
NPPPP1d	70	4.72 ± 0.7
PRO-510-05-01 ^b	80	3.16 ± 0.19
PPX-1005-1	80-90	3.65 ± 0.94

a- Study PRO-NDR-0701

b - same test product series formulation as used in bioavailability clinical study

- reviewer prepared table

The physical make up of nonclinical and clinical test products are also considered comparable on the basis of physical characteristics, also allowing nonclinical test product to be used to predict potential clinical toxicity of the final drug product. The proposed drug product is a 26 mm long rod with a 2.5 mm diameter. The following table lists all nonclinical batches used in testing. The similarities in physical dimensions are evident, most notably for the pivotal chronic dog study with the main difference being an additional 10+ mg of buprenorphine per rod, a difference which has just been dealt with in the previous section as to nonclinical-clinical test product buprenorphine release comparability. Note that for the BDDS and BDDS placebo extract studies, pieces of rods were used, the length of which depended on the study and recommended extract incubation volume (see individual study reviews for actual length).

BDDS and BDDS Test Materials Placebo Used in Nonclinical Studies					
Nonclinical study	type	Lot number	size	mg BPN/implant	GLP
PRO-NDR-0001	3 month PK dogs	13219-64	25 mm long 2.5 mm diameter	45	no
PRO-NDR-0701	3-6 month PK	NPPPP1a-d, PPX-1005-1, PRO-510-05-1	25 mm long 2.5 mm diameter*	60, 70, 80, 80/90	no
PRO-NDR-1201	Effect on PK of heat wrap	LOT PRO-080808004	26 mm long 2.5 mm diameter 113 mg weight	80	yes
PRO-NTR-0106	Extract toxicity (ip)	lot 13810- 66a, 66b, 66c, 66d, 66e, 66f	25.7 mm long 2.35 mm diameter 128.5 mg weight	~70	ISO
PRO-NTR-0214	Chronic dog pilot	lots 13657-06, 13933-17, 13933-19, 13922-22, 13657-44 & 13657-51	26.6 mm long 2.3 mm diameter 131.6 mg weight	90 ± 10	no
PRO-NTR-0215	Chronic dog	lots 13657-06, 13933-17, 13933-19, 13922-22, 13657-44 & 13657-51	26.6 mm long 2.3 mm diameter 131.6 mg weight	90 ± 10	yes
		EVA 13657-22	2.55 mm diameter 149.8 mg weight	0	
PRO-NTR-0107, -0109, -0211	Extract - Genetox battery	lot 13810- 66a, 66b, 66c, 66d, 66e, 66f	25.7 mm long 2.35 mm diameter 128.5 mg weight	~70	SO
	EVA extract in vitro chrom ab & in vivo micronucleus	lots 13657-22 & 13810-01	2.55 mm diameter 149.8 mg weight	0	ISO
PRO-NTR-0103, 0104, 0108, 0102, 0105	Extract - sensitization guinea pig, intracutaneous reactivity rabbit, pyrogen IV rabbit ear, in vitro cytotox mouse fibroblast	lot 13810- 66a, 66b, 66c, 66d, 66e, 66f	25.7 mm long 2.35 mm diameter 128.5 mg weight	~70	ISO
PRO-NTR-0108, 0231	4 week implant rabbit, 26 week implant rabbit	lot 13810- 66a, 66b, 66c, 66d, 66e, 66f	25.7 mm long 2.35 mm diameter 128.5 mg weight	~70	ISO
PRO-NTR-1201	Extractable risk assessment	EVA Lot PRO-P-06-01	26 mm long 2.5 mm diameter	0	NA

* - assumed representative size to proposed drug product
- reviewer prepared table

In summary, test product in nonclinical studies is considered appropriate for the testing for potential human toxicity both in regard to release of buprenorphine and on physical composition. Both of these issues of potential systemic toxicity from buprenorphine and/or EVA and local toxicity related to solid implants, will be addressed in the following nonclinical safety assessment sections.

Systemic and Local Safety of BDDS Implants containing Buprenorphine and EVA

A main focus of the nonclinical testing program was primarily on the evaluation of the systemic exposure (TK) with potential systemic toxicity of the buprenorphine, of any potential BDDS placebo (EVA) related systemic effects, of any local toxicity of BDDS and/or BDDS placebo, and of any other effects noted in ISO studies. Studies in dogs measured the systemic release and toxicity of buprenorphine and local toxicity of BDDS and BDDS Placebo. ISO studies measured the acute systemic toxicity, genotoxicity, sensitization, intracutaneous reactivity, pyrogenicity, and cytotoxicity of BDDS and BDDS Placebo extracts. Additional product quality and performance-related human safety issues include impurities and degradants in the Drug Substance and Drug Product, Extractable and Leachables, and drug product performance under conditions of heat wrapping.

These following nonclinical studies were submitted to support systemic and local safety:

Nonclinical Tests Conducted to Evaluate the Potential Systemic and Local Toxicity of BDDS		
Test	material	species
4 week implant (ISO)	BDDS, placebo, USP control	Rabbit
26 week implant (ISO)	BDDS, placebo, USP control	Rabbit
8 or 12 month implant	BDDS	Dog
1, 1.5, or 10 month implant	BDDS, placebo	Dog
ISO extracts		
Acute systemic	BDDS	Mouse
Mutation	BDDS	Bacteria
Chromosomal aberration	BDDS	CHO cells
Chromosomal aberration	placebo	CHO cells
Micronucleus	BDDS	Mouse
Micronucleus	placebo	Mouse
Sensitization	BDDS	Guinea pig
Intracutaneous reactivity	BDDS	Rabbit
Pyrogenicity	BDDS	Rabbit

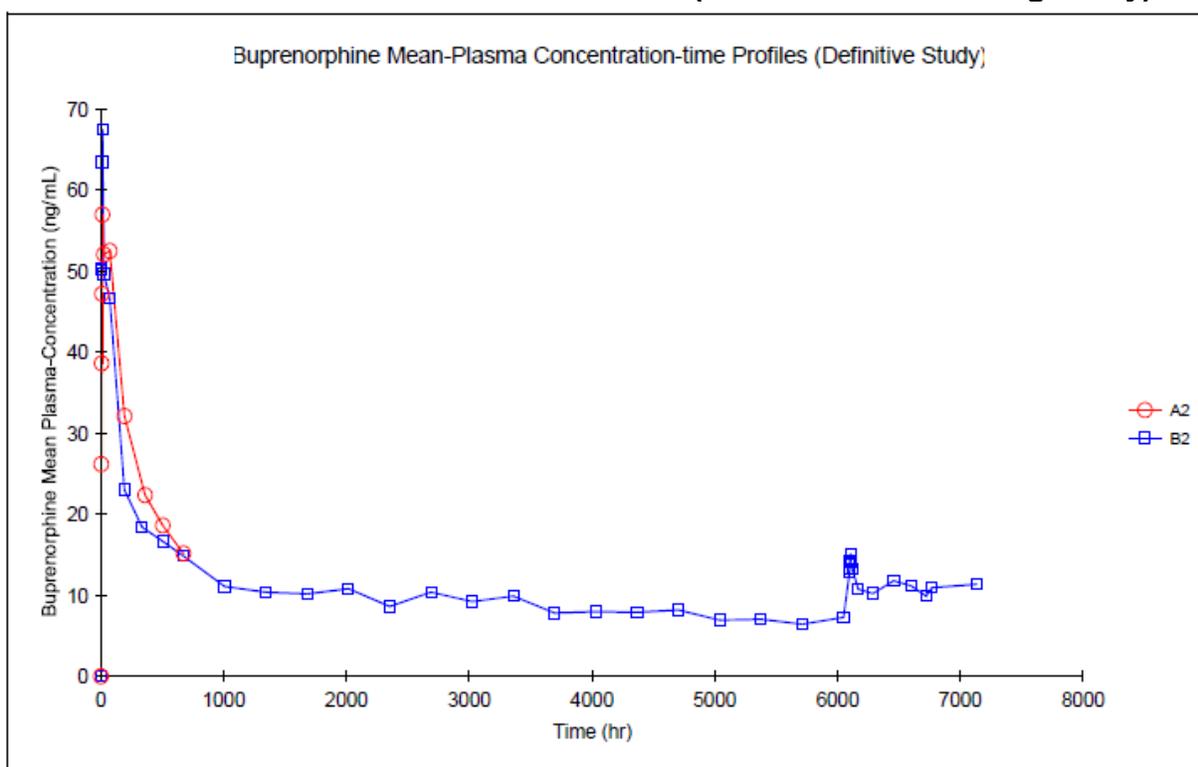
ISO – International Standards Organization method for evaluation of medical devices
- reviewer prepared table

Systemic Safety of Buprenorphine and EVA for Probuphine Implants

The systemic safety profile of buprenorphine administered in BDDS was anticipated to be the same as buprenorphine HCl and no new systemic toxicities arising from the use of buprenorphine in this formulation were expected.

In the definitive 10 months study in dogs, 30 BDDS or 24 BDDS placebo implants were implanted per dog with no notable systemic toxicity other than anticipated from buprenorphine and not at significant severity. Up to 5 implants are proposed for up to 6 months in humans using a comparable drug product as that tested in dogs. In this study, dog systemic exposure levels of buprenorphine were considerably higher with blood steady state concentrations (C_{SS}) of ~ 10 ng/mL (see figure). C_{SS} levels in humans were less during clinical trials at the maximum proposed dose of 4-5 implants (< 1 ng/mL – see figures for individual and pooled buprenorphine clinical data supporting < 1 ng/mL) and to what was observed with approved Suboxone in the bioequivalence clinical study (~ 1.4 ng/mL – no figure, see table of blood level ranges). These comparisons support human systemic safety for buprenorphine based on nonclinical and approved drug data and also support for a 505(b)(2) submission as proposed drug buprenorphine exposure was equal to or less than approved drug buprenorphine exposure.

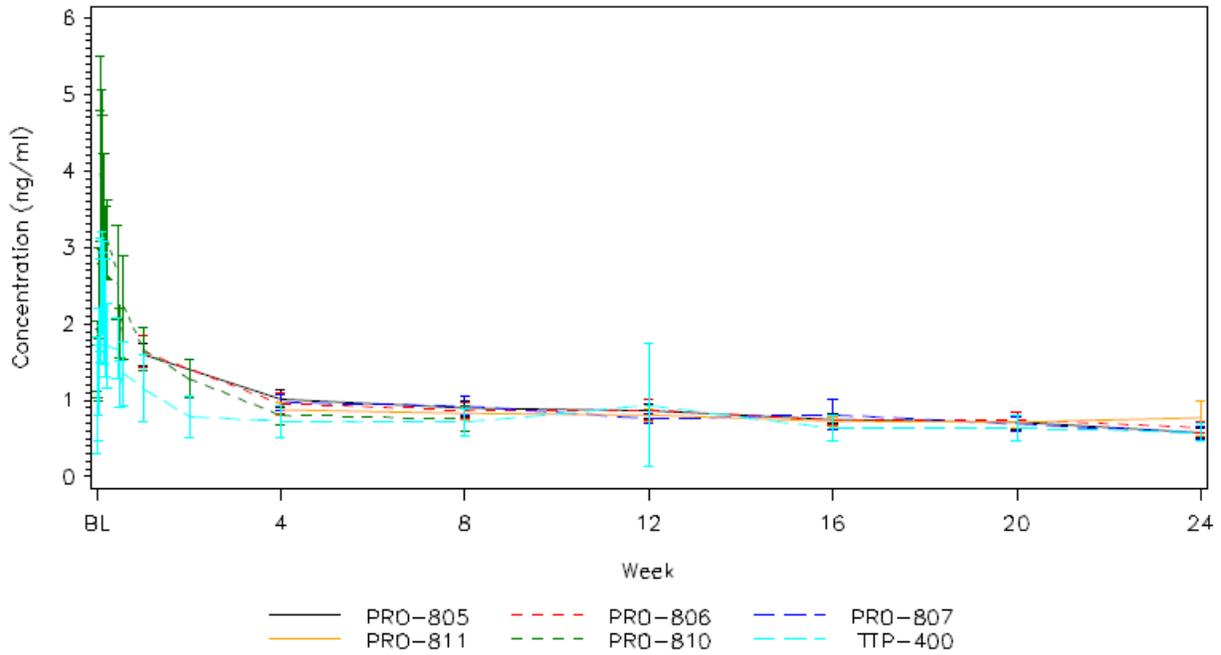
Mean Plasma Concentration-Time Profiles (Definitive Chronic Dog Study)



- when steady state levels of BPN decreased to ~ 8 ng/mL (80%), 6 additional rods were administered at 8.5 months (~ 6000 hr) to maintain it at ~ 10 ng/mL
- Applicant figure

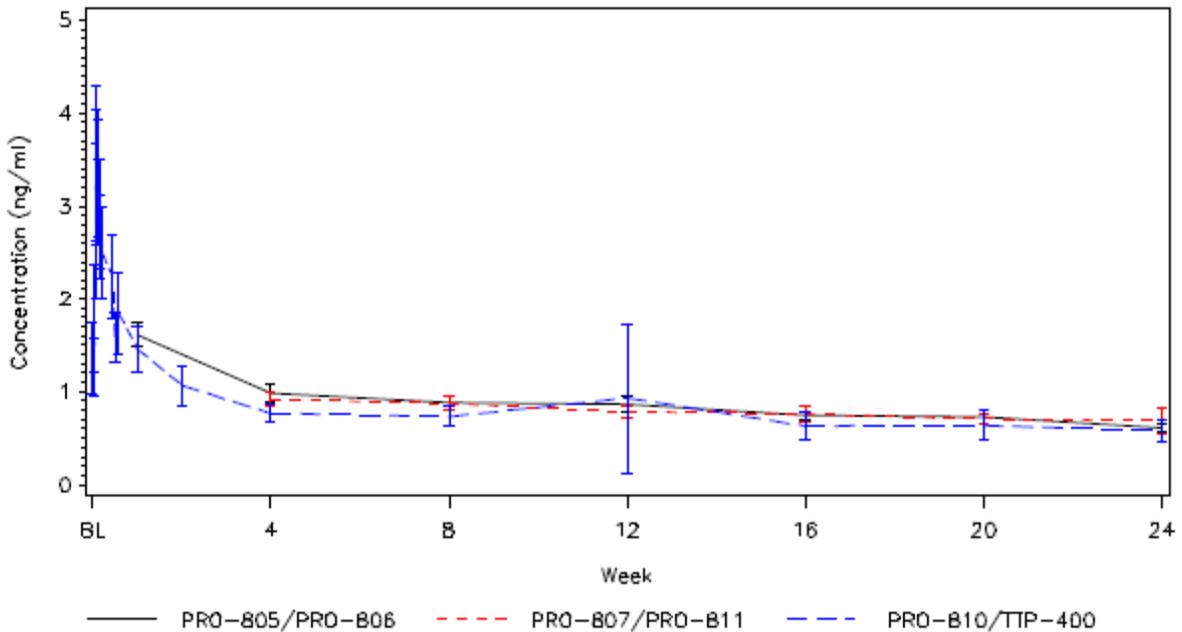
Clinical Studies

Mean ($\pm 95\%$ CI) Plasma Buprenorphine Concentrations over Time, Individual Studies (Pharmacokinetic Population)



- Applicant figure

Pooled Studies – Plasma Buprenorphine Concentrations over Time (Pharmacokinetic Population)



- Applicant figure

Human Blood Levels of Buprenorphine after Suboxone or Probuphine Exposure in Humans			
Drug	Clinical Study	Dose or # of implants ^a	Blood level (ng/mL)
Suboxone	PRO-810	16 mg/day	1.39-1.46
Probuphine	PRO-810	4 rods	0.756-0.862
	PRO-807	4 rods	0.758 ^b
	PRO-811	4 rods	0.766-0.881
	PRO-805	4 rods	0.941 ^c

a - 5th rod optional b - mean concentration c - mean steady state level
 - reviewer prepared table

Exposure Safety Margins - Considering traditional Safety Margin (SM) comparisons for demonstration of human safety, which may not be the most appropriate in this case due to the differing exposure profiles of buprenorphine from the reference drug Suboxone given daily sublingually at 16 mg/day and Probuphine given once every 6 months, the following table demonstrates that proposed buprenorphine exposure from Probuphine will be less than or approximately equal to that from Suboxone and less than as occurred in the pivotal chronic dog study at a nonsystemically toxic dose (only local irritation at implant site - to be discussed in local toxicity section that follows). The human buprenorphine values are from the human Bioavailability Study (PRO-810). The ≤ 1 safety margin for the Suboxone:Probuphine AUC ratio is not considered a safety issue as these are day 1 values for buprenorphine, a time when there is likely still buprenorphine present from a 5-day Suboxone dosing period before Probuphine dosing in study PRO-810. On day 28 of the Probuphine dosing, the Suboxone:Probuphine buprenorphine AUC ratios were 3.2 (4 Probuphine rods – AUC 19.6 ng•hr/mL) and 2.6 (5 Probuphine rods – 24.5 ng•hr/mL extrapolated) compared to the Suboxone AUC of 62.7 ng•hr/mL on day -1 of the clinical trial. Nonclinical data from the chronic dog study (PRO-NTR-0215) clearly supports buprenorphine systemic safety for proposed human dosing with Probuphine.

Safety Margins for Proposed Buprenorphine Levels from Probuphine Compared to Those from Suboxone at the Approved Maximum Recommended Human Dose in the Bioavailability Study (PRO-810) and Compared to Those from the Pivotal Chronic Dog Study (PRO-NTR-0215)^a				
Drug and study population	C _{max} (ng/mL)	SM ^b 4 & 5 rods	AUC _{0-24h} (ng•hr/mL)	SM ^b 4 & 5 rods
Suboxone (sublingual tablet) in humans - 5 days at 16 mg/day	10.4	2.1 & 1.7	66	0.9 & 0.7 ^c
BDDS ^d – dog (at 10 months) - 24 rods for 8.5 months + 6 more rods for 1.5 months	80.3	16 & 13	254	3.4 & 2.7

- a - Approved systemic exposures levels from clinical Suboxone PK or observed Nonclinical TK levels in dog study ÷ Probuphine clinical PK exposure levels
 - b - Safety margin (SM) = approved Suboxone PK or observed animal TK ÷ Probuphine PK from clinical study with 4 Probuphine rods (5 rod levels extrapolated) of 4.9 & 6.3 ng/ml (Cmax) and 75 & 93 ng•h/mL (AUC₀₋₂₄), respectively.
 - c - SM of ≥1 preferred but these values of ~1 considered adequate as day 1 sampling of buprenorphine after dosing with Probuphine has residual buprenorphine present from Suboxone dosing on days -5 to -1 in study PRO-810.
 - d - Buprenorphine Drug Delivery System (BDDS) is the nonclinical testing material equivalent of Probuphine
- reviewer prepared table

In summary, BDDS and BDDS Placebo caused no unexpected systemic toxicity at nonclinical doses greater than proposed human doses. Proposed exposure to buprenorphine from Probuphine are less than the exposure achieved at the Maximum Recommended Human Dose (MRHD) for Suboxone as tested in study PRO-810, thereby supporting the appropriateness of referring to the Agency's prior finding of systemic safety of Suboxone through the 505(b)(2) pathway.

Local Toxicity of Probuphine and EVA Implants

The local toxicity safety profile for BDDS and BDDS placebo focused on the local tolerability of the drug product implants (BDDS), EVA only containing implants (BDDS placebo), and USP negative control polyethylene implants in rabbits and dogs.

Implant studies in rabbits or dogs for 4 weeks, 26 weeks, 8 months, 10 months, and 12 months identified BDDS and BDDS placebo to be significant and somewhat reversible irritants at the implantation sites. While the 4 and 26 weeks studies were ISO implantation studies in rabbits using smaller implants (which tend to be less rigorous than standard local toxicity studies), microscopic evaluation of implant sites was conducted in these studies and was also done for the 10 month general toxicity study in the dog.

Macroscopically, no notable irritation was observed at the implant sites in any of the studies. Macroscopically, the implant site could not be distinguished after a 2 month recovery period when the implants were removed at 8 months in dogs.

Microscopically, BDDS and BDDS placebo implants were moderately irritating at 4 weeks after implantation in male rabbits. At 26 weeks (6 months), BDDS was a moderate irritant and BDDS placebo was a slight irritant in male rabbits suggesting a possible enhanced irritation by buprenorphine as BDDS-related irritation did not decrease. USP negative control implants were slightly irritating at 4 and 26 weeks after implantation. This data indicates that buprenorphine appears to enhance local irritation at the implant site

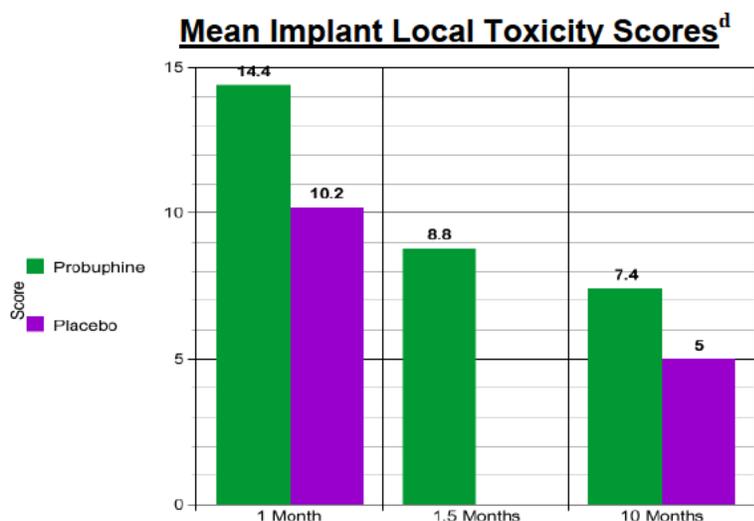
Microscopically, BDDS was moderately to severely irritating and BDDS placebo was moderately irritating after implantation at 1 month after implantation with full sized implants in male and female dogs suggesting a possible enhanced irritation by

buprenorphine. At 1.5 months after implantation BDDS was slightly to moderately irritating after implantation in male and female dogs suggesting a possible reversal in irritation. At 10 months, BDDS implants were slightly to moderately irritating and BDDS placebo implants were slightly irritating indicating possibly reversibility of local effects by 10 months in dogs. Based on these findings, buprenorphine increased the local toxicity greater than observed from EVA alone. Of note is that implants will be replaced in humans every 6 months, a time point not evaluated for reversibility of irritation in dogs.

Taking a closer look at the local toxicity in the pivotal chronic dog study (PRO-NTR-0215), it is noted that the predominant histological observations of fibrosis and inflammation were generally more severe in BDDS treated animals compared to BDDS placebo animals (see table and figure). The severity of local toxicity decreased over time but was substantial during the early phase after implant insertion with the presence of buprenorphine in BDDS apparently causing increased local toxicity compared to BDDS placebo. By ISO scoring, implants were slight irritants by 10 months.

Severity ^a of Local Toxicity Based on Histological Observations in Dogs Treated with BDDS or BDDS Placebo (EVA only) Implants for 1, 1.5 ^b or 10 Months					
Observation	Probuphine			Placebo	
	1 month	1.5 months	10 months	1 month	10 months
Increased fibrosis	1 to 4	1	1 to 2	1 to 3	1
Increased inflammatory cells					
Polymorphonuclear cells	1 to 3	0	0	1	0
Lymphocytes	1 to 3	1 to 2 ^c	1 to 2	1 to 3	0 to 1
Macrophages	1 to 4	0 to 3	0 to 3	1 to 3	0 to 1
Plasma cells	0 to 1	0 to 1	0 to 1	0	0 to 1

a - severity of fibrosis (0 - none, 1 - narrow band, 2 - moderately thick band, 3 - thick band, 4 - extensive band)
 - severity of inflammatory cells (0 - none, 1 - rare, 2 - 5-10 per microscopic field, 3 - heavy infiltrate, 4 - packed)
 b - 10 month animals received additional implants at 8.5 months
 c - 1 of 17 scored sites exhibited a lymphocyte severity score of 4 but all the rest were a severity of 1 and 2 and this score was not considered as a severity of 4 was not observed at 1 month
 - reviewer prepared table



d - Nonirritant (0.0-2.9), Slight Irritant (3.0-8.9)
 Moderate Irritant (9.0-15.0), Severe Irritant (≥15.1)
 - reviewer prepared graph

Other ISO Toxicity Studies of Probuphine and EVA Implants

Other ISO toxicity studies for medical devices using BDDS and BDDS Placebo extracts were conducted to assess acute systemic toxicity, genotoxicity, sensitization, intracutaneous reactivity, pyrogenicity, and cytotoxicity. BDDS extracts did not cause acute systemic toxicity after intraperitoneal injections into the mouse, genotoxicity using a standard *in vivo* and *in vitro* test battery, delayed dermal contact sensitization in the guinea pig, intracutaneous reactivity after subcutaneous injection in the rabbit, a pyrogenic response after intravenous injection in the rabbit ear vein, and cytotoxicity to mouse fibroblast cultures. BDDS Placebo extract did not cause genotoxicity in an *in vitro* chromosomal aberration study using mammalian cells or in an *in vivo* micronucleus assay in intraperitoneally injected mice. The direct applicability of these results to human safety is not known as the dosing solutions were not analyzed to identify extracted chemicals or to quantitate exposure levels to any extracted chemicals. An analytic assessment of the extract is not necessary per ISO protocols for these device-based studies.

In summary, BDDS and BDDS placebo did not cause any additional toxicity in an ISO test battery of BDDS and BDDS placebo extracts.

Other nonclinical safety assessments

Impurities and degradants in Drug Substance and Drug Product and EVA, and extractables from EVA are within acceptable levels according to ICH Q3A and Q3B guidances, the FDA *Guidance for Industry - Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches* (Dec 2008) and the PQRI recommendation document: *Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled Products* (September 8, 2006). These PQRI recommendations are also used for other exposure routes as a matter of FDA practice.

Impurities and degradants - The total dose of buprenorphine is 80 mg per rod with a maximum of 5 rods for a 400 mg dose implanted of which no more than (b) (4) % of buprenorphine is released from the rods over 6 months (clinical trial TTP-400-02-1 which measured residual buprenorphine in extracted rods) which corresponds to (b) (4) mg/day. According to ICH Q3A, safety qualification is required at 0.15% or 1 mg total daily intake with a maximum daily API dose of $\leq 2\text{g/day}$. The Applicant proposes drug substance specifications with individual impurities and/or degradants up to NMT (b) (4) % which exceeds the 0.15% threshold but the drug substance specifications are considered qualified based on approved buprenorphine (same DMF (b) (4) and plus USP monograph) as well as specifications being within the 1 mg TDI threshold. See Chemistry review for more detail.

Excipient - Ethylene vinyl acetate (EVA) is the only excipient used in the manufacture of Probuphine implants. Ethylene vinyl acetate copolymer (EVA) is listed in the FDA Inactive Ingredient Guide (IIG) as being used in other approved products for this dosage

form and route. EVA used in Probuphine implants contains vinyl acetate monomer (VAM). VAM is classified as a 2B carcinogen (possible human carcinogen) by the International Agency for Research on Cancer (IARC) and A3 (proven carcinogen in animals with unknown relevance in human by the American Conference of Governmental Industrial Hygienists (ACGIH). At a specification of \leq (b) (4) ppm vinyl acetate monomer, the potential maximum exposure from 5 rods is (b) (4) mcg if all VAM leaves the rods at one time. This is not the case as the VA leaves the rods over the course of the (b) (4) exposure period making the potential daily exposure less than the concern level for structural alerts/genotoxins of (b) (4) mcg/day assuming that VA migrates from the EVA at no different amount than buprenorphine migrates from Probuphine ((b) (4) % of total) (see Chemistry review).

EVA extractables - specifications were set based on the PQRI recommendation document: *Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled Products* (September 8, 2006). The PQRI recommendations are also used for other exposure routes as a matter of FDA practice. The applicant conducted an extraction study with EVA and packaging components (PRO-NTR-1201) identifying the extracts.

Based on the results of that study and the identified extractables safety limits as per the PQRI document (NMT (b) (4) mcg/day for structural alerts, NMT (b) (4) mcg/day for non-structural alerts, and NMT (b) (4) mcg/day for unknowns) which were agreed upon by the applicant, those agreed upon EVA specification values are as follows using the amount of EVA per rod ((b) (4) mg) x 5 rods (b) (4)



EVA qualification based on the above criteria will be acceptable by an appropriate supplier Certificate of Analysis or else the applicant must conduct testing on the batches of EVA (see Chemistry review).

Heated Probuphine and buprenorphine pharmacokinetics - The effects of external application of heat on the pharmacokinetics of buprenorphine release from Probuphine were determined. Skin surface temperatures increased $\sim 5^{\circ}\text{C}$ ($\sim 40^{\circ}\text{F}$) during heat application. The mean concentration-time profiles showed that buprenorphine plasma levels immediately after dosing was similar in animals with no heat application compared to those after 8 hours of heat application to the implant site. In addition, no heat effect was observed following 8 hours of heat application to the implant site five weeks after implantation compared to that at 4 weeks after implant with no heat application.

Overall Nonclinical Conclusion

Human safety is supported at the maximum proposed chronic dose of Probuphine (4-5 implants) which is intended to provide sustained delivery of buprenorphine for up to 6 months for the maintenance treatment of opioid dependence using an alleged abuse and diversion deterrent formulation. This support is based on Probuphine data satisfying 505(b)(2) submission requirements for buprenorphine exposure, acceptable product quality specifications and stability, and valid nonclinical studies demonstrating acceptable local tolerability with an acceptable clinical pharmacology relationship between nonclinical test product and the proposed drug product.

12 Appendix/Attachments

12.1 DSI Audit of chronic dog study reviewed in section 6.1

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

/s/

GARY P BOND
04/04/2013

ADAM M WASSERMAN
04/05/2013

I concur with Dr. Bond that from the nonclinical perspective this application may be approved.