CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-306

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	21 June 2010
From	Robert B. Shibuya, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	21-306
Applicant	Purdue Pharma, LLC
Date of Submission	30 September 2009
PDUFA Goal Date	30 June 2010 (The initial PDUFA date was 30 March 2010. The clock was extended 3 months to review a revised REMS)
Proprietary Name / Established (USAN) names	Butrans [buprenorphine transdermal system (BTDS)]
Dosage forms / Strength	Transdermal system (patch) 5, 10, 20 mcg/hr
Proposed Indication(s)	1. Relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time
Recommended:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Primary Medical Officer Review	Robert A. Levin, M.D.
Statistical	Jonathan Norton, Ph.D. Dionne Price, Ph.D.
Pharmacology Toxicology Review	Gary Bond, Ph.D. Adam Wasserman, Ph.D.
CMC Review	Zavier Ysern, Ph.D. Prasad Peri, Ph.D.
CMC Biopharmacology	Tapash Ghosh, Ph.D. Patrick Marroum, Ph.D.
Clinical Pharmacology Review	Sheetal Agarwal, Ph.D. Suresh Doddapaneni, Ph.D.
QT Interdisciplinary Review Team	Christopher Tornoe, Ph.D. Christine Garnett, Ph.D. Lihan Yan, Ph.D. Monica Fiszman, M.D. Norman Stockbridge, M.D.
OSE/DRISK	Jeanne Perla, Ph.D. Gita Toyserkani, PharmD Marcia Britt, Ph.D. Jodi Duckhorn, MA Agnes Plante, BSN, RN

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1. Introduction

Butrans™ (previously known as Norspan) is a transdermal system that contains buprenorphine, a mixed opioid agonist/antagonist, in an adhesive matrix. Purdue Pharma, the Applicant, seeks an indication of the management of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

Butrans has a long development history dating to 2000, although the NDA has only been reviewed once (date of action, 31 August 2001). The 2001 review cycle resulted in a 62-item Not-Approvable Letter.

With regard to the number of deficiencies in each discipline, there was some overlap; certain deficiencies pertained to more than one discipline. However, as discussed in each of the separate discipline reviews, the deficiencies were distributed as follows:

- Chemistry/Manufacturing/Controls – 49 deficiencies
- Pharmacology/Toxicology – 2 deficiencies
- Clinical Pharmacology – 3 deficiencies
- Clinical – 11 deficiencies

Two Post-Action meetings were conducted with the Applicant (6 November 2001 and 2 April 2002). Key agreements from the two Post-Action meetings include:

1. An in vivo drug-drug interaction study using Cytochrome P450 inhibitors is acceptable.
2. Additional adequate and well-controlled studies will be required. It is difficult to determine the clinically relevant effect size in clinical trials. Purdue should optimize the clinical trial design to attempt to minimize patient dropout.
3. Pursuant to many errors noted during the first review cycle, Purdue was cautioned to perform a check of all data, analyses, tables, and listings when resubmitting the NDA.
4. Purdue was instructed to analyze safety data by dose.
5. An additional human abuse liability study will not be required if buprenorphine is changed to Schedule III from Schedule V.
6. The Agency is very concerned about the residual buprenorphine in the patch after use (b) (4) which represents a safety and abuse risk. The Sponsor should improve the design of the patch to minimize the residual. However, in the 2 April 2002 meeting, FDA noted that, because there are no set standards for residual drugs in the patch, the current formulation could be approved.

With this resubmission, the Applicant has successfully addressed the CMC (pending adequate responses on three DMFs and some minor information requests), Pharmacology/Toxicology, and Clinical Pharmacology deficiencies noted in the Non-Approval Letter. The Applicant has provided evidence of efficacy in both opioid-naïve and opioid-experienced patients with low back pain. The safety data were updated and re-analyzed in an acceptable manner for review.

The safety of the drug is representative of an opioid; no unexpected toxicities were identified although there were some severe allergic reactions noted that will have to be addressed in labeling.

During the previous review cycle, there were issues about abuse liability that were resolved in 2001 because the moiety has been upscheduled from Schedule V to Schedule III in the Controlled Substances Act.

The other major point of contention was the amount of residual buprenorphine remaining in a used patch (b) (4). Purdue had been asked to optimize the formulation to minimize the drug residual. Apparently, the Applicant has made a minimal effort to reformulation and those efforts have had no success. In a summary dated 20 May 2010, the Office of New Drug Quality Assessment (ONDQA) opined that it was unclear whether further development work would conclusively result in reducing the residual buprenorphine. Thus, ONDQA "reluctantly" recommended approval of the drug. At the time of finalization of this review, the Controlled Substance Staff, remains concerned about the amount of residual buprenorphine.

The Risk Evaluation and Mitigation Strategy (REMS) for this product is envisioned as being very similar to the REMS for OxyContin (NDA 20-553) because the risks of the drugs are similar. At this time, with minor modifications, it appears that the REMS will be acceptable.

2. Background

The buprenorphine moiety was first approved in 1981 (Buprenex, buprenorphine injection, NDA 18-401) with an indication of relief of moderate to severe pain. In 2002, the buprenorphine moiety was approved for the treatment of opioid addiction [Subutex and Suboxone (combination with naloxone), NDAs 20-732 and 20-733].

The Applicant seeks to use one of the principal pharmacologic actions of buprenorphine, analgesia. Purdue, has formulated the drug into a drug-in-matrix patch to be worn for 7 days for an indication of chronic pain requiring opioids for an extended period of time.

The buprenorphine molecule is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Thus, unlike most opioids, buprenorphine has a dose ceiling. Purdue did not conduct studies to determine the maximal effective dose but the proposed labeling has a dose ceiling of 20 mcg/hr. It is important to note that the product is marketed abroad at strengths up to 70 mcg/hr.

While there was a long list of deficiencies noted in the 2001 Not Approvable letter, the review team is in agreement that Purdue has successfully addressed each deficiency except one, the amount of buprenorphine remaining in the patch after use. This issue will be further discussed in Section 3 of this review.

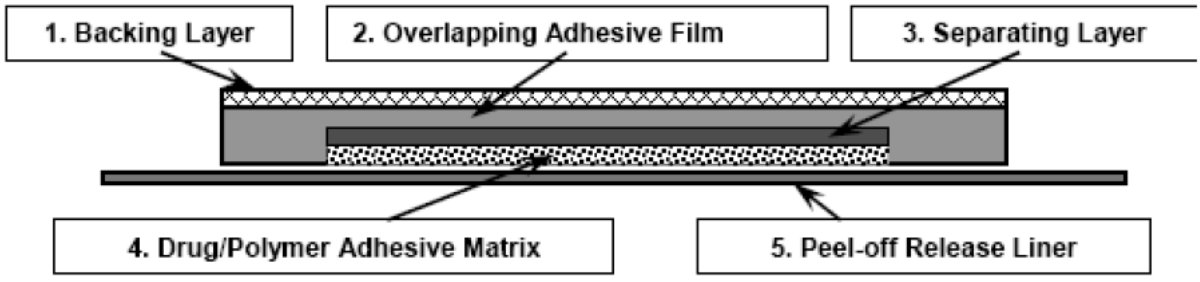
This review will focus on how the Applicant addressed the deficiencies noted in the 2001 Action Letter.

3. CMC/Device

The Chemistry/Manufacturing/Controls (CMC) review was conducted by Xavier Ysern, Ph.D. with the supervisory concurrence of Prasad Peri, Ph.D.

The drug substance is buprenorphine which is dissolved in a polymer matrix. The drug-adhesive matrix is manufactured with a "separating layer", a layer of adhesive film, and a backing layer to keep the product from sticking to clothing. A peel-off release liner is applied to protect the drug-matrix during manufacture and storage. The product is shown schematically in Figure 1.

Figure 1: Schematic of cross-section of Butrans



Cross Section Diagram of BuTrans (not to scale).

Source: Dr. Ysern's review, page 7/102

The product is manufactured in 3 strengths: 5 mcg/hr, 10 mcg/hr, and 20 mcg/hr. Those flux rates correspond to 5 mg, 10 mg, and 20 mg of drug in the entire patch. The dose delivered is controlled by surface area. However, it is important to note that the product has a rim of non-drug-containing adhesive around the periphery of the patch. Thus, the patches cannot be cut to size/dose.

The specific deficiencies noted in the Non-Approval Letter broke down as follows:

- Drug substance manufacture – 1 item
- Drug substance specification – 13 items
- Drug product components and composition – 7 items
- Drug product manufacture and in-process controls – 6 items
- Drug product specification – 9 items
- Drug product analytical procedures – 5 items
- Drug product container-closure system – 3 items
- Drug product stability – 5 items

Except as noted in the last paragraph of this section, the Applicant has adequately responded to all of the CMC deficiencies noted in the 2001 letter. Please see Dr. Ysern's review for additional details. Purdue has made the following additional changes to their manufacturing:

- DMFs for three excipient holders no longer supply excipient for this product
- The packaging includes a (b) (4) pouch.

- The Applicant has modified its procedures to comply with the USP <467> Residual Solvents requirement.

Inspections of the manufacturing, testing, and packaging sites are all acceptable.

Drs. Ysern and Peri have recommended approval, pending the adequate response to queries mostly regarding drug product specifications and a scientific justification to support the amount of residual buprenorphine after the patch is used for 7 days.

As noted in Section 1 of this review, during the review cycle, the Office of New Drug Quality Assurance (ONDQA) questioned the amount of residual buprenorphine in the patch after use. ONDQA is preparing to issue draft guidance regarding the issue of drug residual in drugs for transdermal delivery. After internal vetting, ONDQA has decided that it was unclear if further development work would conclusively result in reducing the residual buprenorphine in the product. Thus, ONDQA "reluctantly" recommended approval.

A CMC Biopharmaceutics consult, by Drs. Tapash Ghosh and Patrick Marroum, was conducted to assess the impact of changes in in vitro dissolution rate and adhesion strength over storage on in vivo performance. Drs. Ghosh and Marroum found that the in vivo plasma concentrations vary widely. However, in conjunction with Drs. Sheetal Agarwal and Suresh Doddapaneni (Office of Clinical Pharmacology), the team felt that tightening the dissolution specifications and a post-approval commitment to collect dissolution data from 12 patches with the potential to require Level 3 testing would suffice in the interim (12-months). The Applicant agreed with this arrangement.

4. Nonclinical Pharmacology/Toxicology

The nonclinical review was conducted by Gary Bond, Ph.D. with the supervisory concurrence of Adam Wasserman, Ph.D.

The Applicant elected to use the 505(b)(1) approval mechanism and submitted a complete pharmacology/toxicology (P/T) package. That package was reviewed during the first review cycle. It is important to note that the carcinogenicity study and the fertility and early embryonic development, the peri- and postnatal development, and embryo-fetal development reproductive toxicology studies were not submitted at that time; Purdue were originally allowed to complete these studies as a postmarketing commitment, but later agreed to submit them with the resubmission. Purdue has completed these studies and they were submitted with the current package.

There were two P/T deficiencies noted following the first review cycle.

- Questions were raised about the potential toxicity of the Duro-Tak patch adhesive
- Because of the question about tolerance and dose escalation, a 6-month chronic nonclinical study was required to assess systemic toxicities

A brief discussion of the four (two deficiencies identified in the 2001 letter, carcinogenicity, and reproductive toxicity) major issues addressed in the current submission follows. Please see Dr. Bond's excellent review for further details.

1. The chronic dermal patch testing in rabbits, dogs, and minipigs supported the use of the 20 mcg/hr dose. Dr. Bond writes, "In rats, absorbed amounts of buprenorphine after skin painting that caused no adverse effects was approximately ~335 times that absorbed in humans from one 20 mcg/h Butrans patch. This addresses the safety concern noted in the Not Approvable Letter that humans may require higher doses of buprenorphine as they become tolerant to its effects."
2. A carcinogenicity study conducted in transgenic mice showed that buprenorphine is not carcinogenic at relevant human dose levels. A two-year rat skin painting study showed that buprenorphine was associated with increased benign interstitial cell tumors of the testis at ~220 times the maximum human exposure. The no carcinogenic effect level approximated 140 and 350 times the maximum human exposure in males and females, respectively.
3. The Applicant addressed the potential toxicity of the Duro-Tak adhesive with chronic rodent studies, toxicity studies, and a literature review. The Applicant's response adequately addressed this issue. Dr. Bond amended his review on 11 May 2010 to confirm that the (b) (4) proposed specification of NMT (b) (4) ppm is acceptable based upon a reconsideration of the (b) (4) carcinogenicity data.
4. The reproductive toxicity studies showed increased stillborns and early deaths, reduced litter size, and/or reduced pup growth in the F1 generation at relevant doses. Therefore, the P/T team recommends a Pregnancy Classification of C for this product, consistent with all buprenorphine-containing products.

Drs. Bond and Wasserman have recommended approval from the pharmacology/toxicology perspective.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review was conducted by Sheetal Agarwal, Ph.D. with the supervisory concurrence of Suresh Doddapaneni, Ph.D.

The 2000 submission contained 17 Clinical Pharmacology studies that addressed the pharmacokinetics/pharmacodynamics of buprenorphine, drug-drug interactions, effects of endogenous and exogenous heat, and the absolute bioavailability of buprenorphine as delivered by Butrans. The 2000 submission was reviewed by Dr. Suliman AlFayoumi. Dr. Agarwal summarized the Clinical Pharmacology findings from the previous cycle as follows (almost verbatim from Dr. Agarwal's review).

1. Exposure-response relationship: There is no exposure-response relationship for buprenorphine patches. A pooled data analysis of the relationships between the pharmacodynamic markers for pain relief and buprenorphine concentration did not reveal any correlation. The buprenorphine concentrations assessed in the analysis ranged from 0 to 500 pg/ml.

2. Absolute bioavailability: The absolute bioavailability of buprenorphine from the three dose strengths of BTDS ranged within 15-16% after a 7-day application period (Study BP97-0501).
3. Dose proportionality: Exposure metrics suggest that dose proportionality exists for all three dose strengths over a 7-day application period. However, the same trend is not evident over a 3-day application period.
4. Flux rates: Studies employing single BTDS 5, 10 and 20 patches over a 7-day application period suggest that their respective mean flux rates are 5, 10 and 20 mcg/hr. However, for a 3-day application period, the mean flux rates are (6-7.5), (5.8-17) and (34-39) mcg/hr for single BTDS 5, 10 and 20 patches, respectively. Hence, the flux rates for the 3-day application period appear to clearly differ from those of the 7-day application period.
5. Interchangeability to different body sites for patch application: Application of BTDS 10 to the midaxillary line, the upper outer arm, the upper chest or the upper back resulted in comparable systemic buprenorphine levels. BTDS applications may be applied interchangeably to all 4 sites for an application period of 7 days.
6. Effect of external heat: Fever (internal heat) did not alter the PK of buprenorphine with BTDS applications. However, application of external heat resulted in 26-55% higher Cmax values relative to application without heat.
7. Special populations:
    a. Renal impairment: An analysis of pooled data from Phase 3 studies showed no clear trends in the relationship of creatinine clearance and buprenorphine plasma levels. There is no need for dose adjustment with renal function.
    b. Age: The effect of age on buprenorphine PK was investigated in study BP96-0702 and using analysis of pooled clinical pharmacology studies. Overall, no significant age effect was observed on buprenorphine PK. There is no need for dose adjustment in the elderly.
    c. Gender: The effect of gender on buprenorphine PK was investigated using analysis of pooled clinical pharmacology studies. Overall, no significant gender effect was observed on buprenorphine PK.
    d. Race: The effect of ethnicity on buprenorphine PK was investigated using analysis of pooled clinical pharmacology studies. Overall, no significant ethnicity effect was observed on buprenorphine PK.
    e. Body weight: The effect of body on buprenorphine PK was investigated using analysis of pooled clinical pharmacology studies. Overall, a small decrease in buprenorphine Cmax and AUC were observed with an increase in body weight (R2 for the correlation of body weight with AUC was 0.024 and for the correlation of body weight with Cmax was 0.025). No dose adjustment is needed based on body weight.
8. Drug-drug interactions (DDI):
    f. Pharmacodynamic (PD) DDI studies suggested that midazolam, diuretics did not exacerebate opioid adverse events, particularly respiratory depression, when co-administered with a BTDS application.

The deficiencies from the 2001 Not Approvable Letter addressed by the Applicant in the current submission and reviewed by Dr. Agarwal include:

- The data relating to hepatic impairment did not allow for a reasonable understanding of the clinical state of disease and pharmacokinetics.
- Drug-drug interactions with CYP450 inhibitors and Butrans had not been adequately addressed.
- Include an analysis of the electrocardiogram (ECG) intervals.

To address the deficiency related to hepatic impairment, the Applicant reanalyzed data from a previously submitted study (BP97-0112), separating the data by Pugh-Child class. The reanalysis shows that in patients with mild to moderate hepatic impairment, peak plasma levels (Cmax) and extent of exposure (AUCt) of buprenorphine did not increase with the severity of hepatic impairment. Similar systemic exposures (AUCt) but a reduction in Cmax were observed when comparing systemic buprenorphine levels (administered as intravenous buprenorphine 0.3 mg) in patients with mild to moderate hepatic impairment and healthy subjects. In addition, no firm conclusions can be made regarding changes in total exposure to norbuprenorphine relative to severity of hepatic impairment due to lack of sufficient data. The Applicant recommended that mild and moderate hepatic impairment patients be started at the lowest 5 mcg/h dose and Dr. Agarwal concurred with that proposal.

The Applicant conducted an interaction study with the potent CYP 3A4 inhibitor, ketoconazole and the Butrans patch. Surprisingly, the Cmax and AUC for buprenorphine, a CYP 3A4 substrate, did not change although the Cmax and AUC increased by 50% for the metabolite, norbuprenorphine. Dr. Agarwal notes that subjects administered buprenorphine, administered via the sublingual route (Suboxone) and in the presence of atazanavir, another CYP 3A4 inhibitor, experienced substantial (1.4- to 2-fold) increases in Cmax and AUC for both buprenorphine and its metabolite. Dr. Agarwal notes that atazanavir is both a 3A4 and a UGT1A1 inhibitor. She opined that that additional activity and the difference in the route of administration (bypassing first-pass metabolism) for Butrans, may have led to the unexpected negative drug-drug interaction study with ketonconazole.

To address the potential for buprenorphine to prolong the QT interval, the Applicant conducted and submitted a thorough QT study (tQT study). This study was reviewed by the QT Interdisciplinary Review Team (QT IRT). The QT IRT's findings will be discussed further in Section 8 of this review. Briefly, the tQT study showed no QT prolongation at the 20 mcg/hr dose but there was clinically significant prolongation at the supratherapeutic dose (40 mcg/hr).

Drs. Agarwal and Doddapaneni are recommending approval from the clinical pharmacology perspective.

6. Clinical Microbiology

Clinical microbiology is not applicable for this product.

7. Clinical/Statistical- Efficacy

The primary clinical review was conducted by Robert Levin, M.D. and the primary statistical review was conducted by Jonathan Norton, Ph.D. with the supervisory concurrence of Dionne Price, Ph.D.

The Applicant submitted two adequate and well-controlled studies to address Deficiency #55 in the 2001 Action Letter. Both studies used patients with moderate to severe chronic low back pain. Study BUP 3024 (Study 24) studied the drug in opioid-naïve patients; Study BUP3015 (Study 15) studied the drug in opioid-experienced patients.

The studies are described in detail in Dr. Levin's excellent review. Briefly, Study 24, which was conducted under a Special Protocol Assessment (SPA) agreement, was a multicenter, randomized, double-blind, placebo-controlled study of Butrans (10 or 20 mcg/hr, as tolerated) versus placebo. Eligible patients had moderate to severe chronic low back pain inadequately treated with non-opioid analgesics or low-dose (< 5 mg oxycodone equivalent daily) opioids. Patients with prolonged QTc intervals were excluded.

Following an analgesic washout period, patients who reported a pain intensity of ≥5/10 were eligible for the study. Eligible patients were started on a 5 mcg/hr patch. Patients were titrated through 10 mcg/hr to a maximum of 20 mcg/hr in an attempt to balance analgesia and adverse events. The goal was to identify patients who 1. Experienced a decrease in pain intensity of ≥2 points on three consecutive days prior to randomization, 2. Had an average pain over the last 24 hours of ≤4 points, and 3. Tolerate a dose of either 10 or 20 mcg/hr.

Patients meeting the continuation criteria were randomized to stay on the optimized dose of 10 or 20 mcg/hr or to be switched to placebo. Patients were maintained on the dose of drug for 12-weeks. Patients randomized to active who started on 20 mcg/hr were allowed one down titration and one up titration over the 12 weeks. Patients were allowed to rescue with immediate-release oxycodone for the first six days post randomization. Following that, acetaminophen was the only permitted prn analgesic. Also permitted were adjuvant analgesics at stable dose (30 days) such as anti-depressants and anticonvulsants) and stable-dose (6 weeks) oral corticosteroids.

The primary efficacy endpoint was the average pain over the last 24 hours at Week 12. There were a number of secondary endpoints including the use of rescue, a questionnaire about sleep, a responder analysis, and other assessments of pain and quality of life. A modified subjective opioid withdrawal scale (SOWS) was conducted daily for the first seven days post-randomization.

A total of 1027 patients qualified for run-in and 541 patients were randomized. Of the approximately 50% of patients who did not qualify for randomization, 23% dropped out for an adverse event and 14% dropped out due to loss of therapeutic effect. Approximately 70% of the patients who were randomized completed the 12-week study. Not unexpectedly, patients in the BTDS dropped out for adverse events at a higher rate than placebo (16% vs. 7%) and patients on placebo dropped out for lack of efficacy at a higher rate (13% to 9%).

The trial met its specified objective using the prespecified analysis methodology which included a hybrid LOCF/BOCF approach for imputing data from early discontinuations. The summary data for the primary efficacy analysis are shown in Table 1, following.

Table 1: Analysis of Primary Efficacy Endpoint (pain intensity over the last 24 hours), Study 24

Weeks/Visits	BTDS (n = 257)	Placebo (n = 284)
Screening[a] (Visit 2)		
n	257	284
Mean (SD)	7.24 (1.263)	7.17 (1.223)
Prerandomization[b] (Visit 3)		
n	257	284
Mean (SD)	2.57 (1.283)	2.56 (1.207)
Double-blind Week 12 (Visit 8)		
n	257	283[d]
Mean (SD)	3.83 (2.738)	4.38 (2.690)
Repeated Measures Analysis/Least Squares Means (SE) at Week 12		
LS mean (SE)	3.81 (0.166)	4.39 (0.152)
Treatment Comparison at Week 12		
Difference in LS means from placebo	−0.58 (0.225)	
P value vs placebo[c]	.0104	
95% CI for difference from placebo	(−1.02, −0.14)	

Source: Dr. Levin's review, page 61/190

The Applicant conducted sensitivity analyses with several imputation methods, summarized in Table 2.

Table 2: Sensitivity analyses, Study 24, Primary Efficacy Endpoint

Type of Analysis	BTDS vs Placebo		
	Difference from Placebo	*P* value	95% CI for Difference from Placebo
Hybrid Weeks 4, 8, 12	−0.62	.0016	−1.01, −0.24
BOCF Week 12	−0.34	.1502	−0.79, 0.12
LOCF Week 12	−0.93	< .0001	−1.33, −0.52
Retained Dropout ITT Week 12	−0.75	.0007	−1.18, −0.31
Valid Pain Score Substitution Week 12	−0.59	.0095	−1.03, −0.14
Per-Protocol Week 12 (hybrid imputation)	−0.52	.0260	−0.98, −0.06

Source: Dr. Levin's review, page 62/190

The table shows that, except for Baseline Observation Carried Forward (BOCF), the analysis was not sensitive to different imputation methods. The "hybrid" imputation method was protocol-specified and was part of the SPA agreement.

The secondary endpoints, analyzed using a gate-keeping strategy to preserve the Type I error, showed a benefit of BTDS over placebo for the MOS-Sleep Scale. There were no statistically significant differences with regard to the use of rescue although the placebo group trended to use more rescue.

Study 24 demonstrated that BTDS is efficacious.

Study BUP3015 (Study 15) was a randomized, double-blind, dose- and active-controlled study in "opioid-experienced" (defined as 30-80 mg of morphine/day) patients with chronic low back pain. Patients were to have had a pain intensity of "none" or "mild" at the time of screening (on opioids). Again, patients were excluded for certain QT parameters or history or family history of Long QT Syndrome.

Following screening, eligible patients started their opioid taper. Patients were tapered over 7 days and had to be on ≤ 30 mg morphine equivalents/day to be randomized. Following the opioid taper, only patients who rated their pain as ≥5/10 with a SOWS that was ≤23 were permitted to continue the study. Those patients were treated with a 10 mcg/hr patch for up to 7 days. The goal was for patients to uptitrate to the 20 mcg/hr patch. The criterion for successful dose escalation was tolerability. Patients who could not tolerate 20 mcg/hr after two attempts within 7 days were discontinued. Following the run-in period of 7 days, patients were randomized to one of three groups:

- BTDS, 20 mcg/hr
- BTDS, 5 mcg/hr
- Immediate-release oxycodone tablets (an unapproved, marketed drug), 10 mg Q6hrs

Patients were to have remained on their stable assigned treatment for 12-weeks. During the double-blind phase, rescue analgesia (ibuprofen, 200 mg or acetaminophen, 500 mg) were permitted. Also permitted were adjuvant analgesics at stable dose (30 days) such as anti-depressants and anticonvulsants) and stable-dose (6 weeks) oral corticosteroids.

During the double-blind phase, patients were to have recorded their pain intensity over the last 24 hours daily. Other instruments such as the Brief Pain Inventory-Short Form, MOS Sleep Scale, Profile of Mood States, SF-36, and Oswestry Disability Index were completed at certain vistis.

The primary efficacy endpoint was the average pain over the last 24 hours (11-point numerical pain rating scale) collected daily. There were several amendments to the Statistical Analysis Plan. The final statistical analysis plan used an ANCOVA model and a linear mixed model; no imputation was done. The final analysis also proposed to compare data at 1, 2 4, 8, and 12 weeks. The Division believes that at landmark analysis at the end-of-treatment (12-weeks) is

the most appropriate comparison. To address issues of multiplicity, the Applicant used a gatekeeping strategy, described in Dr. Levin's review.

As described in Drs. Levin's and Norton's reviews, the protocol-specified primary analysis was unacceptable for several reasons, most notably, we believe that the key comparison should be made at 12 weeks; this is a chronic use drug.

A total of 2066 patients were screened and 1160 entered the run-in period. A total of 662 patients were successfully titrated to 20 mcg/hr BTDS and were randomized. The most common reasons for discontinuation during the run-in period were lack of efficacy (21%) and adverse event (12%). This pattern is predictable since these patients were opioid-experienced.

In the double-blind period, not unexpectedly, patients on the high (20 mcg/hr) dose of BTDS dropped out for adverse events at higher rates than those on the low dose of BTDS. Conversely, patients treated with low dose BTDS dropped out at higher rates because of lack of therapeutic effect. These results are summarized in Table 3.

Table 3: Dropouts in Study 24

Category	Prerandomization Phase Run-in Period[a] BTDS 10/20 (N = 1160)	Double-blind Phase Maintenance Period BTDS 5 (N = 221)	BTDS 20 (N = 219)	OxyIR® (N = 220)
Completed Period/Phase on Study Drug, n (%)	662 (57)	128 (58)	146 (67)	159 (72)
Discontinued Study Drug - All Cases[b, c], n (%)	498 (43)	93 (42)	73 (33)	61 (28)
Adverse event	144 (12)	14 (6)	29 (13)	16 (7)
Lost to follow-up	21 (2)	7 (3)	6 (3)	10 (5)
Subject's choice	23 (2)	11 (5)	7 (3)	5 (2)
Administrative	59 (5)	9 (4)	6 (3)	14 (6)
Lack of therapeutic effect	239 (21)	52 (24)	25 (11)	16 (7)
Did not qualify	12 (1)	0	0	0
Discontinued Study Drug And Completed Double-blind Phase, n (%)[b]		20 (9)	9 (4)	10 (5)
Adverse event		0	3 (1)	1 (< 1)
Lost to follow-up		0	0	0
Subject's choice		1 (< 1)	0	1 (<1)
Administrative		0	0	0
Lack of therapeutic effect		19 (9)	6 (3)	8 (4)
Discontinued Study Drug And Did Not Complete Double-blind Phase, n (%)[b]		73 (33)	64 (29)	51 (23)
Adverse event		14 (6)	26 (12)	15 (7)
Lost to follow-up		7 (3)	6 (3)	10 (5)
Subject's choice		10 (5)	7 (3)	4 (2)
Administrative		9 (4)	6 (3)	14 (6)
Lack of therapeutic effect		33 (15)	19 (9)	8 (4)

Source: Dr. Levin's review, page 88/190

Table 4 shows the primary efficacy analysis for Study 15.

Table 4: Primary Efficacy Analysis, Study 15

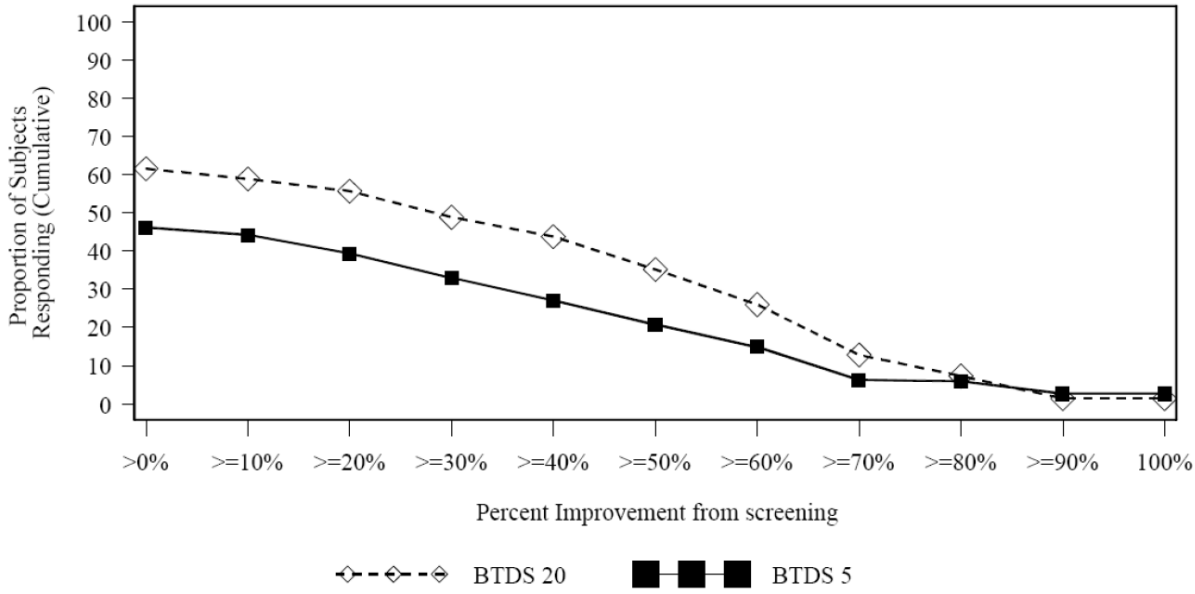
Visits/Weeks	BTDS 5 (N = 221)	BTDS 20 (N = 219)	OxyIR® (N = 220)
Screening[a]			
n	221	219	220
Mean (SE)	6.36 (0.075)	6.46 (0.084)	6.46 (0.079)
Median	6.0	6.5	6.0
Min, Max	4, 10	1, 10	3, 10
Prerandomization[b]			
n	221	219	219
Mean (SE)	2.84 (0.075)	2.91 (0.075)	2.74 (0.074)
Median	3.0	3.1	2.9
Min, Max	0, 7	0, 6	0, 5
Week 4			
n	154	176	184
Mean (SE)	3.79 (0.149)	3.40 (0.128)	3.14 (0.125)
Median	4.0	3.0	3.0
Min, Max	0, 8	0, 8	0, 7
Week 8			
n	138	164	173
Mean (SE)	3.83 (0.162)	3.35 (0.140)	3.24 (0.145)
Median	4.0	3.0	3.0
Min, Max	0, 9	0, 8	0, 10
Week 12			
n	127	142	154
Mean (SE)	4.02 (0.179)	3.35 (0.139)	3.26 (0.152)
Median	4.0	3.0	3.0
Min, Max	0, 9	0, 9	0, 8
Overall Statistics[c]			
Difference from BTDS 5 over weeks 4, 8, and 12		-0.67 (0.163)	-0.75 (0.161)
P value vs. BTDS 5		< .001	< .001
95% CI for difference from BTDS 5		(-0.99, -0.35)	(-1.07, -0.44)

Source: Dr. Norton's review, page 22/34

Dr. Norton confirmed a statistically significant difference favoring high-dose buprenorphine over the low-dose control.

Figure 2 shows Dr. Norton's continuous responder analysis for Study 15, showing consistent separation between the low- and high-dose curves up to very high levels of treatment effect (>70% reduction in pain from baseline).

Figure 2: Responder analysis, Study 15



Source: Dr. Norton's review, page 24/34

Table 4 and Figure 2 support the finding of efficacy for Butrans, in this instance in opioid-experience patients.

The secondary endpoints, again using a gate-keeping strategy to preserve alpha-error, showed statistically significant differences, favoring the high-dose BTDS over low-dose for the MOS-Sleep Scale and the use of supplemental analgesia. The Oswestry Score favored the high-dose BTDS but the difference was not significant.

It is interesting to note that the Applicant terminated Study 15 early, after only 74% of the planned accrual had completed. To ensure that there were no other reasons and to assess whether unblinding had occurred, the Division of Scientific Investigations was consulted to conduct a directed Sponsor inspection.

Dr. Leibenhaut's Clinical Inspection Summary indicates that Purdue was inspected from 12-15 April 2010. Dr. Leibenhaut reported that during 2005, the Applicant was involved in a patient dispute concerning OxyContin. The company downsized, laying off employers and terminating development programs which included Study 15. Review of the numbers of patients accrued to data indicated that the study could have adequate power to show efficacy so Purdue proceeded with the analysis. Dr. Leibenhaut found no evidence of unblinding or other issues during her sponsor inspection.

Drs. Levin, Norton, and Price have recommended approval from the perspective of efficacy.

8. Safety

The review of clinical safety was conducted by Dr. Levin. Please see his excellent review for details.

Including the studies submitted in the original NDA, the Applicant submitted data from 35 clinical trials totaling 6042 patients and subjects who were exposed to BTDS. One hundred eighty three patients were treated for greater than one year. The product is marketed internationally and the Applicant reports that there are over (b) (4) patient-days of exposure at doses ranging from 5 mcg/hr to 70 mcg/hr.

Deficiency #56 from the Non-Approvable Letter required the Applicant to improve the presentation and clarity of the safety data. The Applicant adequately addressed this deficiency by reanalyzing and integrating the previously submitted safety data with data generated during the interim between the 2001 Action and the current submission. Purdue pooled the aggregate safety data into several pools including "all studies," "all Phase 3 chronic pain," "Phase 2 nonchronic pain," and "all clinical pharmacology studies." The Phase 3 chronic pain studies were further subdivided by whether they were controlled or not or of an enriched design or not.

The safety assessment focused on product-specific concerns with this transdermal system that delivers the mixed agonist/antagonist buprenorphine. Those concerns are summarized below:

Buprenorphine-associated:
- Respiratory depression
- CNS depression
- Dependence
- Hepatic events
- Allergic reactions

Device-related:
- Dermatologic complaints
- Potential for dose dumping
- Adhesion

Major Safety Findings

Deaths

There were a total of 18 deaths (15 in patients treated with BTDS) reported in this NDA. Dr. Levin or Dr. DalPan (Medical Officer for first review cycle) reviewed each death in detail and found that, for many deaths, there was inadequate information to determine the exact etiology of death. For instance, for many of the cardiac deaths, there were underlying medical and cardiac morbidities and whether BTDS could have contributed to death cannot be determined. However, there did not appear to be any deaths directly related to BTDS. Dr. Fitzman, of the Division of Cardiovascular and Renal Products reviewed the adverse events related to QT prolongation and found that the incidence of such events was low. She noted that the cardiac adverse event seen most often was "dizziness" but that complaint was not necessarily linked to QT prolongation.

Serious Adverse Events

Over the entire development program, 210 patients reported serious adverse events (SAEs) and four patients who experienced SAEs died. The most common MedDRA System Organ Classes for SAEs were Infections and Infestations (0.6%), Cardiac Disorders (0.5%), Gastrointestinal Disorders (0.5%), and Nervous System Disorders (0.5%).

Compared to other preferred terms, SAEs coded as "chest pain" appeared at a high rate compared other terms as shown in Table 5.

Table 5: Nonfatal SAEs by Preferred Term, all studies

Preferred Term	Number (%) of BTDS-treated subjects with nonfatal serious adverse events N=6042
All Preferred Terms	**210 (3.5)**
Chest pain	21 (0.3)
Dehydration	9 (0.1)
Vomiting	7 (0.1)
Dyspnoea	7 (0.1)
Fall	6 (0.1)
Osteoarthritis	6 (0.1)
Pneumonia	6 (0.1)
Abdominal pain	5 (0.1)
Cellulitis	5 (0.1)
Chronic obstructive pulmonary disease	5 (0.1)
Hip fracture	5 (0.1)
Myocardial infarction	5 (0.1)
Nausea	5 (0.1)
Transient ischaemic attack	5 (0.1)
Cardiac failure congestive	4 (0.1)
Cerebrovascular accident	4 (0.1)
Cholecystitis	4 (0.1)
Gastroenteritis	4 (0.1)
Pulmonary embolism	4 (0.1)

Source: Dr. Levin's review, page 140/190

However, Table 5 includes data from all studies, including long-term open-label data. Table 6 shows the SAEs in controlled trials, to add context.

Table 6: Nonfatal SAEs by System Organ Class and Preferred Term, controlled chronic pain studies.

MedDRA System Organ Class/ Preferred Term	Number (%) of subjects with nonfatal SAEs		
	Placebo (N=995)[a]	Comparator[b] (N=633)[a]	BTDS (N=2130)[a]
All SOCs/All Preferred Terms	**16 (1.6)**	**24 (3.8)**	**50 (2.3)**
Cardiac disorders	**4 (0.4)**	**0**	**5 (0.2)**
Cardiac failure congestive	2 (0.2)	0	1 (<0.1)
Acute myocardial infarction	2 (0.2)	0	0
Gastrointestinal disorders	**2 (0.2)**	**5 (0.8)**	**6 (0.3)**
Pancreatitis	0	0	2 (0.1)
Vomiting	0	2 (0.3)	1 (<0.1)
Diarrhea	0	2(0.3)	0
General disorders/administration site	**1 (0.1)**	**1 (0.2)**	**6 (0.3)**
Chest pain	1 (0.1)	1 (0.2)	2 (0.1)
Infections and infestations	**5 (0.5)**	**3 (0.5)**	**7 (0.3)**
Cellulitis	0	0	2 (0.1)
Gastroenteritis	0	0	2 (0.1)
Pneumonia	2 (0.2)	1 (0.2)	1 (<0.1)
Injury, poisoning and procedural complications	**2 (0.2)**	**2 (0.3)**	**5 (0.2)**
Fall	0	1 (0.2)	3 (0.1)
Nervous system disorders	3 (0.3)	3 (0.5)	6 (0.3)
Transient ischemic attack	0	1 (0.2)	3 (0.1)
Psychiatric disorders	**2 (0.2)**	**0**	**4 (0.2)**
Anxiety	2 (0.2)	0	0
Renal and urinary disorders	**0**	**3 (0.5)**	**2 (0.1)**
Nephrolithiasis	0	1 (0.2)	2 (0.1)
Respiratory, thoracic and mediastinal disorders	**2 (0.2)**	**3 (0.5)**	**9 (0.4)**
COPD	0	1 (0.2)	3 (0.1)
Social circumstances	**0**	**0**	**2 (0.1)**
Drug abuser	0	0	2 (0.1)
Skin and subcutaneous tissue	**0**	**0**	**2 (0.1)**
Hepatobiliary disorders	**1 (0.1)**	**4 (0.6)**	**2 (0.1)**
Musculoskeletal/connective tissue	**0**	**3 (0.5)**	**3 (0.1)**
Vascular disorders	**0**	**0**	**2 (0.1)**

[a] Subjects may experience more than one AE in a SOC
[b] Active comparators are: Oxy/APAP, OxyIR, HCD/APAP
There was ≤ 1 subject in the BTDS-treatment group for the SOC neoplasms, metabolism, investigations, endocrine disorders and blood and lymphatic system.

Source: Dr. Levin's review, page 141/190

Table 6 shows that the rates of SAEs appear comparable between BTDS and the comparators.

Dr. Levin reviewed the SAEs with particular attention to those coded as pancreatitis, drug abuse, drug withdrawal, respiratory failure, convulsion, syncope, and SAEs related to the skin.

For the most part, the SAEs of interest were either not related to the use of BTDS or they are expected with the use of buprenorphine and are adequately addressed in labeling. There was one overdose of note (Patient 51012 in Study 15). This patient experienced respiratory depression. However, her drug panel was positive for benzodiazepines, amphetamines, and barbiturates so the contribution of the BTDS is unclear. However, the records show that this patient was using a heating pad over the BTDS which is important to note.

The seizures appeared to be related to other causes such as intracerebral bleed. There was one case of erythema multiforme reported that was not related to BTDS. There was one serious hypersensitivity reaction. Hypersenstivity reactions will be discussed in further detail later.

Adverse Events Leading to Discontinuation

Across the chronic pain studies, a total of 26% of patients discontinued due to adverse events. The most common reasons were related to the gastrointestinal system, administration site, and nervous system. The key adverse events that led to discontinuation are summarized in Table 7.

Table 7: Adverse Events leading to discontinuation, chronic pain studies

MedDRA system organ class/ preferred term	Number (%) of subjects who discontinued due to adverse events (N=5415)
All SOCs/all preferred terms	**1431 (26.4)**
Gastrointestinal disorders	**630 (11.6)**
Nausea	493 (9.1)
Vomiting	215 (4.0)
Constipation	59 (1.1)
General disorders and administration site conditions	**396 (7.3)**
Application site pruritus	88 (1.6)
Application site rash	72 (1.3)
Application site erythema	68 (1.3)
Fatigue	57 (1.1)
Nervous system disorders	**503 (9.3)**
Dizziness	246 (4.5)
Headache	135 (2.5)
Somnolence	135 (2.5)
Skin and subcutaneous tissue disorders	**213 (3.9)**
Pruritus	54 (1.0)

Source: Dr. Levin's review, page 161/190

In controlled studies, the rate of discontinuations due to adverse events appeared higher than placebo but similar to immediate-release oxycodone, the active comparator.

Common Adverse Events and Adverse Events of Interest

The most common adverse events were those related to opioids or complaints about the application site and included nausea, dizziness, headache, application site pruritus, somnolence, vomiting, and constipation. The incidence of adverse events tended to be higher in the opioid-naïve patients, as expected.

Dr. Levin identified six key safety issues. Conclusions from the safety review are summarized following.

1. Residual buprenorphine in a used patch

   Deficiency #61 in the Not Approvable Letter indicated that Purdue should redesign the patch to minimize the amount of residual drug. The Applicant has done little to address this. Per Dr. Ysern's review, more than (b) (4) of the buprenorphine remains in the patch after 7 days of use. The Transdermal Working Group (TWG) within ONDQA reviewed this issue and has decided that the amount of drug remaining is not an approval issue. The disposal of the patch can also be addressed through the REMS.

2. Hepatotoxicity

   The clinical development program and postmarketing data for Subutex/Suboxone (NDAs 20-732 and 20-733) had cases of cytolytic hepatitis and hepatitis with jaundice. However, these cases were confounded by the high rates of hepatic disease/disfunction in the addict population. Dr. DalPan, in the initial review of the BTDS NDA, found the applicant's data and data analysis lacking although he reported no overt hepatoxicity.

   Dr. Levin revisited this issue in the resubmission. There was one case with ALT/AST > 3x ULN and bilirubin >2 ULN. However, this patient had acute cholecyctitis and did not meet the definition of Hy's Law. The Applicant analyzed LFT data in several ways including defining markedly abnormal values (>3x ULN for transaminases and >1.5x ULN for bilirubin), shift tables, identification of cases with a Standardized MedDRA Query (SMQ) for liver-related investigations, signs, and symptoms, and peak LFT analyses.

   There does not appear to be a relationship between hepatotoxicity and the use of BTDS at the doses studied.

3. QT prolongation

   The Applicant conducted a thorough QT (tQT) study (Study BUP 1011), comparing placebo, BTDS 10 mcg/hr, BTDS 40 mcg/hr, and moxifloxacin. The QT Interdisciplinary Review Team (QT IRT) was consulted to review the study and found the design and conduct of this study to be acceptable. The QT IRT found that the 10 mcg/hr dose had no clinically meaningful effect on QT. However, the supratherapeutic

(40 mcg/hr) dose exceeded the 10-msec threshold at multiple timepoints. This QT prolongation occurred at two-times the maximum labeled dose; the QT IRT found the labeling acceptable.

In addition, the Applicant collected and analyzed ECG data in the clinical trials (Deficiency 58). The Division of Cardio-Renal Products (DCRP) was consulted to review the ECG data and the cardiac adverse events. DCRP conducted an extensive review of these data and concluded that there is a modest QT prolonging effect at 20 mcg/hr. However, DCRP found that the AEs and SAEs suggest that the product "…has a minimal arrythmogenic potential, if any, at the doses studied."

4. Dermatologic complaints/hypersensitivity

A total of eight patients developed SAEs related to the skin. In most cases, BTDS was not felt to be related to the event (example, skin ulceration and necrosis is a patient with diabetes). One patient (27005 in Study BUP3018), developed generalized rash over the face, arms, and chest one day after beginning therapy with BTDS, 10 mcg/hr. Dr. Levin adjudicated the case as likely related to study drug, based on the temporal relationship between the start of BTDS and the onset of the rash.

Not unexpectedly, application site issues appeared in other aspects of the safety evaluation such as the adverse events leading to discontinuation (6.2% due to application site pruritus, rash, or erythema) and common adverse events (~10% related to application site).

However, in the 120-day safety update, the Applicant reported a new SAE (Subject 0008030, Study 3025). This was a 47-year-old woman with OA of the knee who developed left eyelid swelling and hives on her face and neck six days after starting BTDS. Her concomitant medications at the time were glucosamine chondroitin, multivitamin, and fish oil and did have a history of seasonal allergies that did not require treatment. The BTDS was removed and she was treated with diphenhydramine, with initial improvement. However, the next day, she was admitted to the hospital with a swollen tongue and required IV steroids. She was discharged after a 23-hour admission of oral steroids. The hypersensitivity reaction was reported to completely resolve. This appears to be an anaphylactoid reaction.

This prompted a more detailed examination of the postmarketing hypersensitivity/application site data by Purdue. The analysis assessed erythema, pruritus, dermatitis, vesicles, secretion/discharge, dryness, burns, and rashes at the application site. The Applicant also conducted a latency analysis and found that the reactions can be immediate or late with 24% of reactions occurring following 100 days of BTDS treatment.

5. Respiratory Depression

   There was no evidence of clinically significant respiratory depression when the product was used as intended (there was one case of polydrug overdose and a heating pad).

6. Drug Abuse/Withdrawal

   Buprenorphine, as a mixed opioid agonist/antagonist, has the potential to precipitate withdrawal in opioid-dependent humans. A total of 17 subjects had adverse events coded as withdrawal in the safety database. These subjects all had the drug abruptly discontinued; thus the withdrawal was to be expected. No patients or subjects experience withdrawal symptoms upon initiation of drug.

   As Dr. Levin notes, 11 patients were suspected of drug abuse. Many of these subjects also abused other drugs such as cannabis, cocaine, or other opioids. This would appear to be more of a failure of investigators to exclude patients inappropriate for long-term opioid therapy than a peculiarity of BTDS itself.

Other Clinical Deficiencies

Deficiencies 35C and 62 related to patch adhesiveness. The Applicant reported that only 1 patch fell off during clinical trials (in a heavily perspiring patient). In one of the pivotal studies, Study 24, 11% of patients reported some problem with patch adhesion. In the context of being able to tape the edges of this product, this appears acceptable.

Deficiency 57 required an assessment of dose response and adverse events.

Table 8 shows the number and percentage of patients with adverse events including those that led to discontinuation by various groups.

Table 8: Summary of dose-response data, adverse events, by pool

Dose dependency analysis	Analysis group/ treatment period	BTDS dose	Number (%) of subjects				
				All adverse events		All adverse events leading to discontinuation	
			N	n	(%)	n	(%)
Randomized dose in the fixed dosing periods	Nonenriched, forced-titration chronic pain studies (Group A1A)/ double-blind period	BTDS 5	105	99	94.3	27	25.7
		BTDS 10	103	92	89.3	23	22.3
		BTDS 20	104	99	95.2	37	35.6
		Total BTDS	312	290	92.9	87	27.9
	Enriched, maintenance–of-analgesia chronic pain studies (Group A2A)/ double-blind period	BTDS 5	61	26	42.6	4	6.6
		BTDS 10	133	69	51.9	8	6.0
		BTDS 20	156	80	51.6	9	5.8
		Total BTDS	349	175	50.1	21	6.0
	Enriched, fixed duration, chronic pain studies (Group A2B)/ double-blind period	BTDS 5	404	234	57.9	25	6.2
		BTDS 10	120	65	54.2	16	13.3
		BTDS 20	553	389	70.3	72	13.0
		Total BTDS	1077	688	63.9	113	10.5
Dose at onset in the titration-to-effect periods	Nonenriched, forced-titration chronic pain studies (Group A1B)/ double-blind period	BTDS 5	392	135	34.4	*	*
		BTDS 10	340	161	47.4	*	*
		BTDS 20	257	161	62.6	*	*
		Total BTDS	392	300	76.5	*	*
	Enriched, maintenance-of-analgesia chronic pain studies (Group A2A)/ open-label run-in period	BTDS 5	1276	345	27.0	*	*
		BTDS 10	1044	332	31.8	*	*
		BTDS 20	681	295	43.3	*	*
		Total BTDS	1276	747	58.5	*	*
	Enriched, fixed-duration, chronic pain studies (Group A2B)/ open-label run-in period	BTDS 5	1025	198	19.3	*	*
		BTDS 10	2942	828	28.1	*	*
		BTDS 20	2409	1043	43.3	*	*
		Total BTDS	3025	1646	54.4	*	*

Source: Dr. Levin's review, page 122

These data show a trend toward dose response with regard to the incidence of adverse events, typical for an opioid, particularly when the titration is forced as was the case in many of the studies in the clinical development program.

Deficiency 59 (a requirement to justify the interval for dose titration) was resolved prior to this resubmission.

Deficiency 60 requested an abuse liability study. This was circumvented when buprenorphine was upscheduled from Schedule V to Schedule III.

Dr. Levin has recommended approval for this product.

9. Advisory Committee Meeting

There was no Advisory Committee Meeting held for BTDS.

10. Pediatrics

As with all of the extended-release opioids indicated for moderate to severe chronic pain for an extended period of time, pediatric studies will be waived for pediatric patients below the age of 7 because the number of patients available for study is too small and studies are impracticable. The remainder of the pediatric population can be deferred because the adult studies are ready for approval. This plan was reviewed at the Pediatric Research Committee and approved.

11. Other Relevant Regulatory Issues

The Division of Scientific Investigations reported that the four sites inspected had no violations that would bring into question the acceptability of the data. As noted earlier, there was no unblinding or other issue surrounding the Applicant's decision to prematurely terminate Study 15.

The Division of Medication Error Prevention and Analysis (DMEPA) was consulted. The proposed tradename, Butrans was found to be acceptable although the typography proposed by the Applicant (BuTrans with a capital "T") was found to be unacceptable. DMEPA had a number of comments regarding the instructions for use that will be addressed in the labeling meetings and negotiations.

The Division of Drug Marketing and Communications (DDMAC) was consulted for a label review and had several comments which will be implemented in labeling negotiations.

The Division of Pharmacovigilance (DPV)/Office of Surveillance and Epidemiology was consulted to address drug product failure reports for transdermal buprenorphine. DPV found no evidence of patch failure, leakage, or issues with matrix patch adhesion in the available data.

The Division of Risk Management (DRISK) was consulted to assess the Medication Guide. DRISK had various comments to improve comprehension and ensure conformity between the package insert and medication guide which will be implemented in labeling.

The Controlled Substance Staff (CSS) also stressed that the Applicant must reduce the residual buprenorphine in the patch after use. At this time, the issue of the residual drug is being resolved within CDER. CSS also requested routine monitoring and surveillance post marketing to detect abuse, misuse, overdose, diversion, and death.

Risk Evaluation and Mitigation Strategies (REMS)

A REMS was submitted as part of the initial resubmission (30 September 2009). However, on 18 February 2010, pursuant to a request by FDA, Purdue submitted a revised REMS to be consistent with that of their OxyContin product (NDA 20-553). The revised REMS consists of:

- Medication Guide
- Elements to Assure Safe Use
    - Prescriber training with retraining every two years
- Timetable for submission of assessments

The Division of Risk Management has not completed their review of the revised REMS at the time of finalization of this review. However, based on the interim review comments dated 21 April 2010, the basic REMS appears to be acceptable pending some refinements of the REMS documents.

12. Labeling

In addition to recommendations from other disciplines, key points to be emphasized in labeling include:

1. The drug must be carefully labeled with regard to warnings about the abuse potential and potential for fatal respiratory depression, common to all opioids.
2. Similar to Duragesic, the labeling must stress that the drug is not for short-term, acute pain, or prn use. Patients must receive an immediate-release opioid until a sufficient depot is delivered to the skin. Last, the dose must not be titrated at intervals less than 72 hours.
3. The dose must not exceed 20 mcg/hr. The key reason for this is the QT prolongation identified in the tQT study in the context of the fact that the drug is marketed at up to 70 mcg/hr overseas.
4. Anaphylaxis has been reported with this product as well as severe skin reactions with long latency.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

  Approval

- Risk Benefit Assessment

  The Applicant has submitted substantial evidence of effectiveness in patients with chronic low back pain. The safety of the drug was evaluated in over 6000 subjects and patients and there is substantial postmarketing experience. The issue of residual buprenorphine can be specifically addressed in the disposal instructions in the REMS.

- Recommendation for Postmarketing Risk Management Activities

  None

- Recommendation for other Postmarketing Study Commitments

  The Applicant has agreed with the CMC Biopharmaceutics request as follows:

  > We agree with FDA's revised proposal for specification for the 0.5, 8, and 24 hour time point…the tightest range for the 2 hour time point is (b) (4) ..we will revert to L2 and L3 testing as necessary.

- Recommended Comments to Applicant

  None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21306	ORIG-1	PURDUE PHARMA LP	Butrans (buprenorphine) Transdermal System

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/s/

ROBERT B SHIBUYA
06/21/2010